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Synthesis of Substituted Naphthalenes by the Palladium-Catalyzed Annulation of Internal Alkynes

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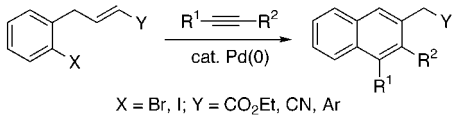
ABSTRACT

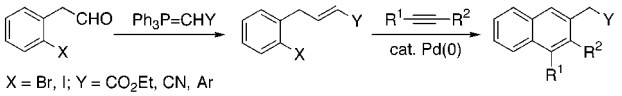


A variety of substituted naphthalenes have been prepared by the palladium-catalyzed carboannulation of internal alkynes. This method (1) forms two new carbon–carbon bonds in a single step, (2) accommodates a variety of functional groups, and (3) affords excellent yields of highly substituted naphthalenes.

Annulation processes have proven quite valuable in organic synthesis because of the ease with which a variety of complicated hetero- and carbocycles can be rapidly constructed. In our own laboratories, it has been demonstrated that palladium-catalyzed annulation methods[1] can be effectively employed for the synthesis of indoles,[2] isoindolo[2,1-*a*]indoles,[3] benzofurans,[4] benzopyrans,[4] isocoumarins,[4,5] α-pyrones,[5,6] indenones,[7] isoquinolines,[8] carbolines,[9] and polycyclic aromatic hydrocarbons.[10]

Highly substituted naphthalenes are common structural units of numerous biologically significant natural products and pharmaceuticals,[11] and improved methods for their construction are highly desirable.[12] Herein, we wish to report the successful application of the palladium-catalyzed annulation chemistry to the synthesis of various substituted naphthalenes using internal alkynes and *o*-(2-alkenyl)aryl halides, which are easily prepared from aldehydes and ylides (Scheme 1).

Scheme 1



Our initial studies focused on achieving optimal reaction conditions for the palladium-catalyzed annulation employing ethyl (*E*)-4-(2-iodophenyl)-2-butenoate (**1**, Scheme 1, X = I, Y = CO_2Et). The reaction of aryl halide **1** and diphenyl-

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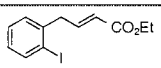
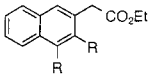
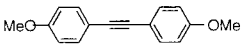
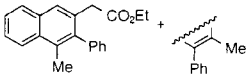
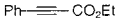
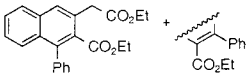
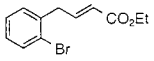
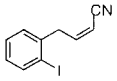
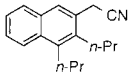
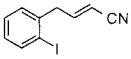
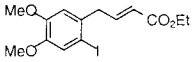
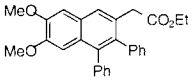
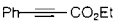
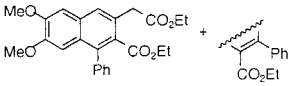
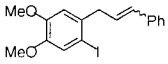
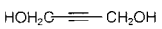
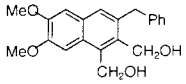
Table 1. Synthesis of Substituted Naphthalenes by the Palladium-Catalyzed Annulation of Internal Alkynes[a]

entry	alkene		alkyne	time (h)	product(s)		% isolated yield
		**1**					
1				12		**2**	86
2				24		**3**	61
3				30		**4**	83
4				48		**5**	60
5				24		**6 + 7**	75[b]
6				12		**8 + 9**	88[c]
7		**10**		40		**2**	75
8		**11**		7		**12**	74
9		**13**		7		**12**	72
10		**14**		24		**15**	71
11				12		**16 + 17**	73 + 8
12		**18**[d]		16		**19**	73

[a] The reactions were run under the following conditions: 0.25 mmol of the aryl halide, 0.5 mmol of the alkyne, 0.5 mmol of Et_3N, 5 mol % of $Pd(OAc)_2$, and 10 mol % of PPh_3 stirred in 3 mL of DMF at 80 °C under an Ar atmosphere. [b] The product was isolated as a 53:47 mixture of isomers **6**/**7**. [c] The product was isolated as a 76:24 mixture of isomers **8**/**9**. [d] Compound **18** was prepared and utilized as a 55:45 mixture of *E*/*Z* isomers.

