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Palladium(II)-Catalyzed Oxidative Dearomatization of Free Naphthols with Two Alkyne Units

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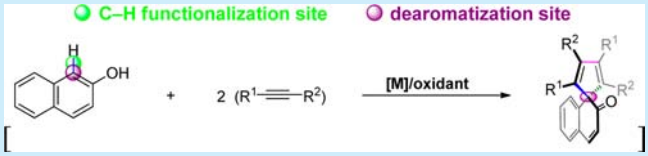
Supporting Information

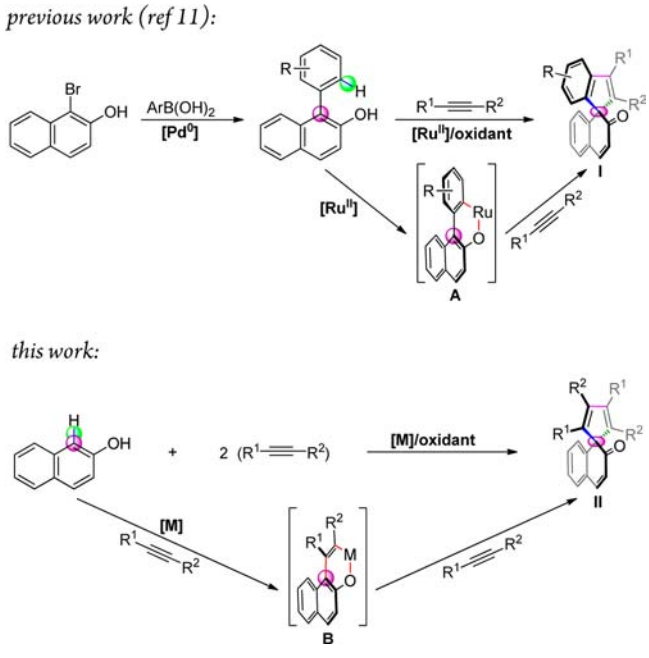
ABSTRACT: Readily available 2-naphthols undergo [2 + 2 + 1] spiroannulation reactions with alkynes in the presence of a Pd^{II} catalyst and an oxidant. This process relies on C−H functionalization and naphthyl ring dearomatization at the 1-position of 2-naphthols to provide a variety of spirocyclic compounds. Using alkyl−aryl alkynes as the coupling partners led to regioisomeric mixtures in favor of the head-to-tail isomer bearing a quaternary carbon stereocenter.



Transition-metal catalysis has proven to be a fascinating platform to forge more efficient and economical tools for the elaboration of readily available phenolic chemicals.[1] Recently, the development of new reliable synthetic methods in this area has been a topic of focus. Of particular interest are the tremendous achievements derived on the basis of two dominant strategies: (a) Relying upon coordination of the metal center to the hydroxyl group, various phenolic derivatives have been successfully converted into different kinds of heterocyclic products such as benzofurans,[2] benzochromenes,[3] coumarins,[2d,4] dibenzofurans[5] and dibenzopyranones[6] by using rhodium-, ruthenium-, or palladium-catalyzed C−H functionalization. (b) With regard to the phenolic ring, metal-catalyzed dearomatization reactions such as nitroalkylation,[7] allylation,[8] alkenylation,[9] and arylation[10] have played an important role to construct diverse 3D architectures with high levels of molecular complexity from these simple planar aromatic compounds. While these two distinct approaches have already gained significant progress, respectively, their scope and utility would be considerably enhanced if they could be merged in a single synthetic operation, thus allowing the simultaneous activation of C−H bond and aromatic scaffold in the phenolic structures.

