Synthesis of Substituted Naphthalenes by 1,4-Palladium Migration Involved Annulation with Internal Alkynes†

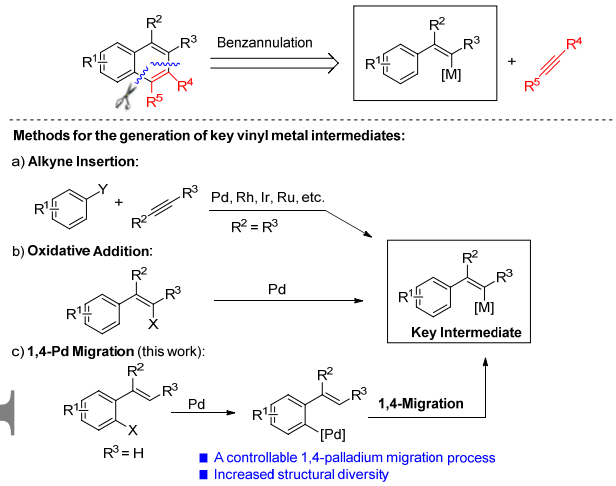
Dong Wei,[a,b] Tian-Jiao Hu,[b] Chen-Guo Feng*,[b,c] and Guo-Qiang Lin*,[a,b]

ABSTRACT The palladium catalyzed annulation of 1-bromo-2-vinylbenzene derivatives with internal alkynes was realized for the efficient synthesis of substituted naphthalenes. A controllable aryl to vinylic 1,4-palladium migration process is the key for success.
KEYWORDS metal migration, naphthalene, palladium, annulation, alkyne

Introduction

The naphthalene core exists extensively in natural products[1] and bioactive molecules.[2] Moreover, substituted naphthalenes have found wide application in optical and electronic materials.[3] As a result, the development of chemoselective and regioselective methods for their synthesis is of great importance. Owing to the scarcity of suitable source material and the difficulty in selectivity control, it is often unapproachable to synthesize a substituted naphthalene by electrophilic aromatic substitution. Intense research interest has been devoted to synthetic methods via benzannulation of properly functionalized arenes,[4] which include annulation via Fisher Carbenes,[5] Diels-Alder reactions,[6] transition-metal-mediated cyclizations,[7] ring rearrangement aromatizations,[8] and acid or base promoted cyclizations.[9]

Scheme 1 Synthesis of naphthalene via benzannulation of (2-aryl)vinyl metal species and internal alkyne



From the standpoint of retrosynthetic analysis, the naphthalene ring can be divided into a (2-aryl)vinyl metal moiety and an alkyne, which represents an obvious but modular synthetic strategy. Pioneered by the work of Sakakibara,[10a] the corresponding (2-aryl)vinyl metal species can be in situ generated via alkyne insertion and then react with a second alkyne to yield the desired naphthalenes. This kind of transformation represents one of the most concise synthetic methods, and now can be promoted by a variety of transition metals.[10] However, the resulting naphthalenes are restricted to the incorporation of two same alkynes. In the meanwhile, the (2-aryl)vinyl metal species originating from oxidative addition of a vinyl halide was also reported by the Larock group,[11] which is limited by the difficulty of accessing corresponding stereodefined vinyl halides, especially for acyclic ones. Therefore, developing a practical and versatile synthetic method by the introduction of a new generation mode of (2-aryl)vinyl metal species is attractive.

1,4-Palladium migration is quite common in organometallic chemistry, which can be used to metalate a remote C-H bond, generating a new organometallic species that is difficult to acquire by other means.[12] Recently, an efficient aryl to vinylic 1,4-palladium process was disclosed by our group.[13] We envision the generated vinylpalladium intermediate might couple with alkynes and provide a new method for the synthesis of substituted naphthalenes.

Results and Discussion

To test our hypothesis, we began our study by testing the annulation of alkene **1a** and alkyne **2a** in the presence of $Pd(OAc)_2$ and various ligands (Table 1). All the tested bis-phosphine ligands were competent to promote the planned reaction sequence. Interestingly, ligands bearing odd-numbered carbon chain gave higher reaction yields than those with even-numbered ones, which may be ascribed to a subtle conformation effect of ligand on the reaction. The importance of ligand conformation was also shown by the fact that DPEPhos (**L6**) gave 99% reaction yield (entry 6) while conformationally rigid Xantphos (**L7**) gave only 66% reaction yield (entry 7). Mono-phosphine ligand can also be used, but was less effective. A screening of solvent found CH_2Cl_2 as another optimal solvent (entry 12). Lowering the reaction temperature to 90 °C, resulted in no product formation (entry 17)

