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Synthesis of 9-Alkylidene-9*H*-fluorenes by a Novel Palladium-Catalyzed Rearrangement

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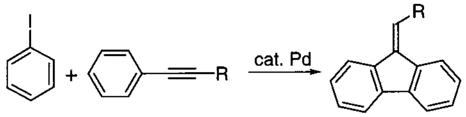
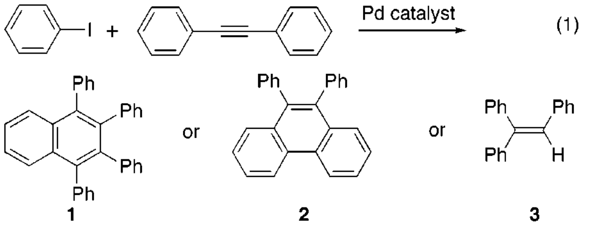
ABSTRACT

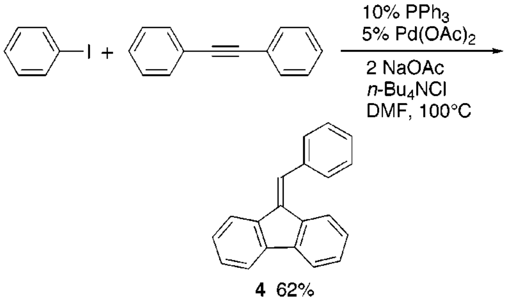


In the presence of a palladium catalyst and NaOAc, aryl iodides react with 1-aryl-1-alkynes to afford 9-alkylidene-9*H*-fluorenes in good yields. This process appears to involve (1) oxidative addition of the aryl iodide to Pd(0), (2) alkyne insertion, (3) rearrangement of the resulting vinylic palladium intermediate to an arylpalladium species, and (4) aryl–aryl coupling with simultaneous regeneration of the Pd(0) catalyst.

Palladium-catalyzed processes have proven remarkably useful in organic synthesis.[1] Oftentimes, only minor variations in reaction conditions have a profound effect on the outcome of the overall process. For example, seemingly minor modifications in the reagents employed in the reaction of iodobenzene and diphenylacetylene have been reported to produce in good yields as the sole product 1,2,3,4-tetraphenylnaphthalene (**1**),[2] 9,10-diphenylphenanthrene (**2**),[3] or triphenylethylene (**3**) (eq 1).[4] We have recently observed another unusual reaction of iodobenzene, diphenylacetylene, and a palladium catalyst that results from only minor variations in the reaction conditions previously reported. By heating iodobenzene (0.25 mmol), diphenylacetylene (0.25 mmol), $Pd(OAc)_2$ (0.0125 mmol, 5 mol %), PPh_3 (0.0250 mmol, 10 mol %), NaOAc (0.50 mmol), and $n\text{-}Bu_4NCl$ (0.25 mmol) in 5 mL of DMF for 12 h at 100 °C, we have been able to isolate 9-benzylidene-9*H*-fluorene in 62% yield (eq 2). While we[5] and others[6] have recently reported a number of simple annulation processes of internal alkynes, where the annulation takes place by simple addition across the acetylene triple bond, this unusual reaction is quite novel.



(1)



(2)

A careful examination of the effect of the reaction conditions on the yield of fluorene has been carried out. The best yields of fluorene **4** are obtained by employing only 1 equiv of alkyne. The addition of catalytic amounts of PPh_3 and an equivalent of some chloride source ($n\text{-}Bu_4NCl$ is

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slightly better than LiCl) improves the yield somewhat. Larger amounts of these reagents proved detrimental to the yield.

Like much of our previous palladium chemistry, the choice of base is critical to the reaction. In the absence of any base, no fluorene is observed. Using 1 equiv of n-Bu_4NCl and 10 mol % of PPh_3, bases other than NaOAc have been observed to give much lower yields of the fluorene **4** and 9,10-diphenylphenanthrene (**2**) as a side product. For example, using K_2CO_3 afforded a 71% yield of the phenanthrene **2** and only 8% of the fluorene **4**. These reaction conditions are virtually the same as those employed by Dyker previously to produce 9,10-diphenylphenanthrene, except that he used n-Bu_4NBr rather than n-Bu_4NCl.[3] The base Na_2CO_3 produced 30% of phenanthrene **2** and 20% of fluorene **4**, while KOAc afforded 12% phenanthrene **2** and 42% fluorene **4**. The base NaOAc produced a 62% yield of the desired fluorene **4** and none of the phenanthrene **2**. This investigation led to the following standard reaction procedure: 1 equiv of aryl halide (0.25 mmol), 1 equiv of alkyne (0.25 mmol), 5 mol % of $Pd(OAc)_2$, 10 mol % of PPh_3, 2 equiv of NaOAc, and 1 equiv of n-Bu_4NCl in DMF at 100 °C.

