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Synthesis of Indenes by Intramolecular *anti*-Hydroarylation of Propargylarenes

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An intramolecular *anti*-hydroarylation of propargylarenes proceeds smoothly with a palladium/carboxylic acid catalyst to form indenes straightforwardly. Indenes having various functional groups were easily prepared. The novel synthetic method is applicable to double hydroarylation to form a 1,5-dihydro-*s*-indacene.

Key words: alkyne, hydroarylation, indene

Intramolecular insertion of alkene and alkyne into C–H bonds is an ideal annulation reaction in organic synthesis.[1] This type of reactions is promoted by a transition-metal or Lewis acid catalyst. In view that indenes are an important structural motif as the ligand of metal complexes[2] as well as organic materials[3] and bioactive molecules,[4] many preparative methods have been developed.[5,6,7] Among all, an intramolecular hydroarylation of propargylarenes is one of a simple and effective entry to synthesis of indenes,[6,7] as the starting materials are easily accessed by the reaction of benzylic electrophiles with acetylide nucleophiles. However, a functional group bound to the propargyl moiety often migrates or is lost during the catalytic reactions.[6] Thus, simple annulation free from migration of functional groups remains the target of present study.[7]

During the course of our study for a combination of alkynes with a palladium catalyst for C–H bond activation,[8,9] we have recently found that aryl(oxyethynyl)-silanes undergo an intramolecular *anti*-hydroarylation via *ortho*-C–H bond activation using a palladium/carboxylic acid catalyst to give benzosiloles (Figure 1A).[9c,9e] We assume that this catalytic system is applicable to the synthesis of indenes without migration of functional groups. Furthermore, toward future synthetic applications, we focused on indene derivatives having an oxyfunctional group as a reactive functional group at C1 and C3 positions. Herein we report an intramolecular *anti*-hydroarylation of oxypropargylarenes under the palladium/carboxylic acid catalyst (Figure 1B).

Based on our previous reports on *anti*-hydroarylation,[9c] we exposed 3-methoxy-3,3-diphenyl-1-(2,6-*i*Pr$_2$-C$_6$H$_3$O)-1-propyne (**1a**) to the Pd(dba)$_2$/PCy$_3$/*t*BuCO$_2$H catalytic conditions. To our delight, desired *anti*-hydroarylation proceeded to give 1-methoxy-1-phenyl-indene **2a** in good yield (Table 1, Entry 1). Further migration of functional groups as the major concern was not observed, whereas a small amount of ester **3a** was generated via an elimination of methoxy group from **1a**. The structure of **2a** was unambiguously determined by X-ray crystallographic analysis (Figure 2A). In the absence of the carboxylic acid, the reaction did not occur at all (Entry 2). When

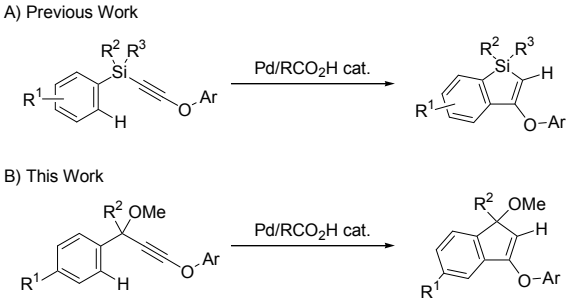
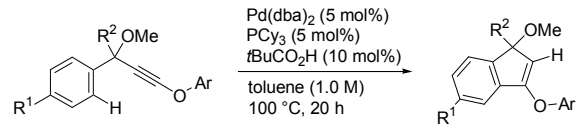