With the optimized conditions in hand, the scope of alkenes was first explored (Table 2). High reaction yields were observed when the position of phenyl ring A was installed by a variety of substituted phenyl groups (**3aa**-**3ga**), as well as naphthalenyl (**3ha**) and thienyl (**3ia**) groups. While the phenyl ring A was replaced by a methyl group, a substrate used recently in the coupling with alkyne for the preparation of tetracyclic compounds,[14] the desired naphthalene **3ja** was still produced under our reaction conditions, albeit in reduced yield. An ester group was also compatible (**3ka**), which provides a useful handle for further derivatization. Introduction of either electron-donating or electron-withdrawing substituents to the C-5 position of phenyl ring B furnished the desired products in high yields (**3ia**-**3pa**). Replacing the phenyl ring B by a pyridyl group was also tolerated (**3qa**). As expected, a substrate bearing a C-4 methyl

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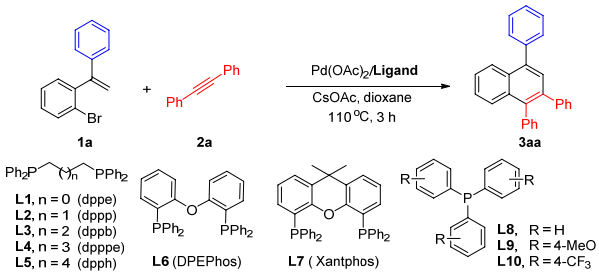
† Dedicated to Professor Xiyan Lu on the occasion of his 90th birthday.

substituented phenyl ring **B** generated two regio-isomers (**3ra** and **3ra'**) in a 1.2:1 ratio, which is in accordance with the proposed migration mechanism.

Table 1 Optimization of reaction conditions[a]

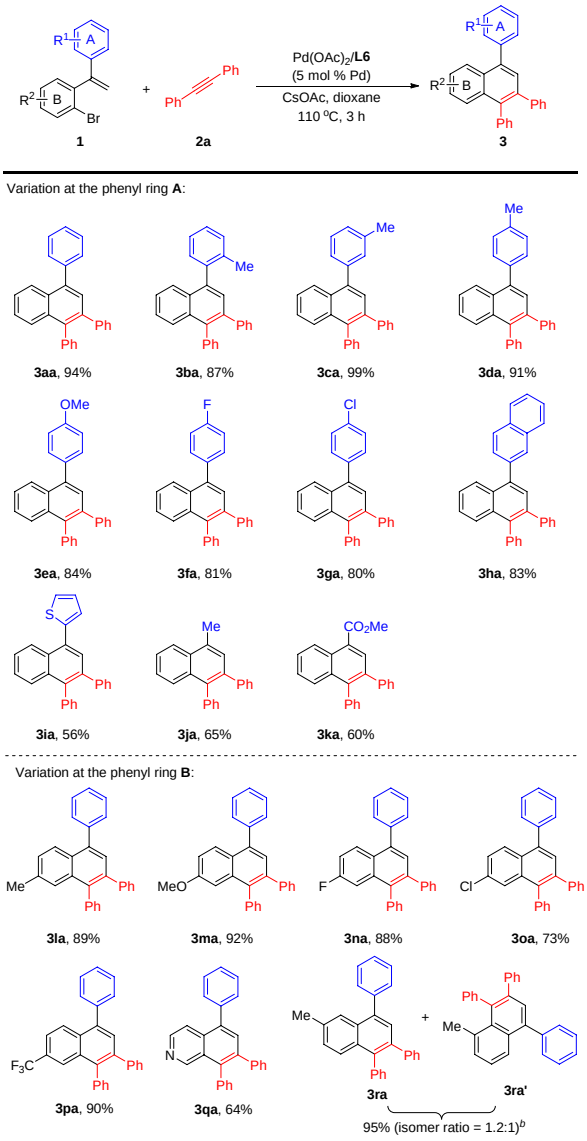


entry	ligand	Temp./°C	solvent	yield[b] /%
1	**L1**	110	dioxane	57
2	**L2**	110	dioxane	93
3	**L3**	110	dioxane	82
4	**L4**	110	dioxane	92
5	**L5**	110	dioxane	85
6	**L6**	110	dioxane	99
7	**L7**	110	dioxane	66
8	**L8**	110	dioxane	53
9	**L9**	110	dioxane	36
10	**L10**	110	dioxane	29
11	**L6**	110	THF	64
12	**L6**	110	CH_2Cl_2	99
13	**L6**	110	toluene	34
14	**L6**	110	MeCN	28
15	**L6**	110	DMF	62
16	**L6**	110	MeOH	26
17	**L6**	90	dioxane	nd
18	**L6**	130	dioxane	95

