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Palladium-Catalyzed Bisolefination of C−C Triple Bonds: A Facile Method for the Synthesis of Naphthalene Derivatives

Chao Feng and Teck-Peng Loh*

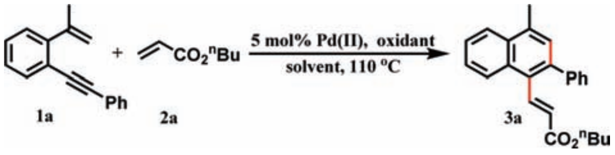
Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, Singapore 637371

Received October 15, 2010; E-mail: teckpeng@ntu.edu.sg

Abstract: A highly efficient and mild palladium-mediated bisolefination of C−C triple bonds is described for the first time. With different types of olefin employed, this reaction terminates in diverse fashions. In addition to the merit of using oxygen as the sole oxidant, this reaction exhibits high reactivities and functionality tolerance simultaneously, thus providing a promising method for the synthesis of naphthalene derivatives.

In the past decades, reactions catalyzed by palladium have found widespread application in organic synthesis.[1] In this regard, nucleopalladation of alkynes continues to be a hot and fantastic arena because of its high efficiency in constructing multiple new chemical bonds, thus leading to various complex structures in one step. Therefore, much effort has been devoted to this area, utilizing different kinds of nucleophiles such as halide,[2] acetate,[3] and amine[4] together with aromatic coupounds[5] for construction of a wide variety of desired structures. Gevorgyan,[6] Yamamoto,[7] and Larock[8] have made great contributions to alkyne-directed transformations. However, to the best of our knowledge, to date there has been no report of bisolefination of C−C triple bonds in palladium chemistry. Toward this end, we envisioned that the use of an alkene as the initiator for nucleopalladation of an alkyne followed by coupling with another alkene would allow the concise construction of triene derivatives.[9] If this approach is feasible, it would be an ideal method for the synthesis of triene derivatives because no prefunctionalized coupling partners such as organohalides and/or organometallics would be required, making it environmentally friendly and cost-effective.[10] In connection with our interest in the search for new coupling reactions for the synthesis of naphthalene derivatives, we present a palladium-catalyzed sequential intra- and intermolecular coupling reaction with molecular oxygen as the sole oxidant to construct naphthalene derivatives with high regioselectivity.

Table 1. Optimization of Reaction Conditions[a]



entry	catalyst	oxidant	solvent	yield (%)[b]
1	$Pd(OAc)_2$	$Cu(OAc)_2/O_2$	DMSO	15
2	$Pd(OAc)_2$	$Cu(OAc)_2/O_2$	toluene	NR
3	$Pd(OAc)_2$	$Cu(OAc)_2/O_2$	DMF	trace
4	$Pd(OAc)_2$	AgOAc/air	DMSO	trace
5	$Pd(OAc)_2$	$Cu(OAc)_2$/air	DMA	trace
6	$Pd(OAc)_2$	O_2	DMSO	20
7	$Pd(TFA)_2$	$Cu(OAc)_2$/air	DMSO	20
8	$Pd(TFA)_2$	$Cu(OTf)_2$/air	DMSO	64
9	$Pd(TFA)_2$	$Cu(OTf)_2$/air	toluene	trace
10	$Pd(TFA)_2$	$Cu(OTf)_2$/air	dioxane	trace
11	$Pd(TFA)_2$	$Cu(OTf)_2$/air	DCE	trace
12	none	$Cu(OTf)_2$/air	DMSO	0[c]
13	$Pd(acac)_2$	$Cu(OTf)_2$/air	DMSO	54
14	$Pd(PPh_3)_4$	$Cu(OTf)_2$/air	DMSO	60
15	$Pd(MeCN)_2Cl_2$	$Cu(OTf)_2$/air	DMSO	70
16	$PdCl_2$	$Cu(OTf)_2$/air	DMSO	78
17	$PdCl_2$	Ag_2O/air	DMSO	trace
18	$PdCl_2$	BQ[d]/air	DMSO	77
19	$PdCl_2$	O_2	DMSO	75

[a] Unless otherwise noted, the reactions were carried out at 110 °C using **1a** (0.1 mmol), **2a** (0.3 mmol), catalyst (0.005 mmol), oxidant (0.02 mmol), and DMSO (0.4 mL) for 24 h under air or oxygen atmosphere. [b] Isolated yields. [c] A quantitative amount of **1a** was recovered. [d] BQ = 1,4-benzoquinone.

