Synthesis of Functionalized 3-Bromoindenes via Pd(II)-catalyzed Tandem Reactions of o-(Alkynyl)styrenes: Taking Dioxygen as Sole Oxidant

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This paper introduced an economic and environmental approach to 3-bromoindenes from simple and readily available o-(alkynyl)styrenes via a Pd-catalyzed cascade cyclization including bromopalladation/Heck cross-coupling/ β -H elimination. With O₂ as the sole oxidant and KBr as bromide source, a series of poly-substituted 3-bromoindenes were synthesized with high chemoselectivity avoiding the use of CuBr₂.

Cascade cyclizations through nucleopalladation of alkynes like halopalladation,¹ acetoxypalladation,² oxypalladation,³ etc. are important and useful tools to carry out the difunctionalization of $C \equiv C$ triple bonds in one transformation that has attracted widespread interest during the past decade. In particular, bromopalladation of alkynes is one of the more efficient and atom-economic methods for the construction of both the C-C and C-Br bonds.⁴ According to the mechanism of literatures mentioned above, a versatile reactive σ-vinylpalladium intermediate A, which would be produced after a nucleophilic addition of bromide onto the Pd(II)-activated C=C triple bond (Scheme 1), plays an important role in the reactions triggered by bromopalladation. In most of these cases, excess CuBr₂ was usually necessary for oxidizing Pd(0) to Pd(II) and as bromide source, which is neither environmentally nor economically favorable. Until now, finding green and low-cost oxidants and bromide sources to replace CuBr₂ is challenging. From the viewpoint of green chemistry, molecular oxygen is undoubtedly the best oxidant and recently has been well developed in the field of organic synthesis.⁵ As for bromide source, KBr is nontoxic and cheaper than CuBr₂.

The indene skeleton is found in several biologically active natural products⁶ and functional materials.⁷ Thus, the development of new methods for their construction is still a hot topic in the field of organic synthesis.⁸ C=C triple bonds of *o*-(alkynyl)styrenes presented excellent activities in cascade reactions through nucleopalladation and functional polycycles like indenes were synthesized through these transformations.^{4a,9} In this paper, we will introduce a new methodology for 3-bromoindene derivatives from the corresponding *o*-(alkynyl)-styrenes via a Pd-catalyzed cascade cyclization including



Scheme 1. Bromopalladation of alkyne.

bromopalladation/Heck cross-coupling/ β -H elimination using dioxygen as the sole oxidant and KBr as the bromide source.

In order to obtain the best reaction conditions, (E)-1-phenyl-3-[2-(phenylethynyl)phenyl]prop-2-en-1-one (1a) was reacted in the presence of different catalysts, bromide sources, oxidants, and solvents, as shown in Table 1. Initially, we focused on the direct synthesis of the desired product 2a in the presence of Pd(OAc)₂ and LiBr in CH₃CN under 1 atm of O₂. However, the desired cascade reaction did not occur and no expected indene was obtained under these conditions (Table 1, Entry 1). Gratifyingly, the yields of 2a dramatically increased to 86% when a mixture of CH₃CN and CH₃COOH was used as the solvent. In the aerobic transformation, CH₃COOH, used as a proton shuttle, was beneficial for the regeneration of the active palladium(II) species (Table 1, Entry 2).¹⁰ When CH₃COOH was replaced by other organic acids like PhCOOH or PivOH (pivalic acid), the reactions occurred but with lower efficiencies (Table 1, Entries 3 and 4). Subsequently, various bromide sources like KBr and tetrabutylammonium bromide (TBAB) were screened and the results showed that KBr was the best choice (Table 1, Entries 5 and 6). Additional studies focused on the efficiencies of other

Table 1. Screening of reaction conditions^a

| Ph Ph | Pd(II) salts (4 mol%) Bromo-source O ₂ (1 atm) Solvents 80 °C | Ph Ph Br |
|----------|--|----------------|
| 14 | | 2a |

| Entry | Catalyst | Bromide sources | Solvents | Yield /% ^b |
|-----------------|----------------------|-------------------|-------------------------------|--------------------------|
| 1 | Pd(OAc) ₂ | LiBr | CH ₃ CN | NR |
| 2 | $Pd(OAc)_2$ | LiBr | CH ₃ CN/AcOH(4:1) | 86 |
| 3° | Pd(OAc) ₂ | LiBr | CH ₃ CN/PhCOOH | 44 |
| 4 | Pd(OAc) ₂ | LiBr | CH ₃ CN/PivOH(4:1) | 49 |
| 5 | $Pd(OAc)_2$ | KBr | CH ₃ CN/AcOH(4:1) | 89 |
| 6 | Pd(OAc) ₂ | TBAB | CH ₃ CN/AcOH(4:1) | 23 |
| 7 | PdCl ₂ | KBr | CH ₃ CN/AcOH(4:1) | 73 |
| 8 | PdBr ₂ | KBr | CH ₃ CN/AcOH(4:1) | 78 |
| 9 | _ | KBr | CH ₃ CN/AcOH(4:1) | 0 |
| 10 | Pd(OAc) ₂ | KBr | DMF/AcOH(4:1) | <5 |
| 11 ^d | Pd(OAc) ₂ | KBr | DMSO/AcOH(4:1) | NR |
| 12 | $Pd(OAc)_2$ | KBr | Toluene/AcOH(4:1) | <5 |
| 13 | Pd(OAc) ₂ | KBr | AcOH | NR |
| 14 ^e | $Pd(OAc)_2$ | KBr | CH ₃ CN/AcOH(4:1) | 84 |
| 15 ^f | $Pd(OAc)_2$ | CuBr ₂ | CH ₃ CN/AcOH(4:1) | 68 |

