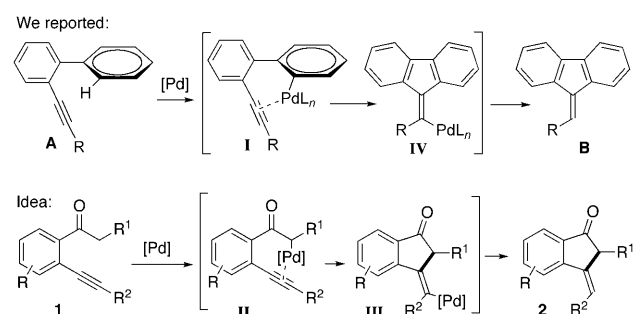# Communications

Palladium-Catalyzed Carbocyclization of Alkynyl Ketones Proceeding through a Carbopalladation Pathway**

Natalia Chernyak, Serge I. Gorelsky, and Vladimir Gevorgyan**

Carbopalladation across carbon–carbon multiple bonds is a powerful strategy for inter- and intramolecular C−C bond formation.[1] Generally, these processes are well-studied for catalytic cascade transformations involving aryl palladium or vinylpalladium species.[2] In contrast, carbopalladations of Pd enolates, which represent another important class of reactive Pd intermediates widely used in organic synthesis,[3] are exceedingly rare. To date, only a few examples of stoichiometric Pd carbopalladation reactions of carbon–carbon double bonds with Pd enolates have been reported [Eq. (1)].[4] To our knowledge, there are no reports on a catalytic version of this reaction. Herein, we report the Pd-catalyzed cascade transformation featuring the catalytic generation of the Pd enolate by a C−H functionalization strategy, coupled with carbopalladation across the C−C triple bond [Eq. (2)].

(1)

(2)
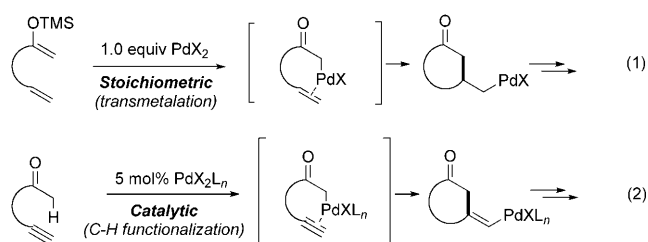
Recently, we reported a hydroarylation reaction of *o*-alkynyl biaryls **A** to produce fluorenes **B**.[5] It was proposed that this reaction proceeds by exclusive 5-*exo*-dig carbopalladation of a triple bond (to give **IV**) in aryl palladium intermediate **I**, which is formed from **A** by aromatic ortho C−H bond activation in the adjacent arene ring (Scheme 1). We hypothesized that the coordination of palladium to a triple bond and a ketone moiety of **1** would eventually lead to the palladium enolate intermediate **II**, which upon intramolecular carbopalladation would lead to vinylpalladium

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Scheme 1. Proposed route for the catalytic formation of Pd enolate.

species **III**. Subsequent protiodepalladation of the latter should lead to indanone **2** and regenerate the palladium catalyst. To this end, we examined cyclization of 1-(2-(phenylethynyl)phenyl)ethanone (**1a**) in the presence of several palladium catalysts. [(Ph₃P)₂PdCl₂] and [(MeCN)₂PdCl₂] were tested first. However, no desired product **2a** was formed under these reaction conditions (Table 1, entries 1 and 2). Next, employment of the Pd(OAc)₂ catalyst, widely used in C−H activation reactions, in THF resulted in complete decomposition of **1a**. Switching to less polar toluene as solvent prevented the decomposition of the starting material, but it did not support the cyclization reaction even at elevated temperatures (Table 1, entry 4).

