

IV.2.6 Carbopalladation of Alkynes Followed by Trapping with Electrophiles

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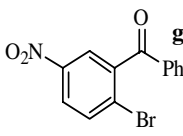
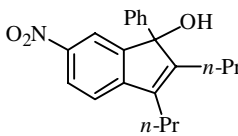
A. INTRODUCTION

In contrast to the diverse insertion chemistry of vinylpalladium intermediates discussed in **Sects. IV.3** and **IV.5**, the reactions of vinylpalladium complexes with electrophiles had not been reported until recently. Although a single report on the annulation of the *o*-mercurio benzaldehyde with diphenylacetylene into the corresponding indenols and indenones catalytic in palladium and stoichiometric in copper had been communicated in 1992,^[1] the more synthetically useful protocol for the catalytic version of this type of transformation remained unknown until 1999. In this section the *intermolecular* carbopalladation of alkynes with aryl halides followed by the *intramolecular* trapping of the formed vinylpalladium species with ketones, aldehydes, and nitriles will be discussed.

B. CARBOPALLADATION OF ALKYNES FOLLOWED BY TRAPPING WITH KETONES.

Palladium has been found to catalyze a nucleophilic cyclizing vinylpalladation of aryl ketones **1** with alkynes **2** to produce the indenols **3** in good yields (**Scheme 1**).^[2] *o*-Bromoacetophenone (**1a**) (1 equiv) reacted with 4-octyne (**2g**) (5 equiv) in the presence of Pd(OAc)₂ (5 mol %) and KOAc (2 equiv) under an argon atmosphere in DMF (0.25 M) (Conditions **A**) at 100 °C to give the indenol **3ag** in 82% isolated yield (**Table 1**, entry 1). Other palladium complexes, such as PdCl₂(PPh₃)₂, Pd(PPh₃)₄, and Pd₂(dba)₃·CHCl₃, also catalyzed this reaction; however, the yields of **3a** in these cases were somewhat lower. When KOAc was replaced with NaOAc the reaction rate slowed down. Use of *t*-BuOK led to the total decomposition of ketone **1**, and K₂CO₃ was found not to be effective as a base in this reaction at all. Diphenylacetylene (**2c**) readily reacted with **1a** under the same conditions to produce the indenol **3ac** in 63% yield (entry 2). After optimization of the reaction conditions the amount of alkyne **2** could be decreased to 1.5 equiv (versus 5 equiv for Conditions **A**) by adding either 10 mol% of PPh₃ (Conditions **B**) or 10 equiv of EtOH (Conditions **C**) to the reaction mixture (**Table 1**). Thus, aryl alkyl ketones **1a,b** reacted with alkyl-substituted alkynes **2h,g** under Conditions **C** to give the indenols **3ah,bg** in moderate yields (53% and 51%, respectively, entries 3 and 4). In

TABLE 1. Cyclizing Vinylpalladation of Aromatic Ketones^a

Entry	Ketone 1		Alkyne 2		Conditions ^b	Temperature/ Time (°C/h)	Products (%) ^c	
	R ¹	R ²	R ³				3	4
1	a Me	g <i>n</i> -Pr	<i>n</i> -Pr		A	100/20	ag 82	
2	a Me	c Ph	Ph		A	100/20	ac 63	
3	a Me	h CH ₂ OMe	CH ₂ OMe		C	100/20	ah 53	
4	b <i>t</i> -Bu	g <i>n</i> -Pr	<i>n</i> -Pr		C	100/24	bg 51	
5	c Ph	g <i>n</i> -Pr	<i>n</i> -Pr		B	100/96	cg 86	
6	c Ph	c Ph	Ph		B	120/24	cc 75	
7	c Ph	h CH ₂ OMe	CH ₂ OMe		C	100/28	ch 64	
8	c Ph	i —(CH ₂) ₁₀ —			B	100/96	ci 76	
9	d <i>p</i> -CF ₃ C ₆ H ₄	g <i>n</i> -Pr	<i>n</i> -Pr		B	100/24	dg 85	
10	e <i>p</i> -MeOC ₆ H ₄	g <i>n</i> -Pr	<i>n</i> -Pr		C	100/48	eg 64	
11	c Ph	j Me	<i>t</i> -Bu		C	100/48	cj 72	—
12	a Me	k Me	Ph		A	100/15	ak 48	20 ^d
13	a Me	l <i>n</i> -Bu	C≡CBu		A	100/15	al 67 ^e	33 ^e
14		g <i>n</i> -Pr	<i>n</i> -Pr		B	80/24		
	f						fg 66	