With this standard procedure in hand, we explored the scope and limitations of the reaction by first examining other alkynes. As shown in Table 1, the alkynes that have been successful in this reaction have an aryl group and another sterically hindered group, such as an aryl, *tert*-butyl, or similar group (entries 1−3). 1-Phenylpropyne gives a messy reaction with little or no fluorene evident. The structural features required of the alkyne can be easily rationalized by examining the mechanism proposed for this process (see Scheme 1).

Various substituted aryl iodides generally work as well as iodobenzene (entries 4−8). The aromatic ring may contain either electron-donating or electron-withdrawing groups. Most aryl iodides bearing a substituent in the *ortho* position, such as 2-iodobenzotrifluoride (entry 4) and 1-*tert*-butyl-2-iodobenzene (entry 5), afforded the expected *E* isomers cleanly. However, other substrates, such as 2-iodotoluene (entry 6), produced mixtures of *Z* and *E* isomers. Aryl iodides bearing functional groups in the *para* position have also afforded mixtures of *Z* and *E* isomers (entries 7 and 8).

The structural assignment of the *Z* and *E* isomers is based on 1D and 2D NMR spectroscopy. For example, the 2D NOESY spectra of **8** (entry 5) clearly show a cross-peak between the protons of the *tert*-butyl group and the vinylic proton H-10. This confirms that **8** exists in the *E* configuration. In some cases, 1D ^1H NMR spectra provide sufficient information to assign the stereochemistry. For example, the ^1H NMR spectra of compounds **11a** and **11b** (entry 8) exhibit doublets for proton H-4 at 8.37 and 8.39 ppm, respectively. In the *Z* isomer **11a**, the phenyl ring present on the vinylic carbon C-10 can exhibit an anisotropic effect[7] on the ring which bears the CO_2Et group. This interaction may shield the protons on that ring, and as a result, the chemical shift of proton H-4 on that ring should appear at a higher field. No such anisotropic interaction can exist in the *E* isomer **11b**, and the signal for H-4 should appear at a lower field. Therefore, the configuration of **11a** and **11b** is tentatively assigned as *Z* and *E*, respectively.

Heteroaromatic iodides have also been examined in the reaction. The reaction of 3-iodopyridine afforded a good yield of a mixture of regio- and stereoisomers (entry 9). All of these isomers are known compounds, and the structural assignments are thus based on the literature.[8]

As one can see from Table 1, in most cases the *E* isomers are the sole or predominant products in the reaction. Previous literature has shown that these types of fluorene compounds undergo interconversions when heated to 140 °C in Decalin.[8a] Therefore, we suspect that the formation of isomers is due to isomerization of the initially formed *E* isomer, which is expected to be produced in the reaction. This has been proven by the following experiments. We were able to separate the *Z* and *E* isomers (**11a** and **11b**) from the reaction of ethyl 4-iodobenzoate and diphenylacetylene by preparative TLC (entry 8). When submitted to the standard palladium reaction conditions, both isomers **11a** and **11b** gave the same 40:60 mixture of **11a** and **11b**, which was exactly the same ratio as that obtained from the original reaction of ethyl 4-iodobenzoate and diphenylacetylene. However, without $Pd(OAc)_2$ present, simple heating of the *E* isomer **11b** for the same period of time in DMF generated a 12:88 mixture of isomers **11a** and **11b**, indicating that $Pd(OAc)_2$ or perhaps Pd(0) plays an important role in the isomerization process.