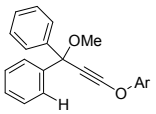
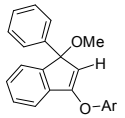
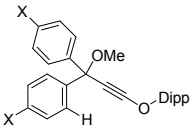
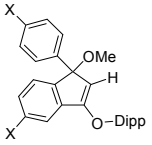
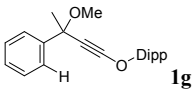
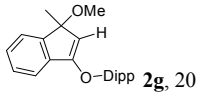
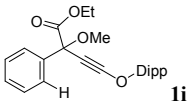
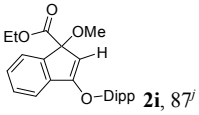
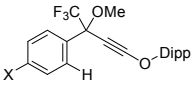
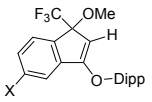
Figure 1. Intramolecular *anti*-hydroarylation via *ortho*-C–H bond activation to form 5-membered cycles

Pd(OC(O)*t*Bu)$_2$ was used as the catalyst instead of Pd(dba)$_2$ and *t*BuCO$_2$H, **2a** was produced only in slightly lower yield (Entry 3). Thus, we have decided the conditions in Run 1 are optimum. The *anti*-hydroarylation proceeded even on a preparative gram-scale, and **2a** was successfully obtained in 81% yield (1.23 g from 3.8 mmol of **1a**) (Entry 4). The substituent effect at alkynyl carbon was remarkable: starting material **1b** or **1c** with a less bulky aryloxy group like 2,5-xylyl or 3,5-xylyl produced indene **2b** or **2c** in a lower yield (Entries 5 and 6). In addition, carbon analog **1d** did not give any annulation product at all. These observations are parallel to those of our benzosilole formation.[9c]

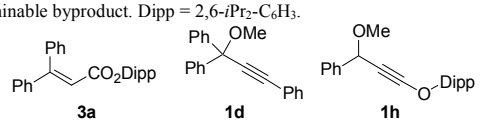
The scope of the substrate was next examined. Substrate **1e** having two electron-deficient *p*-fluorophenyl groups at the propargyl carbon did not affect the reactivity (Entry 7). On the contrary, **1f** containing two electron-rich *p*-tolyl groups gave **2f** in a much lower yield (Entry 8). Addition of equal amount of the catalysts (totally double amounts) slightly improved the yield (Entry 9). Similarly, **1g** substituted with a methyl group on the propargyl carbon afforded **2g** in only a low yield (Entry 10).[10] The reactivity change is attributed to the methoxy group at the propargyl carbon. Electron-donating substituents on the same position promote the elimination of the methoxy group due to stabilizing the carbocation form, thereby lowering the yield of indenes **2**. Also, **1h** having one phenyl group on the propargyl carbon afforded a complex mixture. Thus, two electron-withdrawing substituents at the propargylic carbon are essential for the successful reaction, as seen in the cyclization of ethyl 2-phenyl-3-butynoate **1i** which gave **2i** in an excellent yield (Entry 11).[11] Trifluoromethyl-containing propargyl substrates **1j** and **1k** were similarly converted into the corresponding indenes **2j** and **2k** respectively (Entries 12 and 13).

Table 1. Intramolecular *anti*-hydroarylation of **1**[a]



Entry	**1**	time (h)	**2**, yield (%)[b]
			
1[c]	**1a** (Ar = 2,6-*i*Pr$_2$-C$_6$H$_3$)	20	**2a**, 76 (80)
2[d]	**1a**	20	**2a**, 0
3[e,f]	**1a**	20	**2a**, (76)
4[g]	**1a**	30	**2a**, 81
5	**1b** (Ar = 2,5-Me$_2$-C$_6$H$_3$)	20	**2b**, 47
6	**1c** (Ar = 3,5-Me$_2$-C$_6$H$_3$)	20	**2c**, 44
			
7	**1e** (X = F)	19	**2e**, 74
8	**1f** (X = Me)	20	**2f**, (26)
9[h]	**1f**	40	**2f**, 36
10[i]	 **1g**	23	 **2g**, 20
11	 **1i**	20	 **2i**, 87[j]
			
