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Palladium-Catalyzed Domino Alkenylation/Amination/Pyridination Reactions of 2-Vinylanilines with Alkynes: Access to Cyclopentaquinolines

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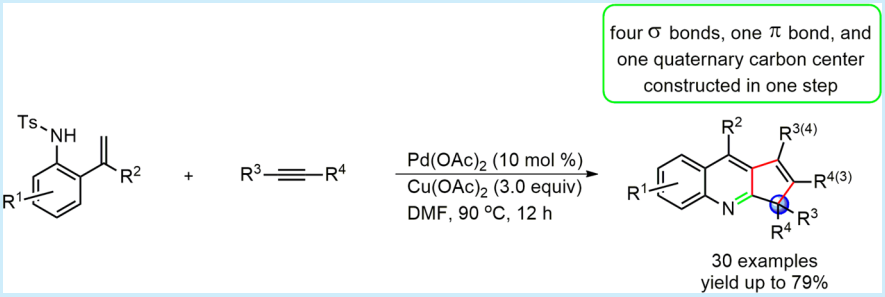
Supporting Information

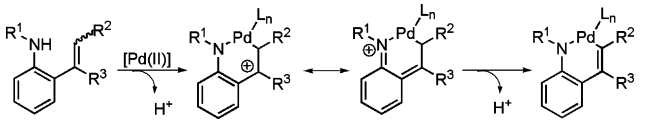


ABSTRACT: A novel domino oxidative annulation of 2-vinylanilines with internal alkynes was developed to constitute a rare class of cyclopentaquinoline derivatives. This transformation encompasses four σ bonds formation, one quaternary carbon center construction, and pyridination steps in one pot under identical conditions, which fascinatingly increases the molecular complexity from easily available starting materials.

A challenge for modern organic synthesis is the creation of efficient processes that can provide the maximum molecular complexity and diversity with a minimum number of purification steps[1] and chemical waste.[2] Domino reactions, which typically bestow the formation of multiple new bonds in one step under identical reaction conditions, are an attractive alternative to reach this near ideal goal. In past decades, myriad efforts have been devoted to the development of efficient domino reactions, from academia to industry.[3]

Recently, cascade oxidative annulations based on transition-metal-catalyzed C−H bond activation involving insertion of one or two unsaturated bonds have attracted considerable attention due to their outstanding ability to construct benzoheterocycles from readily available starting materials.[4] In particular, for 2-vinylphenols and 2-vinylanilines, oxidative annulations employing alkynes, allenes, carbon monoxide, isocyanides, and carbon dioxide as cycloaddition partners were developed to generate benzoxepine,[5] chromene,[6] coumarin,[7] quinolinone,[8] benzoazepine,[9] 2-aminoquinoline,[10] indole,[11] and spirocylic derivatives.[12] Our group is interested in exploring new transformations of 2-vinylanilines to potentially useful nitrogen-containing heterocycles through palladium-catalyzed oxidative heteroannulation reactions.[9a,10a] Importantly, during the investigation, we found that the vinylic C(sp^2)−H bond is activated probably via nucleophilic attack of the conjugated alkene on the electrophilic palladium(II) followed by a base-assisted deprotonation process (Scheme 1),[9a,10a] which offers the possibility to sequentially difunctionalize the terminal vinyl group of 2-vinylanilines in one pot. We herein disclose a novel domino oxidative annulation of 2-vinylanilines with internal alkynes via difunctionalization of the terminal vinyl group. The transformation is suggested to encompass the consecutive formation of two C(sp^2)−C(sp^2) and one C(sp^3)−N bonds, 1,2-migration of an aryl group, and elimination of a tosyl group in a single step under identical reaction conditions.