[a] Reaction condition: **1a** (0.19 mmol, 1.0 equiv), **2a** (0.19 mmol, 1.0 equiv), $Pd(OAc)_2$ (0.05 equiv), ligand (0.1 equiv for **L1**-**L7** and 0.2 equiv for **L8**-**L10**), CsOAc (2.0 equiv), solvent (1 mL). [b] Determined by ^1H NMR spectroscopy using CH_2Br_2 as an internal standard.

Next, the scope of alkynes was examined (Scheme 3). The coupling with various symmetrical, internal alkynes bearing two different aryl groups proceeded smoothly to afford **3ab**-**3af** in good to excellent yields. While the reaction with two thienyl-substituted alkynes gave reduced reaction yield (**3ag**), only a trace amount of product was detected by GC-MS analysis with di-butyl substituted alkyne (**3ah**). Although the application of non-symmetrical alkynes usually brings a mixture of two regioisomers, it is possible to control the regioselectivity by applying alkynes with marked differences in the two substituents. For example, excellent regioselectivies were observed with 1-phenyl-2-(trimethylsilyl) acetylene (>20:1) and methyl phenylpropiolate (14:1). The structure of the corresponding major isomers **3ak** and **3al** were determined by X-ray crystallographic structure analysis (Scheme 4),[15] which can be explained by the regioselectivity preference in the alkyne insertion step via an alkenylpalladium intermediate,[11,16] and was further confirmed by a control experiment with alkenyl bromide **4** as the coupling partner (eq 1).

Scheme 2 Synthesis of naphthalene via benzannulation of (2-aryl)vinyl metal species and internal alkyne[a]



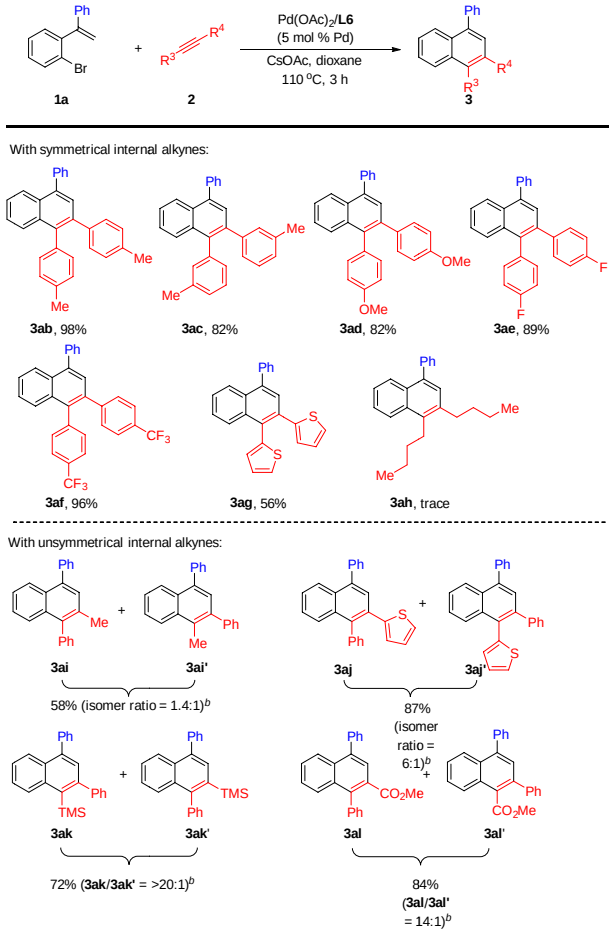
[a] Reaction condition: **1** (0.30 mmol, 1.0 equiv), **2a** (0.30 mmol, 1.0 equiv), $Pd(OAc)_2$ (0.05 equiv), **L6** (0.1 equiv), CsOAc (2.0 equiv), dioxane (1.5 mL). Yield refers to isolated product. [b] Isomer ratio was determined by ^1H NMR analysis of the crude product.

Two gram-scale reactions were carried out to demonstrate the practicability of the developed method, which offered the desired products in comparable reaction yields to those observed on small reaction scale (eqs 2 and 3).