^aReaction conditions: **1a** (0.25 mmol), Pd salts (4 mol %), bromide salts (1.5 equiv) in solvent (1.5 mL) at 80 °C for 15 h; 1 atmosphere of O₂ was kept by a balloon. ^bDetermined by GC. ^cWith PhCOOH (1.5 equiv). ^dNR: No reaction. ^cThe reaction was carried out in a oxygen bomb ($p_{O_2} = 8$ atm). ^fWith CuBr₂ (4 equiv) to replace 1 atm of O₂.

palladium catalysts, such as $PdCl_2$ and $PdBr_2$. When these Pd salts were used, the reaction gave more complicated results (Table 1, Entries 7–9). The additional studies indicated that solvent plays an important role in the transformation; only the mixture of CH₃CN and CH₃COOH was effective, which may due to strong coordination between acetonitrile and Pd(II) (Table 1, Entries 10–13). When the pressure of O₂ was increased to 8 atm, the yield of **2a** cannot be improved obviously (Table 1, Entry 14). As previously described, Cu(II) salts were often used as oxidants in Pd-catalyzed oxidations. However, the yield was only 68% when CuBr₂ (4 equiv) was employed as both oxidant and bromide source (Table 1, Entry 15). Thus, the best conditions for this cascade cyclization were as follows: 4 mol % Pd(OAc)₂, 150 mol % KBr in CH₃CN/CH₃COOH under 1 atm of O₂ at 80 °C for 15 h.

Under the optimal reaction conditions, the activity of different substituted o-(alkynyl)styrenes were tested, which are summarized in Table 2. We initially examined substrates bearing electron-rich or electron-poor aryl group at one side of the $C \equiv C$ triple bond and corresponding tandem reaction were carried out successfully (Table 2, Entries 1-5). When substrates bearing linear or cyclic alkyl groups at one side of C=C triple bond were tested, the expected products 2f and 2g were produced in 78% and 80% yields, respectively (Table 2, Entries 6 and 7). However, when the R¹ group was 2-hydroxy-2-propyl, the desired tandem reaction through bromopalladation/Heck crosscoupling/B-H elimination did not occur, which might be due to its steric bulk (Table 2, Entry 8). Subsequently, substrates with electron-rich or electron-poor R³ substituents underwent the reaction, leading to fluoro- and methoxy-substituted indenes in good yields (Table 2, Entries 9 and 10). In addition, the scope of the cascade cyclization was expanded to a variety of o-(alkynyl)styrenes bearing alkoxycarbonyl at one side of the C=C double bond, which furnish the corresponding 3-bromoindenes in 85-91% yields (Table 2, Entries 11-15).

Consequently, a possible mechanism was proposed according to a previous report on oxygen-promoted halopalladation chemistry (Scheme 2). Initially, a nucleophilic addition of bromide onto the Pd(II)-activated C=C triple bond of substrate 1 affords the reactive σ -vinylpalladium intermediate A.³ The C=C double bond of A is easily activated by the Pd(II) complex and an intramolecular carbopalladation reaction occurs subsequently to generate the intermediate B.¹¹ Then, the intermediate B undergoes β -H elimination to give the expected product 2 and HPdOAc.¹² The resulting Pd(0) species is additionally oxidized to Pd(OAc)₂ by the O₂/HOAc system to complete this catalytic cycle and Pd(II) salts enters the next catalytic cycle.^{5a,13} Furthermore, oxygen plays a key role in inhibiting the protonolysis of the intermediate B and in promoting β -H elimination.

The Suzuki cross-couplings of arylboronic acids and aryl bromides are widely used to prepare fused polycyclic aromatic hydrocarbons, which exhibit excellent photoelectric properties in the field of organic electronics.¹⁴ Consequently, the activities of **2a** and **2k** in the Suzuki cross coupling were tested and two kinds of poly-substituted indenes (isolated yield: **3a** in a yield of 89%; **3k** in a yield of 92%) were obtained in high yield (Scheme 3, **2a** and **2k**).

In conclusion, we have discovered a unique and direct approach for constructing 3-bromoindenes from simple and readily available *o*-(alkynyl)styrenes via a Pd-catalyzed cascade **Table 2.** Pd-catalyzed cyclization of o-(alkynyl)styrenes to functional 3-bromoindenes^a



^aReaction conditions: **1** (0.5 mmol), Pd(OAc)₂ (4 mol %), KBr (1.5 equiv) in AcOH/CH₃CN (1.5 mL, the ratio of volume is 1:4) under 1 atmosphere of O_2 at 80 °C for 15 h. ^bIsolated yield. ^cNo reaction.



Scheme 2. Proposed mechanism.



Scheme 3. The activity of 2 in the Suzuki cross-coupling.

cyclization including bromopalladation/Heck cross-coupling/ β -H elimination. The reaction conditions are mild and atomeconomic in which O₂ (1 atm) is used as the sole oxidant and KBr is used as the bromide source.

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Supporting Information is available electronically on J-STAGE.

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