Scheme 1. Pd-Catalyzed Vinylic C−H Bond Activation of 2-Vinylanilnes



Initially, the reaction of free amine **1a** and 1,2-bis(4-methoxyphenyl)acetylene (**2a**) was tested under anticipated conditions for oxidative annulation, $Pd(OAc)_2/Cu(OAc)_2$ in acetonitrile at 90 °C. Only a trace amount of the product was formed. Successful amine-directed C−H bond activation normally requires a strong electron-withdrawing group to modulate the nucleophilicity of the nitrogen.[13] Therefore, the substrates with different electron-withdrawing protecting groups, such as Ac, Bz, Ts, and Ms were next investigated. Delightfully, the substrate **1e**, employing tosyl as the protecting group,

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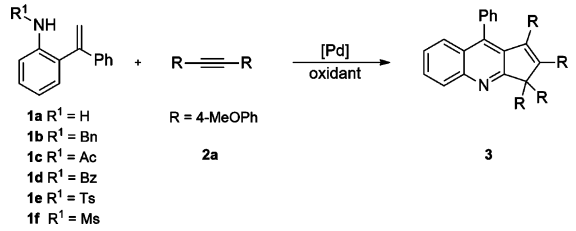
afforded **3ea** in 63% isolated yield (Table 1, entry 5). Overdose of alkyne **2a** or $Cu(OAc)_2$ was not beneficial to the yield of quinoline **3ea** (Table 1, entries 6 and 7). The choice of solvent had a dramatic impact on the reaction efficiency, and the optimal DMF provided quinoline **3ea** in 78% yield (Table 1, entries 8–14). Employing Ms as the protecting group instead of Ts resulted in a significant drop in yields (Table 1, entry 15). The performance of this transformation also relied significantly on the nature of oxidants, and copper acetate was proven to be optimal. The employment of silver salts, such as Ag_2CO_3, AgOAc, and Ag_2O, offered the product in moderate yields, while the utilization of two organic oxidants, $PhI(OAc)_2$ and BQ, merely resulted in trace amount of the product. Engaging O_2 as oxidant or lowering the loading of $Pd(OAc)_2$ delivered inferior yields (Table 1, entries 21 and 22). Surprisingly, the rhodium complex $[Cp^*RhCl_2]_2$ and ruthenium complex $[Ru(p\text{-cymene})Cl_2]_2$ did not show catalytic activity in this transformation.

With the optimized reaction conditions established, the reactivity of other 2-vinylanilines with 1,2-bis(4-methoxyphenyl)acetylene (**2a**) was explored, and the results are summarized in Table 2. The substrates with alkyl groups, e.g., Me, *i*Pr, and *t*Bu, *para* to the nitrogen on the aniline moiety, furnished the corresponding products **3ga**, **3ha**, and **3ia** in 62%, 68%, and 62% yield, respectively, demonstrating alkyl substituents *para* to the nitrogen slightly impede the reaction efficiency. Strong electron-donating group MeO *para* to the nitrogen was well tolerated, giving the desired product **3ja** in 79% yield. Strong electron-withdrawing substituents, such as CO_2Et (**3ka**) and NO_2 (**3la**), located on the same position, hampered the performance of this process, and especially, the *para*-nitro product (**3la**) was only obtained in 38% yield. The above results clearly show that an electron-rich aniline moiety facilitates this transformation.

The reaction was also compatible with halogen substituents, e.g., Cl (**3ma**) and Br (**3na**), which is interesting because the carbon–halogen bond is susceptible to further structural elaboration. When R^2 was *p*-Me-phenyl, *m*-Me-phenyl, *p*-MeO-phenyl, *m*-MeO-phenyl *p*-Cl-phenyl, *p*-F-phenyl, and 1-naphthyl, the corresponding products **3oa**–**3ua** were obtained in moderate yields (56–79%), indicating no direct correlation exists between the yield and the electron density of the aryl group. The substrate with a thienyl group produced the anticipated product **3va** in poor yield (35%), probably due to the strong coordination and absorption properties of the sulfur atom with transition metals. The substrates were smoothly converted to the desired products when R^1 was a substituent

Table 1. Optimization of Reaction Conditions[a]