Table 1: Optimization of the reaction conditions.[a]

Entry	[Pd] source	Ligand (mol%)	Solvent[b]	T [°C]	2a [%][c]
1	[(Ph₃P)₂PdCl₂]		toluene	120	0
2	[(MeCN)₂PdCl₂]		toluene	120	0
3	Pd(OAc)₂		THF	50	0[d]
4	Pd(OAc)₂		toluene	120	0
5	Pd(OAc)₂	Ph₃P (10)	toluene	120	20
6	Pd(OAc)₂	binap (5)	toluene	120	39
7	Pd(OAc)₂	dppf (5)	toluene	120	50
8	Pd(OAc)₂	d-*i*-prpf (5)	toluene	120	89
9	**Pd(OAc)₂**	**d-*i*-prpf (6)**	**toluene**	**120**	**95**

[a] Reaction conditions: alkynyl ketone 1 (0.5 mmol), palladium catalyst (0.05 mmol), 12 h. [b] All reactions were performed at an alkyne concentration of 0.5 M. [c] Yields were determined by GC-MS analysis versus internal standard. [d] Decomposition of the starting material was observed. binap = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl, dppf = 1,1′-bis(diphenylphosphino)ferrocene, d-*i*-prpf = 1,1′-bis(diisopropylphosphino)ferrocene.

Further optimizations revealed that the employment of the Pd(OAc)$_2$ catalyst in combination with Ph$_3$P ligand enabled the exclusive 5-*exo*-dig carbocyclization of **1a**, producing **2a** in 20% yield, as a single regio-[6] and stereoisomer (Table 1, entry 5), albeit with unexpected *E*-geometry of the double bond! Employment of BINAP resulted in a slight improvement of the reaction yield (Table 1, entry 6). Use of 1,1′-bis(diphenylphosphino)ferrocene (dppf) led to further improvement of the reaction yield (Table 1, entry 7). Switching to electron-rich 1,1′-bis(diisopropylphosphino)ferrocene (d-*i*-prpf) resulted in the dramatic improvement of the reaction outcome (Table 1, entry 8).[5] Finally, employment of 6 mol% d-*i*-prpf allowed us to obtain **2a** in 95% yield (Table 1, entry 9).

Next, the scope of this Pd-catalyzed cyclization was examined (Table 2). We found that this reaction was efficient for a wide range of alkynyl ketones **1**, providing the alkylidene indanones **2a–l** as single *E* isomers in good to excellent yields (Table 2). Various functional groups, such as F (Table 2, entries 4, 9), OMe (Table 2, entries 3, 7, 14), Cl (Table 2, entry 6), and CN (Table 2, entry 7) were perfectly tolerated under the reaction conditions. Cyclization of pyridine derivatives of *o*-alkynyl ketones occurred uneventfully as well, producing **2k** (Table 2, entry 11) and **2l** (Table 2, entry 12) in 86% and 52% yield, respectively. Notably, the Pd-catalyzed cyclization of *o*-alkynyl aryl ketones possessing aryl substituents α to the carbonyl group (R^1 = Ar) resulted in formation of isomeric indenone structures **2m** (Table 2, entry 13) and **2n** (Table 2, entry 14) in good yields. The cyclization of a substrate possessing a fluorine substituent ortho to the carbonyl function was effective as well, providing indanone **2o** in 75% yield (Table 2, entry 15).

Naturally, we were intrigued by the unexpected *E*-geometry of the double bond in the product **2**. Different potential reaction pathways could account for the formation of *E*-alkylidene indanone **2** from **1** in this Pd-catalyzed cyclization reaction (Scheme 2). The first scenario (path A) features a well-known π-philic activation of the triple bond in **1** with Pd^{II} catalyst (**3**)[2a,7] and subsequent intramolecular 5-*exo*-dig carbocyclization of the enol tautomer **4** to produce *trans*-addition intermediate **5**. Protiodepalladation of the latter furnishes *E*-alkylidene indanone **2** directly. Alternatively, the reaction may occur by the initial coordination of the palladium catalyst to the carbonyl group in alkynyl ketone **1** to form **6**, which upon deprotonation would produce a Pd enolate species **7** (path B). The subsequent coordination of Pd in **7** to the triple bond would form the alkyne-coordinated Pd enolate **8**. This species, upon intramolecular carbopalladation of the triple bond, would lead to a vinylpalladium species **9**. The subsequent *E–Z* isomerization of the double bond[8] would furnish isomeric vinylpalladium intermediate **5**, which upon protiodepalladation would produce *E* isomer **2**.