^aIn a typical procedure after completion of the reaction under the conditions indicated in the table, the reaction was quenched (H₂O), the mixture extracted (Et₂O-H₂O), and the extract dried (Na₂SO₄) and concentrated. The product was purified by column chromatography (Silica gel, eluent: hexane-ethyl acetate).

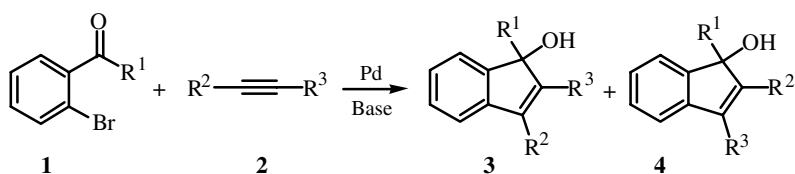
^bConditions **A**: see text. **B**: A mixture of the ketone **1** (1 mmol), alkyne **2** (1.5 mmol), KOAc (2 mmol), Pd(OAc)₂ (5 mol %), and PPh₃ (10 mol %) in DMF (0.25M) was stirred under an Ar atmosphere. **C**: The same mixture as above plus EtOH (10 mmol) was stirred under the conditions indicated in the table.

^cIsolated yield unless otherwise specified.

^d**4ak** was contaminated with a small amount of **3ak**.

^eThe products **3al** and **4al** were isolated as an inseparable mixture in 75% combined yield. The ratios were determined by ¹H NMR spectroscopy.

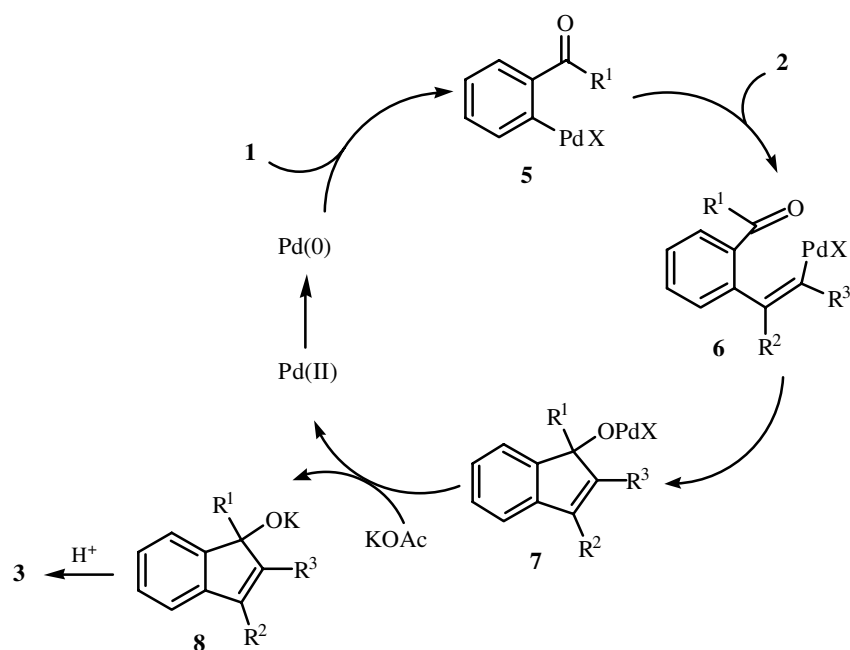
contrast to the alkyl-substituted ketones **1a,b**, the diarylketone **1c**, under Conditions **B** and **C**, smoothly reacted with 4-octyne (**2g**), diphenyl- (**2c**) and dimethoxymethylacetylene (**2h**), and cyclododecyne **2i** producing the indenols **3cg,cc,ch,ci** in 86%, 75%, 64%, and 76%, respectively (entries 5–8). Substituted diarylketones **1d** (*p*-CF₃) and **1e** (*p*-MeO) easily underwent carbocyclization with **2g** giving **3dg,eg** in 85% and 64% yields (entries 9 and 10). Although the reaction of **1c** with the unsymmetrical alkyne **2j** with a bulky *t*-butyl substituent produced **3cj** in 72% yield as a single regioisomer (entry 11), the reactions of **1a** with phenylpropyne **2k** and di-*n*-butylbutadiyne **2l** were less regioselective;