1a R^1 = H
1b R^1 = Bn
1c R^1 = Ac
1d R^1 = Bz
1e R^1 = Ts
1f R^1 = Ms

R = 4-MeOPh

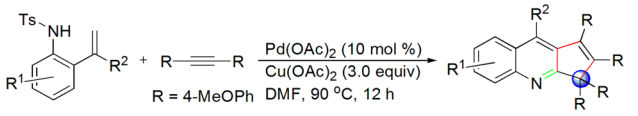
2a

3

entry	1	oxidant	solvent	yield (%)[b]
1	**1a**	$Cu(OAc)_2{\cdot}H_2O$	CH_3CN	trace
2	**1b**	$Cu(OAc)_2{\cdot}H_2O$	CH_3CN	0
3	**1c**	$Cu(OAc)_2{\cdot}H_2O$	CH_3CN	trace
4	**1d**	$Cu(OAc)_2{\cdot}H_2O$	CH_3CN	0
5	**1e**	$Cu(OAc)_2{\cdot}H_2O$	CH_3CN	63
6[c]	**1e**	$Cu(OAc)_2{\cdot}H_2O$	CH_3CN	55
7[d]	**1e**	$Cu(OAc)_2{\cdot}H_2O$	CH_3CN	57
8	**1e**	$Cu(OAc)_2{\cdot}H_2O$	dixone	16
9	**1e**	$Cu(OAc)_2{\cdot}H_2O$	PhMe	15
10	**1e**	$Cu(OAc)_2{\cdot}H_2O$	DMF	78
11	**1e**	$Cu(OAc)_2{\cdot}H_2O$	DMSO	15
12	**1e**	$Cu(OAc)_2{\cdot}H_2O$	DCE	8
13[e]	**1e**	$Cu(OAc)_2{\cdot}H_2O$	iPrOH	12
14	**1e**	$Cu(OAc)_2{\cdot}H_2O$	CH_3NO_2	19
15	**1f**	$Cu(OAc)_2{\cdot}H_2O$	DMF	50
16	**1e**	Ag_2CO_3	DMF	60
17	**1e**	AgOAc	DMF	57
18	**1e**	Ag_2O	DMF	46
19	**1e**	$PhI(OAc)_2$	DMF	trace
20	**1e**	BQ	DMF	trace
21[f]	**1e**	$Cu(OAc)_2{\cdot}H_2O$(30%) + O_2	DMF	46
22[g]	**1e**	$Cu(OAc)_2{\cdot}H_2O$	DMF	41
23[h]	**1e**	$Cu(OAc)_2{\cdot}H_2O$	DMF	0
24[i]	**1e**	$Cu(OAc)_2{\cdot}H_2O$	DMF	0

[a]All reactions were carried out with 0.3 mmol of **1**, 0.6 mmol of **2a**, 10 mol % of $Pd(OAc)_2$, 3.0 equiv of $[Cu^{2+}]$, $[Ag^+]$, $PhI(OAc)_2$, or BQ, 5 mL of solvent, sealed flask, 90 °C, 12 h. [b]Isolated yield. [c]3.0 equiv of **2a**. [d]4.5 equiv of $[Cu^{2+}]$. [e]DCE = dichloroethane. [f]0.3 equiv of $[Cu^{2+}]$ and 1.0 atm of O_2. [g]5 mol % of $Pd(OAc)_2$. [h]5 mol % of $[Ru(p\text{-cymene})Cl_2]_2$. [i]5 mol % of $[Cp^*RhCl_2]_2$.