A possible mechanism was proposed based on the current experimental observations and previous reports,[13] in which alkene **3r** was used as the model substrate to elucidate the regioselectivity in this reaction (Scheme 5). The reaction is initiated by the oxidative addition of starting substrate **3r**, and is followed by a 1,4-palladium migration process, which may be promoted by the generation of less sterically encumbered vinylpalladium **B**. Insertion of internal alkyne produces intermediate **C** and undergoes a subsequent cyclization with the phenyl ring B from two different directions to afford **3ga** and **3ga'**,

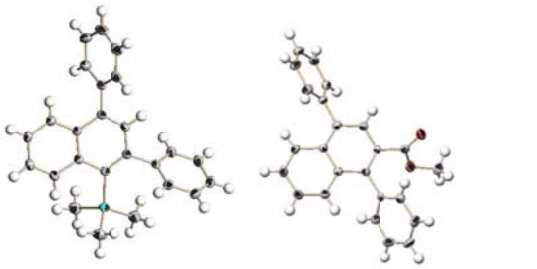
respectively.

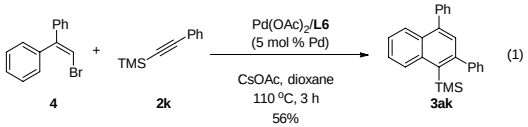
Scheme 3 Scope of internal alkynes[a]

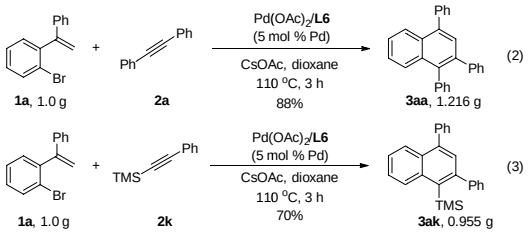


[a] Reaction condition: **1a** (0.30 mmol, 1.0 equiv), **2** (0.30 mmol, 1.0 equiv), $Pd(OAc)_2$ (0.05 equiv), **L6** (0.1 equiv), CsOAc (2.0 equiv), dioxane (1.5 mL). Yield refers to isolated product. [b] Isomer ratio was determined by ^1H NMR analysis of the crude product.

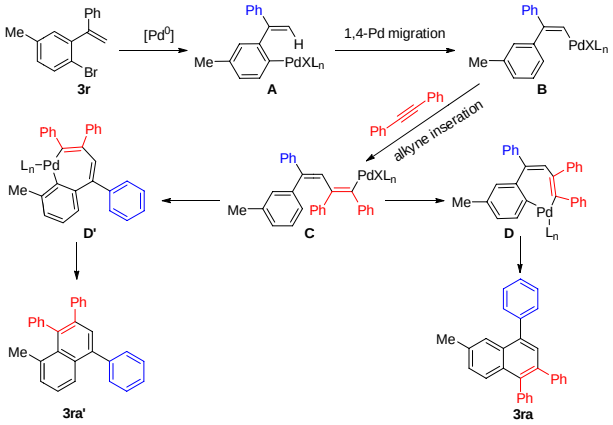
Scheme 4 X-Ray crystallographic structure of **3ak** and **3al**







Scheme 5 Proposed mechanism for palladium-catalyzed naphthalene synthesis



Conclusions

In summary, we developed a convenient protocol for the modular synthesis of substituted naphthalenes. A wide variety of substituted naphthalene compounds were prepared in good to excellent yields. The success of this transformation involves a key 1,4-palladium migration step.

Supporting Information

The supporting information for this article is available on the WWW under https://doi.org/10.1002/cjoc.2018xxxxx.

Acknowledgement

Financial support from the National Natural Science Foundation of China (21472212, 21572253, 21772216), the Strategic Priority Research Program of the Chinese Academy of Sciences (XDB 20020100) and The Key Research Program of Frontier Science (QYZDY-SSW-SLH026) is acknowledged.

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(The following will be filled in by the editorial staff)
Manuscript received: XXXX, 2017
Revised manuscript received: XXXX, 2017
Accepted manuscript online: XXXX, 2017
Version of record online: XXXX, 2017

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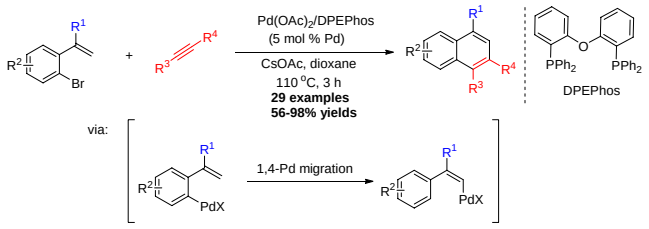

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