Pergamon

Tetrahedron Letters 40 (1999) 4089–4092

TETRAHEDRON
LETTERS

Synthesis of Indenols and Indanones *via* Catalytic Cyclic Vinylpalladation of Aromatic Aldehydes

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Received 2 March 1999; accepted 29 March 1999

Abstract: *o*-Bromobenzaldehyde **1**, in the presence of a palladium catalyst, smoothly underwent consecutive intermolecular carbopalladation with internal alkynes **2** and then intramolecular nucleophilic vinylpalladation of the aldehyde function to produce the indenol derivatives **4** in high yields. Further heating of **4** under more elevated temperature caused complete isomerization to the corresponding indanones **8**. A mechanism for this nucleophilic vinylpalladation of aromatic aldehydes is proposed.

Transition metal-catalyzed carbocyclizations,[1] and particularly cyclic carbopalladations,[2] provide nowadays powerful and versatile synthetic approaches towards various types of carbo- and heterocycles. Larock recently reported an effective methodology for the synthesis of indenones **3** *via* the palladium-catalyzed annulation of iodobenzaldehyde (**1**, X=I) with internal alkynes **2** (Method **A**, Scheme).[3] Very recently we have developed a synthesis of 1-substituted indenols *via* intramolecular nucleophilic vinylpalladation of aromatic ketones.[4] In continuation of our study on the nucleophilic vinylpalladation of keto function equivalents,[4] herein we report the synthesis of indenols **4** and indanones **8** through the catalytic cyclic vinylpalladation of aromatic aldehydes **1** (Scheme).

We found that *o*-bromobenzaldehyde (**1a**) (1 mmol) reacted at 60 °C with oct-4-yne (**2a**) (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

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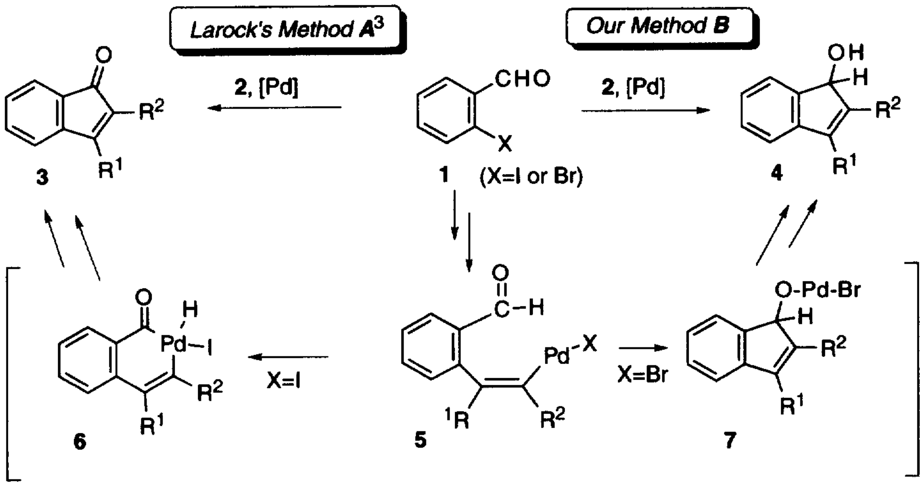
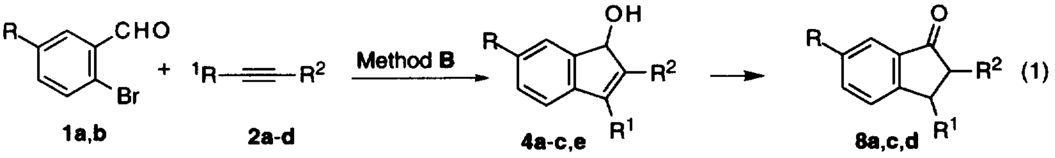
PII: S0040-4039(99)00656-5



Scheme

(0.25M) (Method **B**) to afford indenol **4a** in 71 % isolated yield (eq 1). The analogous reaction of **1a** with cyclic alkyne **2b** gave indenol **4b** in 73 % yield. Reaction of **1a** with unsymmetrical alkyne **2c** afforded **4c** as a single regioisomer (eq 1). Methoxysubstituted bromobenzaldehyde **1b** also smoothly reacted with **2a** under the conditions of the method **B** to produce **4e** in reasonable yield.