Table 2. Scope of 2-Vinylanilines[a]

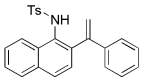


1

R = 4-MeOPh

2a

3

entry	1	R^1	R^2	3	yield (%)[b]
1	**1e**	H	Ph	**3ea**	78
2	**1g**	4-Me	Ph	**3ga**	62
3	**1h**	4-*i*Pr	Ph	**3ha**	68
4	**1i**	4-*t*Bu	Ph	**3ia**	62
5	**1j**	4-MeO	Ph	**3ja**	79
6	**1k**	4-CO_2Et	Ph	**3ka**	51
7	**1l**	4-NO_2	Ph	**3la**	38
8	**1m**	4-Cl	Ph	**3ma**	62
9	**1n**	4-Br	Ph	**3na**	49
10	**1o**	H	4-Me-Ph	**3oa**	71
11	**1p**	H	3-Me-Ph	**3pa**	58
12	**1q**	H	4-MeO-Ph	**3qa**	59
13	**1r**	H	3-MeO-Ph	**3ra**	56
14	**1s**	H	4-Cl-Ph	**3sa**	58
15	**1t**	H	4-F-Ph	**3ta**	64
16	**1u**	H	1-naphthyl	**3ua**	79
17	**1v**	H	2-thienyl	**3va**	35
18	**1w**	4-Me	4-Me-Ph	**3wa**	60
19	**1x**	4-Me	4-Cl-Ph	**3xa**	66
20	**1y**	4-Me	Me or *i*Pr	**3ya**	0
21	**1z**			**3za**	46

[a]All reactions were carried out with 0.3 mmol of **1**, 0.6 mmol of **2a**, 10 mol % of $Pd(OAc)_2$, 3.0 equiv of $Cu(OAc)_2$, 5 mL of DMF, sealed flask, 90 °C, 12 h. [b]Isolated yield.

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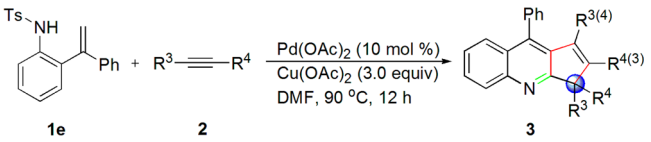
rather than an H atom and R^2 was a functionalized phenyl group (**1w** and **1x**). When R^2 was a methyl or *i*-propyl, rather than an aromatic group, the reaction did not occur (Table 2, entry 20). The catalytic system is also applicable to the 2-vinylnaphthalen-1-amine derivatives. The substrate **1z** offered the corresponding product **3za** in acceptable yields (46%). The structures of **3oa**, **3qa**, and **3wa** were determined by X-ray diffraction analysis.

The scope of alkynes was next examined by the reaction of *N*-tosyl-2-(1-phenyl-vinyl)aniline (**1e**) with a range of alkynes (Table 3). The symmetrical acetylenes **2a** and **2b** with two

Table 3. Scope of Alkynes[a]



1e 2 3

entry	2	R^3	R^4	3	yield (%)[b]
1	**2a**	4-MeO-Ph	4-MeO-Ph	**3ea**	78
2	**2b**	4-EtO-Ph	4-EtO-Ph	**3eb**	69
3	**2c**	4-MeO-Ph	4-Me-Ph	**3ec**	56 (11:10)[c]
4	**2d**	4-MeO-Ph	Ph	**3ed**	45 (13:10)[c]
5	**2e**	4-Me-Ph	4-Me-Ph	**3ee**	23
6	**2f**	Ph	Ph	**3ef**	15
7	**2g**	Ph	CO_2Me	**3eg**	0
8	**2h**	Et	Et	**3eh**	0

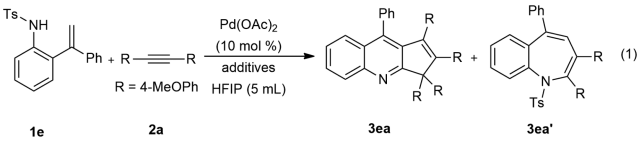
[a]All reactions were carried out with 0.3 mmol of **1e**, 0.6 mmol of **2**, 10 mol % of $Pd(OAc)_2$, 3.0 equiv of $Cu(OAc)_2$, 5 mL of DMF, sealed flask, 90 °C, 12 h. [b]Isolated yield. [c]Ratio of two regioisomers.