acetylene was chosen as the model system for optimization of this process. Using 10 mol % of $Pd(OAc)_2$ and 3 equiv of carbonate bases, such as Na_2CO_3 and $NaHCO_3$, afforded the desired naphthalene **2** in 40% and 49% yields, respectively. However, the use of $Pd(PPh_3)_4$ as a catalyst and Na_2CO_3 as a base gave none of the desired product. When the organic bases Et_3N and *n*-Bu_3N were employed, the reactions gave 76% and 71% yields of naphthalene **2**,

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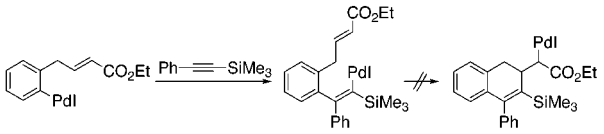
respectively, in the presence of 10 mol % of $Pd(OAc)_2$. Further optimization work showed that 5 mol % of $Pd(OAc)_2$ and 2 equiv of Et_3N are necessary to achieve decent yields of naphthalene **2** in this palladium-catalyzed annulation chemistry. We have also explored the effect on the reaction yield of other variables, such as the ligand, certain additives, and various amounts of the alkyne. The optimal reaction conditions thus far developed employ 0.25 mol of aryl halide **1**, 2 equiv of diphenylacetylene, 5 mol % of $Pd(OAc)_2$, 10 mol % of PPh_3, and 2 equiv of Et_3N as a base in 3 mL of DMF stirred at 80 °C, which affords an 86% yield of naphthalene **2** (Table 1, entry 1).

By using our optimal reaction conditions, the scope of the annulation process has been explored using a variety of substrates carefully selected in order to establish the generality of the process and its applicability to commonly encountered synthetic problems (Table 1). While the reaction of aryl halide **1** and diphenylacetylene afforded naphthalene **2** in 86% yield (entry 1), only a 61% yield of naphthalene **3** was obtained from the reaction of aryl halide **1** and di(*p*-methoxyphenyl)acetylene (entry 2). The decrease in the yield of the reaction indicates that electron-rich diarylacetylenes disfavor the annulation chemistry. However, when an electron-deficient diarylacetylene, such as di(*p*-ethoxycarbonylphenyl)acetylene was allowed to react with aryl halide **1**, an 83% yield of naphthalene **4** was obtained (entry 3), comparable to the yield obtained from the reaction of aryl halide **1** and diphenylacetylene (entry 1). When 4-octyne, a dialkylacetylene, was allowed to react with aryl halide **1**, a 60% yield of naphthalene **5** was obtained (entry 4).

To test the regioselectivity of this annulation process, 1-phenylpropyne was allowed to react with aryl halide **1**, and a 53:47 mixture of two regioisomers **6** and **7** was obtained in a 75% overall yield (entry 5). According to our previous work, the bulkiness of the substituents on the acetylene plays a major role in determining the regioselectivity of alkyne insertion. The arylpalladium intermediate is more likely to add to the less hindered end of the carbon−carbon triple bond.[2−10] In this naphthalene synthesis, the regioselectivity appears to be significantly lower than we have normally observed in the annulation of unsymmetrical alkynes. Similarly, the reaction of aryl halide **1** and ethyl phenylpropiolate afforded a 76:24 mixture of two regioisomers **8** and **9** (entry 6). In this case, the major product **8** results from aryl addition to the 3-position of the propiolate. Electronic effects appear to play a major role here. As in most Heck reactions, the aryl group of the Pd intermediate is more likely to add to the end of the carbon−carbon multiple bond furthest removed from the electron-withdrawing ester moiety, which results in naphthalene **8** as the major product.

The reactions of aryl iodide **1** and 2-butyne-1,4-diol and 3-phenyl-2-propyn-1-ol failed to afford any recognizable product. It appears that the problem may be transesterification of the ester group by the acetylenic alcohols. No recognizable naphthalene products could be obtained when bulky symmetrical or unsymmetrical alkynes, such as di-*tert*-butylacetylene, phenyl(trimethylsilyl)acetylene and 4,4-dimethyl-2-pentyne, were allowed to react with aryl halide **1**. Presumably, the problem here is the difficulty in adding the hindered vinylic palladium intermediate across the relatively hindered internal alkene to place three bulky substituents in contiguous positions on the resulting carbocyclic ring (Scheme 2).