Scheme 1

the indenols **3ak** and **3al** with bulkier substituents α to the hydroxyl group were contaminated with the minor regioisomeric products **4ak** and **4al**, respectively (entries 12 and 13). As expected, this reaction is limited to internal alkynes. Under the conditions employed, terminal alkynes did not undergo cyclovinilation of **1**, but Sonogashira-type coupling. The nitro-substituted benzophenone **1f** underwent the reaction with **2g** to give **3fg** in 66% isolated yield (entry 14). Surprisingly, the yields of the indenols **3** were found to be consistently higher with aryl bromides **1** than with the corresponding aryl iodides.

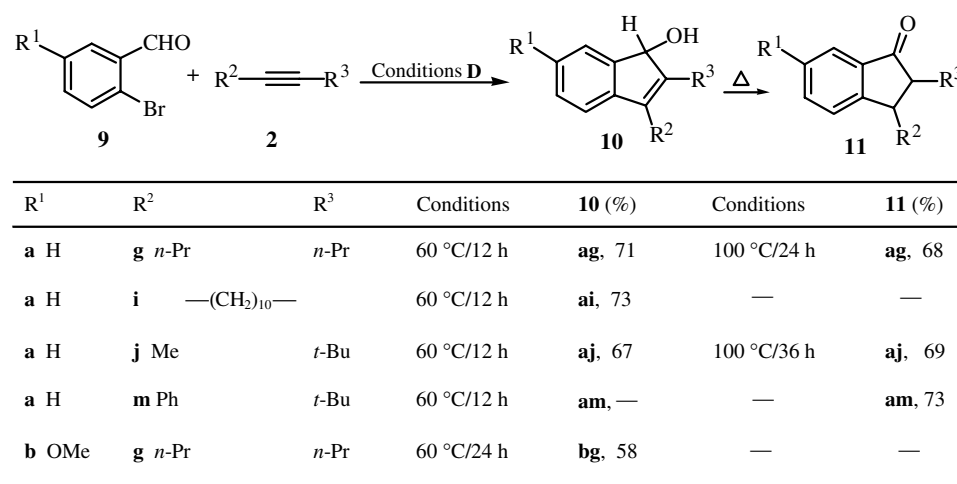
As far as the mechanism of the observed intramolecular vinylpalladation of ketones is concerned, the reaction obviously starts with an oxidative addition of the catalytically active palladium(0) species to the C—Br bond of **1** to give **5**, which would arylpalladate the triple bond of **2**^{[3]–[5]} to form the vinylpalladium species **6**. The intramolecular nucleophilic addition of the vinylpalladium moiety to the keto group of **6** would produce the indenyloxypalladium species **7**. The added potassium acetate would transmetallate **7** to the potassium alkoxide **8**, which upon subsequent protonolysis would give the reaction indenol **3** and would regenerate the catalyst (**Scheme 2**). Although a more detailed mechanistic study is needed, the proposed catalytic cycle quite reasonably explains the observed overall cyclovinilation of *o*-bromoaryl ketones with internal alkynes. Thus, the observed regioselectivity in the arylpalladation of unsymmetrical alkynes **2j–l** with **5** (**Table 1**, entries 11–13) is in a good agreement with the known regiochemical trend for the carbopalladation of alkynes.^[6] Furthermore, the order of reactivity of differently substituted ketones [*p*-CF₃C₆H₄ (**1d**, $t_{1/2}$ = 4 h) > C₆H₅ (**1c**, $t_{1/2}$ = 16 h) >> *p*-MeOC₆H₄ (**1e**, $t_{1/2}$ = 120 h)] provides additional support for the nucleophilic character of the observed transformation **6** → **7** (**Scheme 2**).^[2]