To begin our study, 1-(phenylethynyl)-2-vinylbenzene was first reacted with butyl acrylate under various conditions, but the reaction gave intractable mixtures in all cases. Considering that this may have been due to β-hydride elimination, we installed a methyl group at the α-position of the styrene derivative. Fortunately, the reaction proceeded as expected, albeit in low yield. With this promising preliminary result in hand, different catalysts, solvents, and oxidants were screened, and the results are summarized in Table 1. As shown in Table 1, our attempts to use $Pd(OAc)_2$ as the catalyst were not successful (entries 1−6). When the catalyst was changed to $Pd(TFA)_2$ with $Cu(OAc)_2$/air as the oxidant, there was still no improvement in the yield of the product. Surprisingly, the yield was dramatically increased to 64% when $Cu(OTf)_2$/air was used the oxidant (entry 8). After many attempts, it was found that the reaction proceeded well in DMSO (entries 8−11). As expected, there was no reaction in the absence of palladium catalyst (entry 12). With this optimum oxidant system of $Cu(OTf)_2$/air in hand, various palladium catalysts were screened to ascertain their efficiency in the reaction (entries 13−16). These results showed that while many types of palladium catalysts could catalyze this reaction, the use of palladium chloride as the catalyst gave the best results (78% yield; entry 16). Further examination of several oxidant systems using palladium chloride as the catalyst proved that 1,4-benzoquinone (BQ)/air and molecular oxygen were also suitable for this reaction (entries 18 and 19), providing yields comparable to that for the $Cu(OTf)_2$/air system. On the basis of economic considerations, the optimized reaction conditions were affirmed as follows: 5 mol % $PdCl_2$ as the catalyst and molecular oxygen as the oxidant in DMSO at 110 °C for 24 h.

With the optimized reaction conditions in hand, we next investigated the scope of the reaction using different types of external olefins. As shown in Table 2, both acrylate and styrene derivatives reacted efficiently to afford the desired products in good to excellent yields. It is noteworthy that styrene derivatives with both electron-donating and electron-withdrawing substituents could be smoothly transformed into the desired products in good yields

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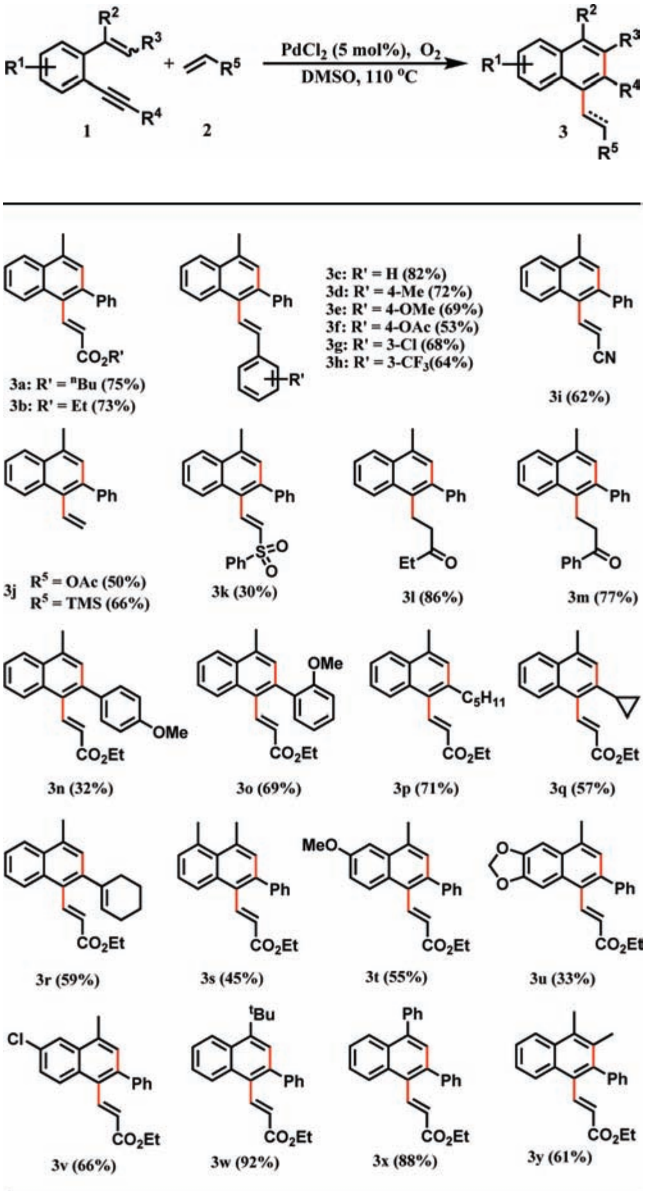
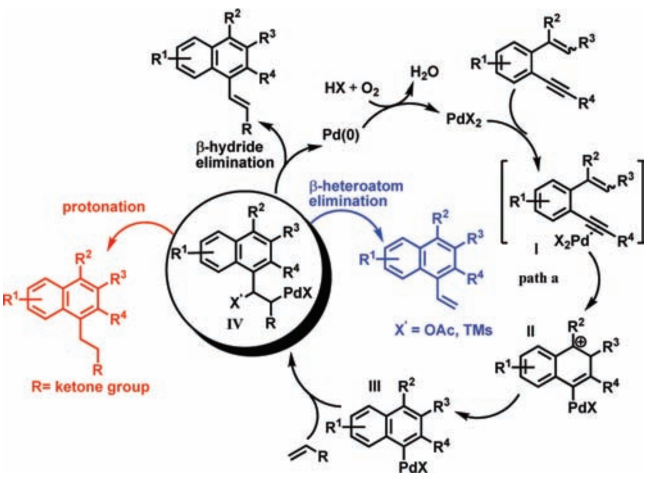
Table 2. Reaction Scope[a]