1a: R=H	**2a**: $R^1=R^2=Pr$	12h/60°C	**4a**, 71%	24h/100°C	**8a**, 68%
1a	**2b**: $R^1,R^2=$ $-(CH_2)_{10}-$	12h/60°C	**4b**, 73%	-	-
1a	**2c**: $R^1=Me$; $R^2={}^tBu$	24h/60°C	**4c**, 67%	36h/100°C	**8c**, 69%
1a	**2d**: $R^1=Ph$; $R^2={}^tBu$	12h/60°C	**4d**, -		**8d**, 73%(NMR)
1b: R=OMe	**2a**	24h/60°C	**4e**, 58%(NMR)	-	-

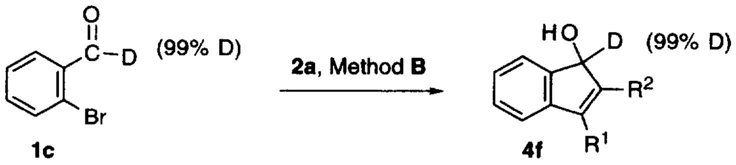
Surprisingly, we found that, if the reaction mixtures were stirred for longer at 60 °C after the completion of the formation of indenols **4**, considerable isomerization to indanones **8** was observed. This transformation was complete upon heating at more elevated temperature. Thus, reaction of **1a** with **2a** under the conditions of Method **B** for 12 hours at 60 °C, followed by stirring for 24 hours at 100 °C, produced indanone **8a** in 68 % isolated yield (eq 1). Similar treatment of **1a** with **2c** gave the indanone **8c** in 69 % yield. Remarkably, the reaction of **1a** with aryl containing alkyne **2d**, even under the conditions of Method **B**, did not stop at the stage of formation of the indenol **4d**, instead the indanone **8d** was formed in 73 % yield (eq1). The isomerization of the indenols **4** into the indanones **8** was confirmed by a test experiment. Hence, stirring **4a** at 100 °C in the presence of $Pd(OAc)_2$ (5 mol %) and KOAc (2 equiv.) for 24 hours in DMF produced indanone **8a** quantitatively. It is worth noting that the aforementioned isomerization did not proceed during prolonged heating of **4a** at 100 °C in DMF in the absence of the palladium catalyst and/or the base.

As a final remark, we would like to give some comments on the mechanism of formation of indenols **4**, in comparison with Larock's mechanism for the formation of indenones **3** (Scheme).[3] In Larock's case, iodobenzaldehyde reacted with internal alkynes **2** in the presence of $Pd(OAc)_2$ (5 mol %), NaOAc or Na_2CO_3 (4 equiv.) and n-Bu_4NCl (1 equiv.) in DMF at 100°C (Method **A**, Scheme) to give the *substitution products*, the indenones **3** (Scheme).[3] In contrast, we found that *o*-bromobenzaldehyde, under the conditions of Method **B**, produced *nucleophilic addition products*, the indenols **4** (Scheme). It is logical to propose that these two methodologies follow different mechanistic pathways.

The vinylpalladium intermediate **5** may be formed through a Heck-type sequence;[5] i.e. oxidative addition of Pd(0) to the aryl halide **1**, followed by vinylarylation of the internal alkyne **2**. Then, according to Larock,[3] the vinylpalladium inserts into the C-H bond of the aldehyde function to form the Pd(IV) intermediate **6**, which after consequent dehydrohalogenation and reductive elimination of the Pd(0) produces the *substitution product*, indenone **3** (Scheme).[3]

We believe that the vinylpalladium species **5** is an early stage intermediate in our protocol as well (Scheme, Method **B**). However, under the conditions of Method **B**, rather than insertion into the C-H bond nucleophilic vinylpalladation of the C=O group of the aldehyde takes place to form the indenyloxypalladium species **7**, which after subsequent transmetallation with KOAc and protonolysis gives the *nucleophilic addition product*, the indenol **4** (Scheme).

An alternative explanation for the formation of indenols **4** would involve Larock's mechanism to form the indenone **3**, which under the conditions of Method **B**, undergoes transfer hydrogenation[6] with EtOH, present in the reaction mixture, to give the indenols **4**. In order to examine this proposal, we synthesized a deuteriated bromobenzaldehyde **1c**,[7] and subjected it to the reaction with **2a** under the conditions of Method **B** (eq 2). If our



(2)

reaction proceeds through Larock's mechanism (Scheme), the loss of deuterium at the stage **6** → **3** is unavoidable. However, the experiment revealed formation of **4f** in 77 % isolated yield with 99 % of the deuterium attached to the C-1 position of indenol, thus negating the alternative proposal mentioned above.

Further mechanistic study on formation of indenols **4** and their isomerization to indanones **8** is now underway in our laboratories.

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