Scheme 2

C. CARBOPALLADATION OF ALKYNES FOLLOWED BY TRAPPING WITH ALDEHYDES

Further development of the above-mentioned protocol led to the methodology for the synthesis of indenols **10** and indanones **11** through the catalytic intramolecular vinylpalladation of aromatic aldehydes **9** (Scheme 3).^[7] Thus, *o*-bromobenzaldehyde (**9a**) (1 mmol) reacted at 60 °C with 4-octyne (**2g**) (1.5 mmol) in the presence of Pd(OAc)₂ (5 mol %), KOAc (2 mmol), and EtOH (10 mmol) under an argon atmosphere in DMF (0.25 M) (Conditions **D**) to afford the indenol **10ag** in 71% isolated yield (Scheme 3). The analogous reaction of **9a** with cyclododecyne **2i** gave indenol **10ai** in 73% yield. Reaction of **9a** with the unsymmetrical alkyne **2j** afforded **10aj** as a single regioisomer (Scheme 3). 5-Methoxy-2-bromobenzaldehyde (**9b**) also smoothly reacted with **2g** under Conditions **D** to produce **10bg** in reasonable yield.

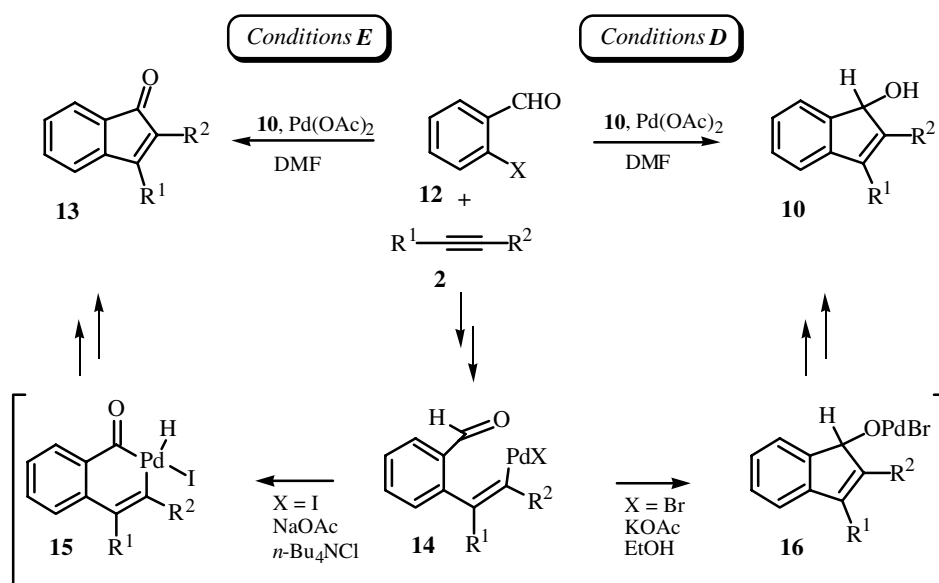


Scheme 3

Surprisingly, when the reaction mixtures were stirred for longer times at 60 °C after the formation of indenols **10** had been complete, a considerable fraction isomerized to indanones **11**. This transformation could be taken to completion by extended heating at more elevated temperature (100 °C). Thus, reaction of **9a** with **2g** under Conditions **D** for 12 h at 60 °C, followed by stirring for 24 h at 100 °C, produced indanone **11ag** in 68% isolated yield (Scheme 3). The analogous treatment of **9a** with **2j** gave the indanone **11aj** in 69% yield. Remarkably, the reaction of **9a** with the aryl-substituted alkyne **2m**, even under Conditions **D**, did not stop at the stage of the indenol **10am**; instead the indanone **11am** was formed in 73% yield. The isomerization of the indenols **10** into the indanones **11** was confirmed by a test experiment. Hence, stirring of **10ag** at 100 °C in the presence of Pd(OAc)₂ (5 mol %) and KOAc (2 equiv) for 24 h in DMF produced indanone **11ag** quantitatively. Notably, this isomerization did not occur upon prolonged heating of **10ag** at 100 °C in DMF in the absence of the palladium catalyst and the base.

Recently, Larock and co-workers reported an efficient method for the synthesis of indenones **13** by the Pd-catalyzed annulation of *o*-iodobenzaldehyde **12** with internal