To verify the possibility of the electrophilic mechanism for this transformation (Scheme 2, path A), the carbocyclization of alkynyl ketone **1a** was tested in the presence of several π-philic metal salts, including AuCl, AuCl$_3$, PtCl$_2$, electrophilic [Ph$_3$PAuOTf], and Cu(OTf)$_2$,[9] known to mediate cyclizations by π-philic activation of the alkyne moiety. However, no formation of the desired product **2a** under

Table 2: Pd-catalyzed 5-*exo*-dig carbocyclization of **1**.

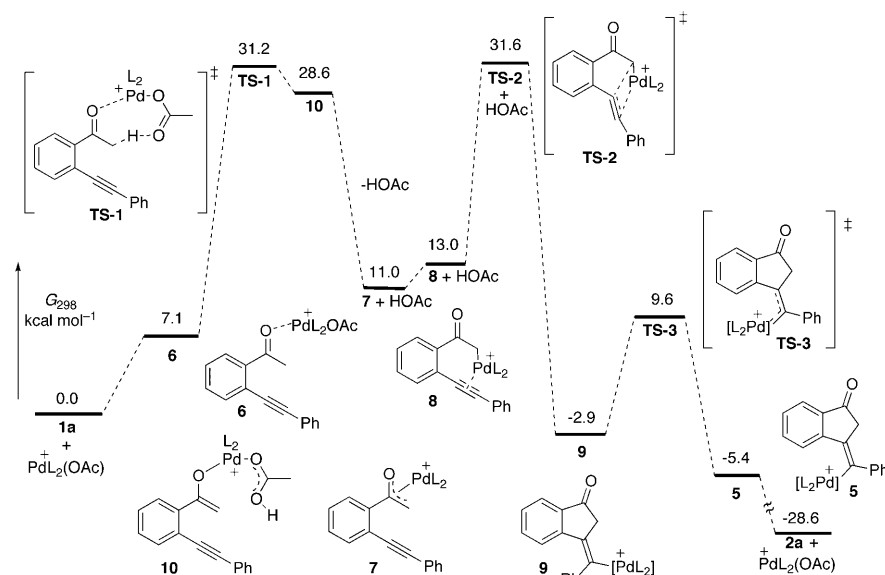| Entry	Product	Yield [%][a]	Entry	Product	Yield [%][a]
1	**2a** (Ph)	92	9	**2i** (F; Py-3)	98
2	**2b** (Tol-*p*)	98	10	**2j** (MeO; Py-3)	86
3	**2c** (C$_6$H$_4$OMe-*p*)	93	11	**2k** (Tol-*p*)	86
4	**2d** (F; Tol-*p*)	98	12	**2l** (Py-3)	52
5	**2e** (C$_6$H$_4$CF$_3$-*p*)	93	13	**2m** (Ph, Ph)	73
6	**2f** (C$_6$H$_4$Cl-*p*)	69	14	**2n** (C$_6$H$_4$OMe-*p*, Py-3)	81
7	**2g** (MeO; C$_6$H$_4$CN-*p*)	76	15	**2o** (F; Tol-*p*)	75
8	**2h** (Py-3)	71			

[a] Yield of isolated product. See the Supporting Information for details.

these reaction conditions was observed.[10] This observation, together with the shown earlier low efficiency of Pd(OAc)$_2$[9f] alone to catalyzed this transformation, did not support the possibility of the electrophilic path A for this transformation.