strongly electron-efficient alkoxyaryl groups reacted smoothly and gave the corresponding products **3ea** and **3eb** in good yields. The unsymmetrical acetylenes **2c** and **2d** with one strongly electron-efficient alkoxyaryl group were also suitable for this transformation and provided the anticipated products in moderate yields, which contains two regioisomers. The symmetrical acetylene **2e** with two weakly electron-efficient alkylaryls and **2f** with two unfunctionalized phenyls gave poor yields of products **3ee** and **3ef**. The electron-deficient acetylene **2g** and dialkylacetylene **2h** failed to deliver the expected products **3eg** and **3eh**. It is noteworthy that 4,4′-(ethyne-1,2-diyl)bis(*N*,*N*-dimethylaniline) did not participate in this transformation.

To gain mechanistic insight for the reaction, the following control experiments were conducted (Scheme 2). Employing HFIP (hexafluoroisopropanol) instead of DMF as solvent, the reaction of **1e** and **2a** offered a mixture of **3ea** (29%) and benzazepine **3ea′** (14%) (Scheme 2, eq 1). Using $Pd(OAc)_2$-Ag_2CO_3-HFIP as the catalytic system delivered benzazepine **3ea′** as the main product (65%) at room temperature (Scheme 2, eq 1). However, unfortunately, other substrates gave inferior yields under this condition, such as substrates **1i** and **1q** delivered the corresponding benzazepines **3ia′** and **3qa′** in acceptable yields (50% and 51%) (Scheme 2, eq 2). The above results delineate the intermediacy of eight-membered palladacycle **6** (Scheme 3) in this transformation. Performing the reaction of **1e** and **2a** under the standard conditions in the presence of radical scavengers, i.e., TEMPO (2,2,6,6-tetramethylpiperidine-*N*-oxyl) or BHT (3,5-di-*tert*-butyl-4-hydroxytoluene), slightly lowered the yields of **3ea**, which disfavors the reaction via a free-radical process (Scheme 2, eq 3).

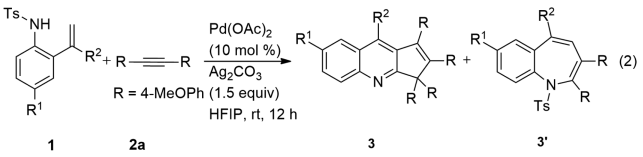
Based on the above preliminary observations and our previous results about palladium-catalyzed oxidative annulation of 2-

Scheme 2. Control Experiments



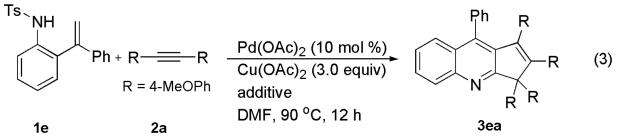
1e 2a 3ea 3ea'

additives	t (°C)	yield (%) **3ea**/**3ea'**
$Cu(OAc)_2{\cdot}H_2O$ (3.0 equiv)	90	29/14
Ag_2CO_3 (1.5 equiv)	60	trace/30
Ag_2CO_3 (1.5 equiv)	rt	15/65



1 2a 3 3'

1	R^1	R^2	yield (%) **3**/**3'**
1i	*t*-Bu	Ph	trace/50
1q	H	4-MeO-Ph	trace/51



1e 2a 3ea

additive	yield (%) **3ea**
TEMPO (1.2 equiv)	60
TEMPO (3.0 equiv)	61
BHT (1.2 equiv)	63