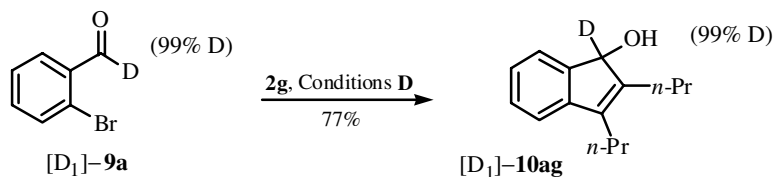
alkynes **2** (Scheme 4).^[8] This deserves some comments with regard to the mechanism of formation of indenols **10**, in comparison with Larock's mechanism for the formation of indenones **13** (Scheme 4). In the reaction of the *o*-iodobenzaldehyde with internal alkynes **2** in the presence of Pd(OAc)₂ (5 mol %), NaOAc or Na₂CO₃ (4 equiv), and *n*-Bu₄NCl (1 equiv) in DMF at 100 °C (Conditions E, Scheme 4), the indenones **13** were formed as the *oxidative coupling* or *substitution products*.^[8] In contrast, *o*-bromobenzaldehyde under Conditions D, produced the *reductive coupling* or *nucleophilic addition products*, the indenols **10** (Scheme 4).^[7] Although the reaction modes look rather similar, it appears that these two transformations follow different mechanistic pathways. The vinylpalladium intermediate **14** may be formed through a Heck-type arylpalladation of the alkyne **2**.^{[3]–[5]} According to Larock et al.,^[8] the vinylpalladium halide **14** then inserts into the C—H bond of the aldehyde group to form the Pd(IV) intermediate **15**, which after subsequent dehydrohalogenation and reductive elimination reforms the Pd(0) species and gives the *substitution product*, indenone **13**. A vinylpalladium halide of type **14** must also be an intermediate en route to the indenols **10** (Scheme 4, Conditions D). However, under Conditions D, rather than insertion into the C—H bond, a nucleophilic vinylpalladation of the C=O group of the aldehyde takes place to form the indenyloxypalladium species **16**, which after subsequent transmetalation with KOAc and protonolysis gives the *nucleophilic addition product*, the indenol **10** (Scheme 4).^[7]



Scheme 4

An alternative explanation for the formation of indenols **10** would involve a transfer hydrogenation of a first formed indenone **13** with EtOH, present in the reaction mixture under conditions D, to give the indenols **10**. This, however, could be ruled out, as the *o*-bromodeuteriobenzaldehyde [D₁]-**9a** under Conditions D gave [D₁]-**10ag** in 77% isolated yield with 99% of the deuterium label attached at the C-1 position (Scheme 5). Although the reasons for such a dramatic change in the reaction courses upon a slight modification in the conditions are not clearly understood, one may speculate the proposed