To further shed light on the possible reaction mechanism of the Pd-catalyzed cyclization of *o*-alkynyl ketones, density functional theory (DFT) calculations of the possible reaction pathways A and B were performed (Scheme 3).[11] Accordingly, pathway A was ruled out owing to the high free energy (49.3 kcal mol^{-1}) of the corresponding transition state from **4** to **5**.[12] In contrast, pathway B, having the lower energy profile and consisting of two major steps with nearly equivalent energy barriers (**TS-1** and **TS-2**), was found to be the most probable pathway for this transformation.[12] Thus, reaction starts with the formation of a complex **6** upon slightly endothermic coordination of compound **1** with the palladium catalyst. The subsequent intramolecular deprotonation of the
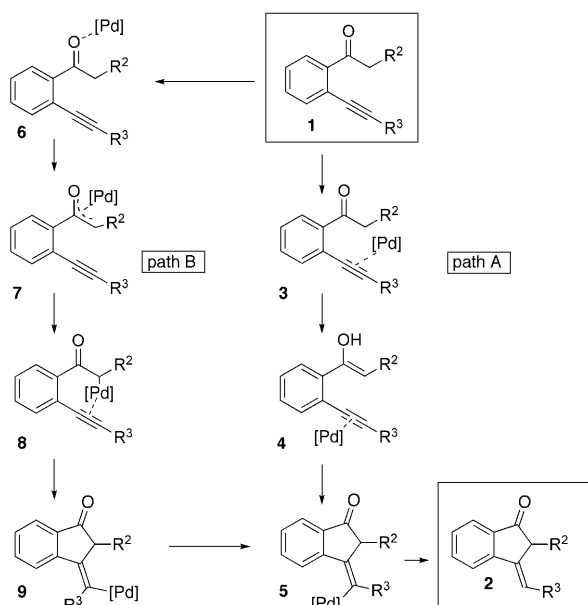
Scheme 2. Plausible reaction pathways for carbocyclization of **1**.

Scheme 3. Gibbs free energies for the Pd-catalyzed carboyclization of **1a** (L = PMe₃).[13]

depalladation of the latter leads to the *E* product **2a** ($\Delta G = -28.6$ kcal mol⁻¹; Scheme 3).

In conclusion, we have developed the Pd-catalyzed regio- and stereoselective carbocyclization of *o*-alkynyl ketones, featuring the carbopalladation of the triple bond with Pd enolate species. This methodology allows for the synthesis of a variety of alkylidene indanones as single *E* stereoisomers in good to excellent yields. DFT calculations of the reaction mechanism revealed that the formation of the Pd enolate intermediate occurs by deprotonation assisted by the Pd^II acetate ligand. It was also demonstrated that the intramolecular carbopalladation of the alkyne with Pd enolate produces *E*-vinylpalladium species, which upon *Z–E* isomerization of the double bond transforms into thermodynamically more favorable *Z* isomer. Protiodepalladation from the latter produces indanones with unexpected *E* geometry of the methylene double bond.

Experimental Section

An oven-dried 3 mL Wheaton V-vial containing a stirring bar, was charged with 2′-alkynyl ketone **1** (0.5 mmol), Pd(OAc)₂ (5.6 mg, 0.025 mmol), and d-*i*-prpf (13 mg, 0.03 mmol) under N₂ atmosphere. Dry toluene (1 mL) was added, and the reaction vessel was capped with a pressure screw cap. The reaction mixture was heated at 100–120 °C for 2–8 h until judged complete by GC/MS analysis. The resulting mixture was cooled down to room temperature and filtered through a layer of silica gel with the aid of EtOAc. The filtrate was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel (eluent: hexanes/EtOAc 20:1 to 10:1), thus affording the corresponding indenone product **2**.

methyl group of the ketone by the acetate ligand of the Pd^II catalyst, via transition state **TS-1** ($\Delta G^{\ddagger} = 31.2$ kcal mol⁻¹), produces **10** (28.6 kcal mol⁻¹), which, upon loss of the AcOH molecule, easily converts into palladium π complex **7** (11.0 kcal mol⁻¹). Notably, this process is quite different from the concerted metalation–deprotonation (CMD) step in the Pd^II-catalyzed coupling reactions, in which proton transfer to the base and Pd–C bond formation occurs at the same time.[14] Next, the reaction intermediate **7** transforms into the key alkyne-coordinated Pd enolate **8**. The subsequent rate-limiting carbopalladation of the triple bond (**TS-2**, $\Delta G^{\ddagger} = 31.6$ kcal mol⁻¹) produces vinyl palladium species **9**, which upon *E–Z* isomerization (**TS-3**, $\Delta G^{\ddagger} = 9.6$ kcal mol⁻¹) transforms into the isomer **5** ($\Delta G = -5.4$ kcal mol⁻¹). Protio-

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