On the basis of the structure of the products from this reaction (Table 1) and our present understanding of organopalladium chemistry, especially the active role of Pd(IV) as an intermediate in organopalladium chemistry,[9] we propose the following mechanism for this reaction (Scheme 1). The oxidative addition of Pd(0) to iodobenzene produces the arylpalladium intermediate **13**, which rapidly inserts the alkyne to produce the vinylic palladium species **14**. This in turn undergoes oxidative addition to the neighboring aryl C−H bond to generate Pd(IV) intermediate **15**, which isomerizes to the new stereoisomeric Pd(IV) intermediate **16** differing from **15** only in its stereochemistry about palladium. Reductive elimination of **16** leads to Pd(II) intermediate **17**, which undergoes single bond rotation and oxidative addition to the neighboring phenyl ring to afford Pd(IV) intermediate **18**. Two consecutive reductive eliminations finally afford the product and HI and regenerate the

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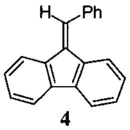
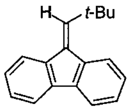
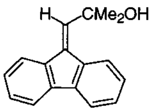
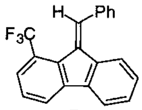
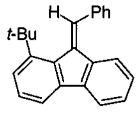
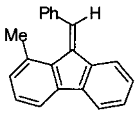
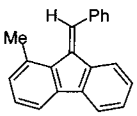
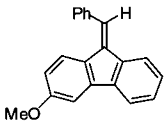
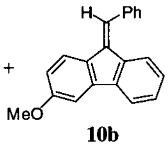
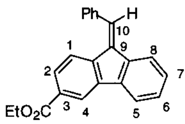
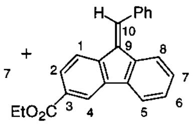
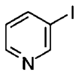
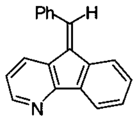
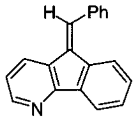
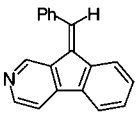
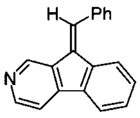
[8] (a) Prostakov, N. S.; Moiz, S. S.; Soldatenkov, A. T.; Zvolinskii, V. P.; Cherenkova, G. I. *Khim. Geterotsikl. Soedin.* **1971**, 1398. (b) Prostakov, N. S.; Varlamov, A. V.; Anismov, B. N.; Mikhailova, N. M.; Vasil'ev, G. A.; Zakharov, P. I.; Galiullin, M. A. *Khim. Geterotsikl. Soedin.* **1978**, 1234.

[9] (a) Canty, A. J. *Acc. Chem. Res.* **1992**, *25*, 83, and references therein. (b) Catellani, M.; Frignani, F.; Rangoni, A. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 119. (c) Catellani, M.; Chiusoli, G. P.; Costa, M. *Pure Appl. Chem.* **1990**, *62*, 623.

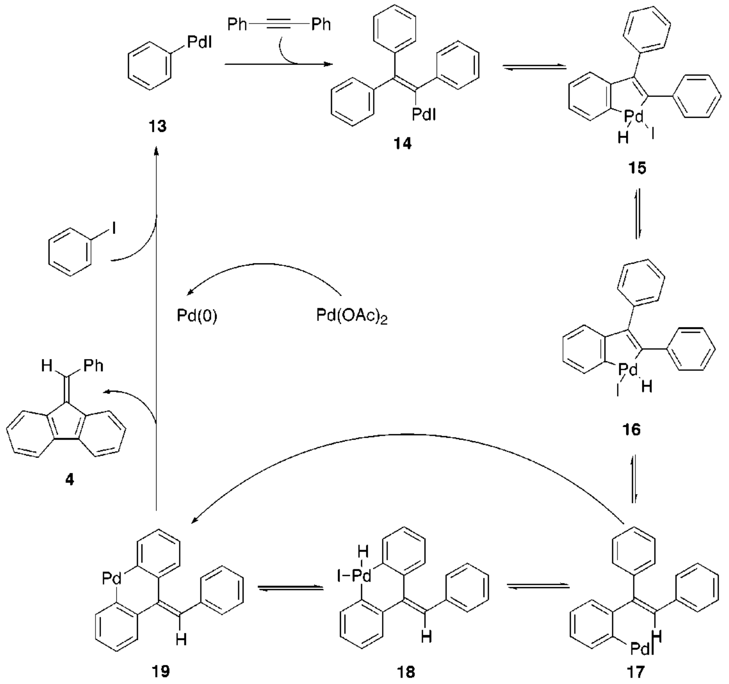
Table 1. Palladium-Catalyzed Cross-Coupling of Aryl Halides and 1-Aryl-1-alkynes[a]