12	**1j** (X = H)	20	**2j**, 86
13	**1k** (X = OMe)	20	**2k**, 86

[a] A mixture of **1** (1 equiv.), Pd(dba)$_2$ (5 mol%), PCy$_3$ (10 mol%), pivalic acid (10 mol%), and toluene (1 M) was heated at 100 °C. [b] Isolated yields. Numbers in parenthesis are NMR yields. [c] **3a** was generated in 9% yield. [d] Absence of pivalic acid. [e] Pd(OPiv)$_2$ (5 mol%) was used instead of Pd(dba)$_2$ and pivalic acid. [f] **3a** was generated in 5% yield. [g] **1a** (1.51 g, 3.8 mmol), Pd$_2$(dba)$_3$ (0.19 mmol), PCy$_3$ (0.38 mmol), pivalic acid (0.38 mmol), in toluene (3.8 mL), at 100 °C for 30 h to form **2a** (1.23 g, 3.0 mmol). [h] After stirring for 20 h, Pd(dba)$_2$ (5 mol%), PCy$_3$ (10 mol%), and pivalic acid (10 mol%) were further added to the mixture, which was stirred at 100 °C for 20 h. [i] Toluene (0.5 M). [j] The isolated product includes an indeterminable byproduct. Dipp = 2,6-*i*Pr$_2$-C$_6$H$_3$.



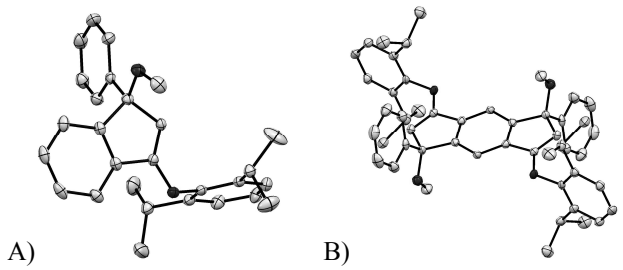
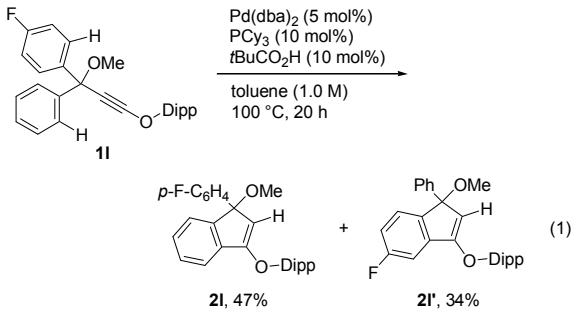
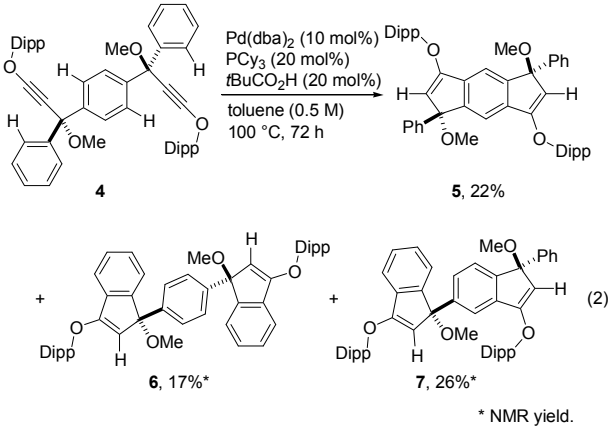


Figure 2. ORTEP diagrams of A) **2a** and B) **5**.