[a] Unless otherwise noted, the reactions were carried out at 110 °C using **1** (0.1 mmol), **2** (0.3 mmol), $PdCl_2$ (0.005 mmol), and DMSO (0.4 mL) for 24 h under an oxygen atmosphere. The yields in parentheses are isolated yields.

(**3c**−**h**). Vinyl cyanide also worked well for this transformation (**3i**). Interestingly, when trimethylsilyl-substituted ethylene or vinyl acetate was used as the terminating coupling reagent, product **3j** was obtained, suggesting the involvement of a β-heteroatom elimination process in the reaction.[11] Vinyl phenyl sulfone was not a good coupling partner, as it afforded the target product in low yield (**3k**). Intriguingly, when a vinyl ketone was used as the external coupling partner, reductive products containing an alkyl chain were obtained (**3l** and **3m**). This result indicated that the final protonation step of the catalytic cycle proceeded much faster than β-hydride elimination in such cases. To further investigate the scope of the internal enyne, ethyl acrylate was chosen as the intermolecular coupling partner. Substrate **1n** with a methoxy substituent at the para position of the tethered phenyl group gave the product in low yield. This might have been due to competition between the alkyne and methoxy groups to form a complex with palladium. In comparison, substrate **1o** with a methoxy substituent adjacent to the alkyne group was smoothly transformed into the desired product in good yield, which further proved the involvement of a competitive complexation in the reaction with **1n**. Moreover, alkyl- and alkenyl-tethered substrates were also efficiently converted into the corresponding products in moderate to good yields (**3p**−**r**). Substrate **3s** with a methyl group ortho to the alkenyl moiety resulted in a moderate yield, mainly because of repulsion between the two adjacent methyl groups. Substrates possessing alkoxy substituents on the aromatic ring of styrene derivatives could also be successfully transformed into the corresponding products, albeit in low yield (**3t** and **3u**). In addition, a halogen atom on the aromatic ring was inert in this reaction, allowing it to be used for further transformation (**3v**). Furthermore, a variety of substituents on the alkenyl moiety can be used in this reaction. For instance, both *tert*-butyl and phenyl groups at the α-position of the styrene derivatives were transformed into the corresponding products in excellent yields (**3w** and **3x**). To further demonstrate the practical utility of this protocol, a gram-scale reaction was carried out using **1x** and **2b** to afford the product **3x** in 85% yield.[12] It is important to note that this strategy was also applicable to the annulation of α,β-disubstituted substrates regardless of the configuration of the double bond. For example, the reaction of an *E*/*Z* mixture of α,β-dimethylstyrene derivative **1y** proceeded selectively to give the desired *E*-configured product **3y** in good yield.

Scheme 1. Proposed Mechanism



A proposed mechanism is illustrated in Scheme 1. Initially, Pd^{II} coordinates with the triple bond, forming the π-complex **I**. This initial step makes the alkynyl group electron-deficient and instantaneously triggers the intramolecular carbopalladation to afford intermediate **II**. From intermediate **II** shown here, we can understand that the R^2 substituent is so crucial for this reaction primarily because of its role in stabilization of the carbocation generated. Subsequently, deprotonation and external olefin insertion occur to produce intermediate **IV**, which, after β-hydride elimination, generates the cyclic product as well as Pd^0, which can be reoxidized to the Pd^{II} species by molecular oxygen. We believe that the success of this transformation relies on the dual roles of the palladium catalyst, namely, its Lewis acidity and late-transition-metal character.

In conclusion, we have demonstrated the first palladium-catalyzed bisolefination of C−C triple bonds. This transformation is believed to be an efficient and sustainable process in which molecular oxygen is the exclusive oxidant with water as the only byproduct generated. Additionally, this reaction provides a facile method for the synthesis of naphthalene derivatives that are of tremendous importance in medicinal chemistry. Further studies to extend the bisolefination of C−C triple bonds to intermolecular three-component reactions are in progress.

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Supporting Information Available: Additional experimental procedures along with chromatograms and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) The experimental procedure for the gram-scale reaction is included in the Supporting Information.

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