To address this daunting challenge, we recently reported an example of transition-metal-catalyzed transformation of 1-aryl-2-naphthols through a joint C−H activation/dearomatization strategy (Scheme 1, top).[11] This reaction hinges on the ability of a ruthenium(II) catalyst to cleave the C−H bond being directed by hydroxyl group to form a key intermediate ruthenacycle **A**, followed by alkyne migratory insertion and naphthol dearomatization to produce a class of rather attractive spirocyclic molecules **I**. Notably, the whole process was pushed forward from 1-bromo-2-naphthol to **I** by the consecutive palladium(0) and ruthenium(II) catalysis. To develop a more economical reaction featuring the dual activation concept, we proposed a concise route for the synthesis of spirocyclic compounds **II** from 2-naphthol via a one-step metal-catalyzed oxidative dearomatizing reaction (Scheme 1, bottom). The key point of this proposal is the replacement of intermediate **A** with a metallacycle **B**, which needs to be generated from 2-naphthol and 1 equiv of alkyne by a metal catalyst. Encouragingly, the relevant metal-promoted C−H metalation[2,4a−c,12] and subsequent formation of metallacycles similar to **B**[2c,4a,b] have been recently disclosed. Herein, we describe the successful execution of our new proposal of metal-catalyzed [2 + 2 + 1] dearomatizing annulation of free 2-naphthols with alkynes via a novel combination of C−H functionalization and dearomatization.

Scheme 1. Metal-Catalyzed Dearomatization of 2-Naphthols



To test our hypothesis, we began the study by choosing 2-naphthol (**1a**) and diphenylacetylene (**2a**) as the standard

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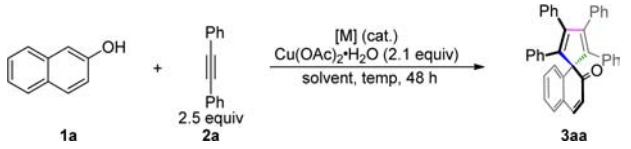
coupling partners to evaluate the catalysts and reaction conditions for the envisioned oxidative annulation. First, $[RuCl_2(p\text{-cymene})_2]$ and $[(Cp^*RhCl_2)_2]$, which were very effective for the oxidative dearomatizing annulations of *ortho*-substituted phenolic derivatives with alkynes in our[11] and others' prior work,[13] were combined with different oxidants $[Cu(OAc)_2$, Ag_2CO_3, Ag_2O, AgOAc] to examine the reaction behavior in a variety of solvents at 90−120 °C. Disappointedly, the spirocyclic compound **3aa** was not formed, and both starting materials were not consumed. In this context, we turned our attention to other types of catalysts (Table 1). To our delight, $Pd(OAc)_2$, which has

Table 1. Optimization of the Reaction Conditions



1a 2a 3aa

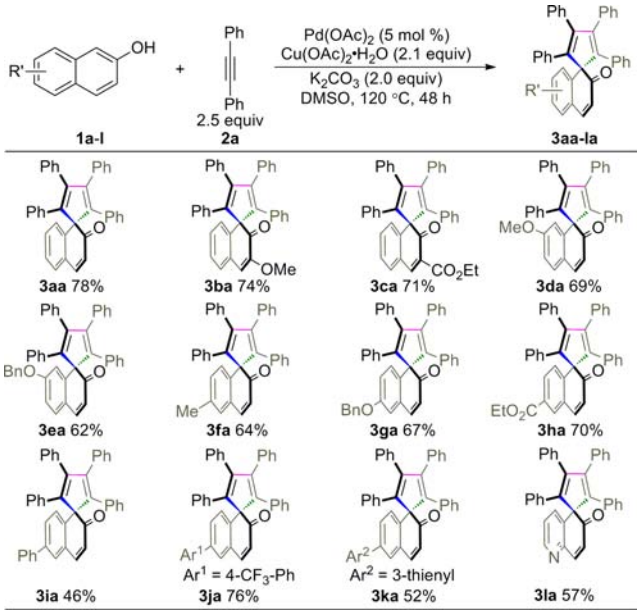
entry	[M] (mol %)	temp (°C)	solvent	yield[a] (%)
1	$Pd(OAc)_2$, 5.0	90	DMF	24
2	$Pd(OAc)_2$, 5.0	90	dioxane	0
3	$Pd(OAc)_2$, 5.0	90	THF	0
4	$Pd(OAc)_2$, 5.0	90	$ClCH_2CH_2Cl$	0
5	$Pd(OAc)_2$, 5.0	90	^{t}AmOH	0
6	$Pd(OAc)_2$, 5.0	90	DMSO	43
7	$PdCl_2$, 5.0	90	DMSO	22
8	PEPPSI-IPr, 5.0	90	DMSO	27
9	$Pd(OAc)_2$, 5.0	120	DMSO	55
10[b]	$Pd(OAc)_2$, 5.0	120	DMSO	78