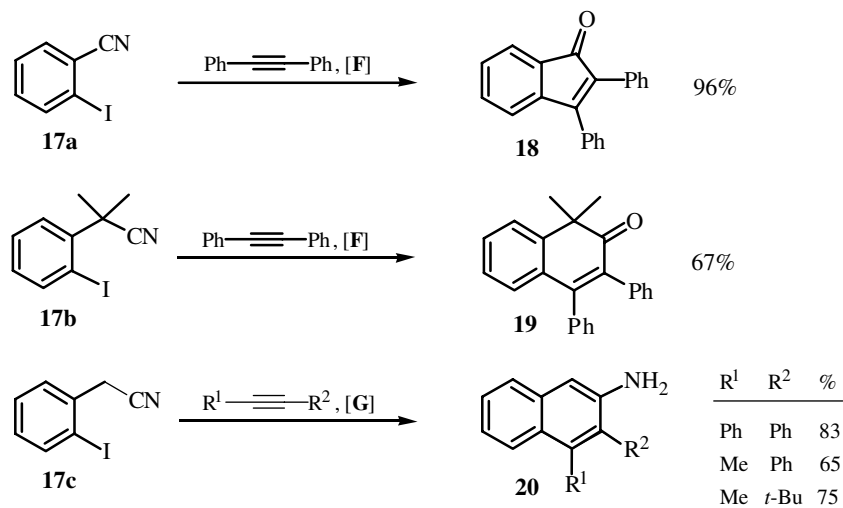
palladium(IV) intermediate **15** would be stabilized in the presence of a quaternary ammonium salt in dipolar aprotic solvent (Jeffery conditions).^[9] In fact, these conditions have previously been found to favor processes via Pd(IV) intermediates.^[10] Under Conditions **D**, on the other hand, a direct nucleophilic addition of the vinylpalladium halide moiety of **14** to the aldehyde function apparently is more favorable, and this will drive a reaction toward the indenols **10** (Scheme 4).^[7]



Scheme 5

D. CARBOPALLADATION OF ALKYNES FOLLOWED BY TRAPPING WITH NITRILES

Simultaneously with the report of Quan, Gevorgyan, and Yamamoto on the intramolecular nucleophilic vinylpalladation of ketones,^[2] Larock, Tian, and Pletnev disclosed an intramolecular addition of vinylpalladiums to nitriles (Scheme 6).^[11]



[F] = 10 mol % Pd(dba)₂, 3 equiv of alkyne 1 equiv of Et₃N,
DMF/H₂O = 9:1, 130 °C, 24 h.

[G] = 5 mol % Pd(OAc)₂, 3 equiv of alkyne, 2 equiv of Et₃N,
1 equiv of *n*-Bu₄NCl, DMF, 100 °C, 48 h.

Scheme 6

In the presence of $\text{Pd}(\text{dba})_2$ (10 mol %) and Et_3N (1 equiv) in DMF/ H_2O at 130 °C, *o*-iodobenzonitrile **17a** cocyclized with diphenylacetylene (3 equiv) to afford, after the subsequent hydrolysis, 2,3-diphenylindenone (**18**) in 96% yield (Scheme 6). An extension of this cocyclization methodology was demonstrated with the transformation of 2-*o*-iodophenyl-2-methylpropionitrile (**17b**), which gave the benzannulated ketone **19** in good yield (Scheme 6). Surprisingly, β -naphthylamines **20** were obtained when the *o*-iodophenylacetoneitrile (**17c**) was employed instead of **17b** (Scheme 6). The reaction proceeded smoothly with symmetrical and unsymmetrical internal alkynes to give the β -naphthylamines **20** in good yields (Scheme 6). It is assumed that in all cases an intramolecular vinylpalladation of the nitrile produces an iminyl palladium intermediate. However, in the latter cases, due to the presence of a hydrogen atom α to an iminyl palladium moiety, a tautomerization occurs rather than hydrolysis.^[11]

Cascade *intermolecular* carbopalladations of alkynes followed by *intramolecular* trapping with electrophiles represent not only a novel type of organic transformation involving vinylpalladium intermediates, but also provide synthetically useful routes toward differently substituted indenols,^[2,7] indanones,^[7] indenones,^[8] and naphthylamines.^[11] Although these protocols are restricted to the *intramolecular* trapping with electrophiles, a wide application of this methodology toward the synthesis of various types of complex carbocyclic compounds may be anticipated in the near future.

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