We further examined the electronic effect. Substrate **1l** having phenyl and *p*-fluorophenyl groups on the propargylic carbon gave two possible products **2l** and **2l'** in 47% and 34% yields (58:42), respectively (eq 1). **2l** is the annulation product to the phenyl group, where as **2l'** is derived from annulation into the *p*-fluorophenyl group. The observed ratio suggests that an electron-rich aryl group is more reactive as was the case of the previously reported benzosilole formation.[9c]



With the success of the *anti*-hydroarylation in hand, we extended the reaction design to a double annulation starting with bis(propargyl)arenes. 1,4-*trans*-Bis(1-phenyl-propargyl)benzene **4**, which was prepared by the reaction of bis(benzoyl)benzene with lithium aryloxyacetylide, was heated in the presence of double amounts of the catalysts to give three possible products, 1,5-dihydro-*s*-indacene **5**, 1,4-bisindenyl benzene **6**, and unsymmetric biscycle **7** in roughly similar yields (eq 2). Condensed cycle **5**, insoluble in hexane or dichloroethane, could be facile isolated and purified by reprecipitation followed by recrystalization using hot benzene.[12] The structure of **5** was determined by X-ray crystallographic analysis (Figure 2B).



Plausible reaction mechanism is shown in Figure 3 based on the results and our previous benzosilole formation.[9c,9e] First, palladium complex **A** coordinated by **1**, PCy$_3$, and pivalic acid is generated. *syn*-Hydropalladation of **A** occurs regioselectively to form vinyl palladium pivalate **B**. Stereoisomerization takes place to reduce the steric repulsion between bulky CPh$_2$(OMe) and Dipp,[13] thereby

affording *Z*-complex **C**. Subsequent C–H activation leads to the formation of palladacycle **D** via a concerted-metalation-deprotonation pathway or an S_EAr mechanism.[14] Finally, reductive elimination produces the indene **2** and regenerates a palladium(0) complex.

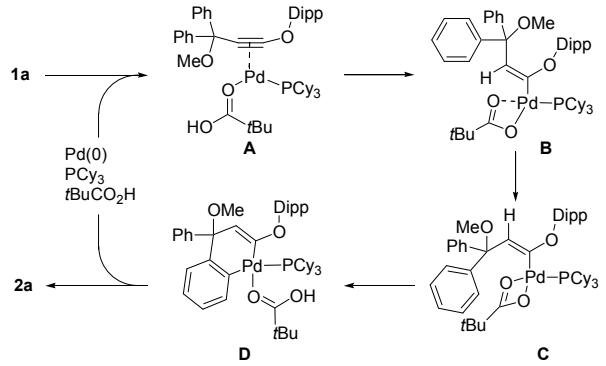
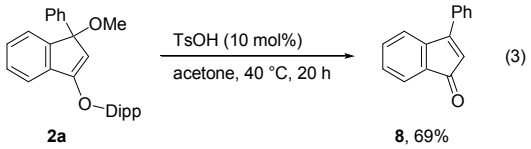


Figure 3. Plausible mechanism using **1a** as a representative substrate

The product **2a** was treated with 0.1 equiv. of *p*-toluenesulfonic acid in acetone, giving 3-phenyl-1-indenone (**8**) in 69% yield via elimination of both methoxy and Dipp groups (eq 3).



In conclusion, a simple palladium(II)/carboxylic acid dual catalyst is demonstrated to be highly effective and induce *anti*-hydroarylation of aryloxypropargylarenes. This reaction proceeds via *ortho*-C–H bond activation without further isomerization and gives oxyfunctionalized indenes. This method allows the construction of not only various indenes but also an 1,5-dihydro-*s*-indacene by a bis(propargyl)benzene. Current efforts are directed toward the transformation of the product, the construction of other cyclic molecules, and the development of indene-based functional molecules.

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Supporting Information is available on http://dx.doi.org/10.1246/cl.******.

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10 Reaction using **1f** afforded **2f** along with an inseparable complex mixture. In the case of the reaction with **1g**, a complex mixture was only detected.
11 A small amount of indeterminable byproduct was included in the product. Detail of this will be the subject of the future work.
12 Other two products **6** and **7** could not be perfectly isolated except of small amounts of them.
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