entry	aryl halide	alkyne	time (h)	product(s)	% isolated yield (ratio)
1	PhI	Ph—≡—Ph	12	 **4**	62
2	-	Ph—≡—t-Bu	20	 **5**	61
3	-	Ph—≡—CMe$_2$OH	20	 **6**	55
4	o-F$_3$CC$_{16}$H$_4$I	Ph—≡—Ph	48	 **7**	75
5	o-t-BuC$_6$H$_4$I	-	96	 **8**	35
6	o-MeC$_6$H$_4$I	-	12	 **9a** +  **9b**	61 (40 : 60)
7	p-MeOC$_6$H$_4$I	-	18	 **10a** +  **10b**	45 (40 : 60)
8	p-EtO$_2$CC$_6$H$_4$I	-	15	 **11a** +  **11b**	45 (40 : 60)
9		-	48	 **12a** +  **12b**  **12c** +  **12d**	76 (19 : 14 40 : 27)

[a] Reaction conditions: 5 mol % of Pd(OAc)$_2$, 10 mol % of PPh$_3$, 1 equiv of aryl iodide, 1 equiv of alkyne, 2 equiv of NaOAc, and 1 equiv of n-Bu$_4$NCl in DMF at 100 °C.

Pd(0) catalyst. Alternatively, intermediate **17** may undergo electrophilic aromatic substitution to produce species **19** directly, thus avoiding the Pd(IV) intermediate **18**. To our knowledge, the novel migration of vinylic palladium(II) intermediate (**14**) to an arylpalladium(II) species (**17**) has not been observed previously, although Dyker has suggested the formation of intermediate Pd(II) palladiacycles similar to **15** and **16** without the HI.[10] Dyker's intermediates are suggested to arise from vinylic halides by oxidative addition of Pd(0), but they undergo further oxidative addition of a

Scheme 1

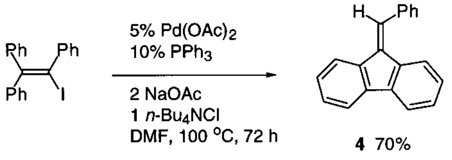


second molecule of vinylic halide to eventually give complicated dimeric products.

It appears that phenanthrene **2** is formed in the presence of K_2CO_3 by either cyclization of **14** to a palladiacycle like **15** or **16**, but without the HI present, or reductive elimination of HI from intermediates **15** or **16** to produce the same palladiacycle, which in turn undergoes oxidative addition by another molecule of iodobenzene, eventually leading to phenanthrene **2**.

From the proposed mechanism, it is obvious that the alkyne must have an aryl group on one end of the triple bond and a sterically bulky group on the other end of the alkyne to get the alkyne insertion regiochemistry necessary to eventually form the fluorene product. Previous alkyne annulation work has clearly shown that the regiochemistry of alkyne insertion into an arylpalladium bond is dominated by steric effects.[5,6]

Vinylic palladium intermediate **14** is a proposed intermediate in the overall process. Since this intermediate should be easily generated by the oxidative addition of Pd(0) to the corresponding vinylic iodide, one might expect to observe the formation of fluorene **4** from 1,2,2-triphenyl-1-iodoethylene under our reaction conditions. Indeed, the expected product **4** was obtained from the reaction in 70% yield (eq 3). Thus, 9-alkylidene-9*H*-fluorenes can also be readily prepared from vinylic iodides by this novel palladium-catalyzed rearrangement.



(3)

In conclusion, the Pd-catalyzed coupling of aryl iodides and 1-aryl-1-alkynes provides an efficient synthetic route to 9-alkylidene-9*H*-fluorenes. This unusual process is believed to involve an unprecedented intramolecular migration of a vinylic palladium intermediate to an arylpalladium species. On the basis of the proposed mechanism, the synthesis of a 9-alkylidene-9*H*-fluorene has also been achieved from a vinylic iodide. We are presently studying the scope of this novel palladium migration chemistry and will report on that chemistry shortly.

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Supporting Information Available: The standard palladium-catalyzed cross-coupling procedure, characterization of all fluorenes prepared, and ^{1}H and ^{13}C NMR spectra for all fluorene products in Table 1. This material is available free of charge via the Internet at http://pubs.acs.org.

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