vinylanilines,[9a,10a] a possible mechanism for this transformation is presented in Scheme 3, with **1e** and **2a** as the model substrates. Initially, aniline **1e** reacts with Pd(II) species to form palladacycle complex **4** via vinylic C−H bond activation. Alkyne **2a** coordinates to the palladium center of Pd(II) species **4** and inserts to the Pd−C bond generating eight-membered palladacycle **6**, which is converted to intermediate **7** by acid hydrolysis (also can be converted to benzazepine **3ea′** by reduction elimination). The left vinylic $C(sp^2)$−H bond (marked in red) in species **7** is activated via nucleophilic attack of the adjacent alkene on the electrophilic palladium(II) followed by an AcO^--assisted deprotonation, engendering palladacycle **9**. The involvement of another alkyne **2a** in a same fashion gives intermediate **10**, which cyclizes to **11** in the presence of palladium under oxidative conditions. Compound **11** is oxidized to carboncation intermediate **12** by $Cu(OAc)_2$, and then 1,2-migration of the aryl group on the adjacent quaternary carbon center produces carbon-cation intermediate **13**. The elimination of Ts^+ from **13** with the assistance of the AcO^- group yields the product **3ea**.

In conclusion, a novel domino oxidative annulation of 2-vinylanilines with internal alkynes has been developed based on palladium-catalyzed sequential vinylic C−H alkenylation/amination/pyrindination. This transformation encompasses four bonds formation, one quaternary carbon center con-

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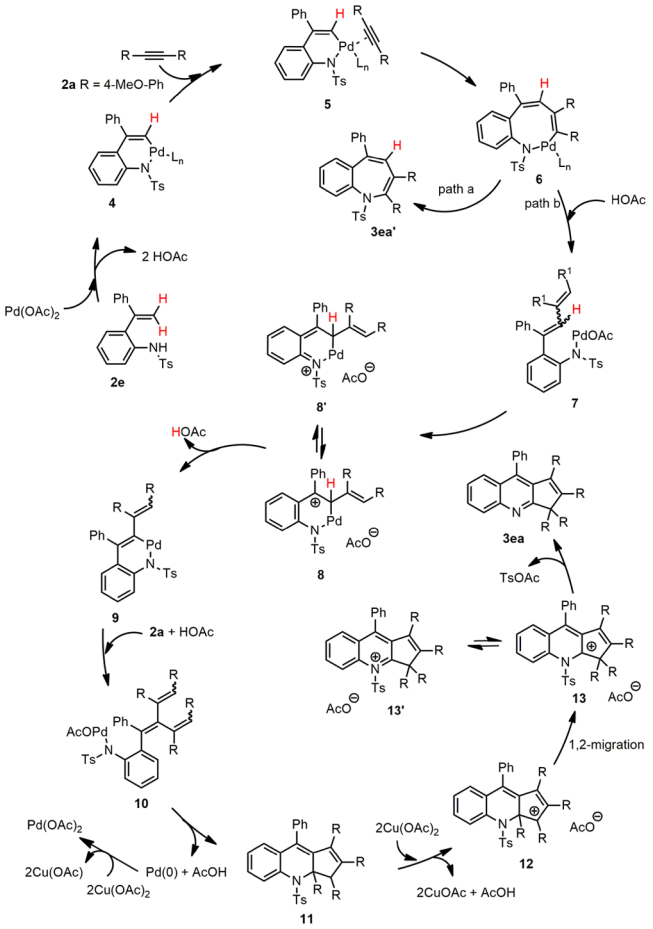
Scheme 3. Proposed Catalytic Cycle



struction, and pyridination steps in one pot under identical conditions, which fascinatingly increases the molecular complexity and constitutes a rare class of cyclopentaquinoline derivatives. To our knowledge, it is the first example of 1,1-difunctionalization of the terminal vinyl on 2-vinylanlines, and we believe it provides a platform for exploring new transformations of 2-vinylanilines or their analogues to valuable nitrogen-containing heterocycles.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03164.

Characterization data of new compounds, including X-ray crystal structures of **3oa**, **3qa**, and **3wa**, ^{1}H and ^{13}C NMR spectra, and HRMS (PDF)

Accession Codes

CCDC 1579067−1579068 and 1579070 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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