Scheme 2

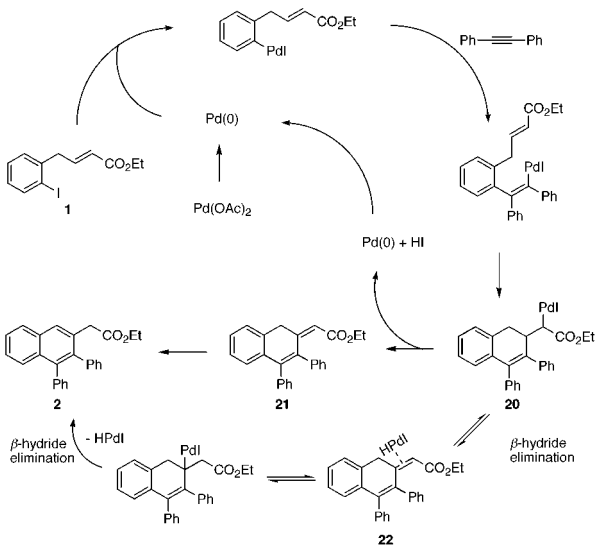


Compound **10** was prepared to test if the annulation process also works well with aryl bromides. The reaction of aryl bromide **10** and diphenylacetylene afforded naphthalene **2** in 75% yield (entry 7). Although this yield is lower than the yield from the reaction of aryl iodide **1** and diphenylacetylene (entry 1), this result is still encouraging, because we now can use aryl bromides instead of aryl iodides. When nitriles **11** and **13**, which are *E*/*Z* isomers, were allowed to react with 4-octyne, they both reached completion in 7 h and afforded very similar yields (entries 8 and 9). This result indicates that the geometry of the carbon−carbon double bond has little effect on this annulation process. The reaction of aryl halide **14**, bearing two methoxy groups on the aromatic ring, and diphenylacetylene afforded naphthalene **15** in 71% yield (entry 10). Compared to the parent system (entry 1), this reaction required a longer reaction time and resulted in a slightly lower yield. When aryl halide **14** was allowed to react with ethyl phenylpropiolate, two regioisomers **16** (73%) and **17** (8% yield) were isolated (entry 11). Comparing this result with that from the reaction of aryl halide **1** and ethyl phenylpropiolate (entry 6), it is clear that the introduction of electron-rich substituents, such as methoxy groups, onto the benzene moiety increases the regioselectivity in this annulation process.

This reaction does not require the presence of a strong electron-withdrawing functional group, such as an ester or nitrile, although these substrates are particularly easy to prepare. The phenyl-substituted aryl iodide **18** has been found to react well with 2-butyne-1,4-diol to produce naphthalene **19** in 73% yield (entry 12). This result confirms our suspicion that the earlier problem with alkynols had more to do with transesterification of the ester group than any inherent problems with the alcohol functionality.

A mechanism for the reaction of aryl halide **1** and diphenylacetylene is proposed in Scheme 3. First of all, Pd(0) oxidatively inserts into the carbon−iodide bond of the aryl iodide to generate an arylpalladium species. Addition of the arylpalladium species to the carbon−carbon triple bond, followed by an intramolecular *cis*-addition to the carbon−carbon double bond generates an alkylpalladium species **20**. Intermediate **20** can undergo β-hydride elimination to form intermediate **21**, which subsequently isomerizes to naphthalene **2**. Alternatively, the intermediate **20** may undergo reversible palladium hydride elimination to an alkene

Scheme 3



complex **22**, which undergoes readdition of the palladium hydride to the double bond with the opposite regiochemistry. Further palladium hydride elimination would produce the observed aromatic product.

In conclusion, an efficient synthesis of highly substituted naphthalenes has been developed in which two new carbon−carbon bonds are formed in a single step. This method accommodates a variety of functional groups and affords the anticipated highly substituted naphthalenes in excellent yields. Research on the scope and limitations of this method is currently underway in our laboratory.

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Supporting Information Available: General experimental procedures and characterization data for all starting materials and products. This material is available free of charge via the Internet at http://pubs.acs.org.

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