[a]Isolated yield. [b]K_2CO_3 (2.0 equiv) was added.

succeeded in enabling the [3 + 2][14] and [2 + 2 + 1][15] oxidative spiroannulation reactions with alkynes, was observed to favor the desired [2 + 2 + 1] dearomatizing annulation by employing stoichiometric $Cu(OAc)_2$ as the oxidant[16] and DMF as the solvent, giving product **3aa** in 24% isolated yield (entry 1). The structure of **3aa** was unambiguously assigned by X-ray crystallography. Optimization of the reaction solvents revealed that 1,4-dioxane, THF, $ClCH_2CH_2Cl$, and ^{t}AmOH were totally ineffective for the title transformation (entries 2−5) and DMSO was the better solvent to give **3aa** in 43% yield (entry 6). Next, palladium sources such as $PdCl_2$ and PEPPSI-IPr were also found to be applicable, albeit with lower activities (entries 7 and 8). Finally, the reaction was further improved by elevating the temperature to 120 °C (entry 9), and the addition of 2 equiv of K_2CO_3 led to a higher yield of **3aa** (78% yield) (entry 10). Notably, there is one literature precedent of metal-catalyzed dearomatization of phenolic compounds with alkynes via the [2 + 2 + 1] cycloaddition strategy, and it was achieved by palladium(0)-catalyzed cyclization of 4-phenol diazonium salts with alkynes to generate spiro[4,5]decatetraene-7-ones.[17] By comparison, this new approach is operationally simple and allows the direct utilization of free 2-naphthols without prior functionalization.

With the optimized reaction conditions in hand, the reaction scope was first examined by employing a variety of substituted 2-naphthols to react with **2a**, and the results of the catalytic reactions are summarized in Scheme 2. Overall, the substituents on C3 (**1b**,**c**), C6 (**1f**−**k**), and C7 (**1d**,**e**) positions of 2-naphthol could be varied with methoxy (**1b**,**d**), carbethoxy (**1c**,**h**), benzyloxy (**1e**,**g**), methyl (**1f**), phenyl (**1i**), and other aromatic groups (**1j**,**k**), and the spirocyclic products **3b**−**k** were

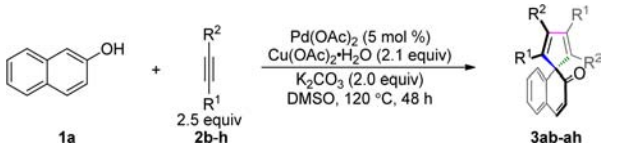
Scheme 2. Survey of the Scope of 2-Naphthols



successfully prepared in 46−76% yields. It is noteworthy that heterocyclic quinolin-6-ol (**1l**) was also tolerable under the palladium catalysis conditions to give **3la** in 57% yield.

Next, the investigation of the substrate scope was extended to the symmetrical alkynes (Table 2). In addition to diphenylacetylene **2a**, a broad range of other symmetrical alkynes (**2b**−**h**) bearing various aromatic groups were tolerated in the oxidative dearomatizing annulation process, and the desired spirocyclic products **3ab**−**ah** were obtained in 41−75% yields. Satisfactorily, the aromatic motifs could be substituted with diverse electron-withdrawing (**2b**,**c**,**f**), electron-neutral (**2d**), and electron-donating groups (**2e**) at the *ortho*- (**2b**), *meta*- (**2c**), or *para*-position (**2d**−**f**). Moreover, the alkyne **2g** containing heterocyclic groups such as 2-thienyl could undergo the envisioned annulation with **1a** to give **3ag** in 41% yield. Additionally, the use of a dialkylacetylene (**2h**) was also allowed under the standard reaction conditions.

Table 2. Survey of the Scope of Symmetrical Alkynes



entry	R^1	R^2	3	yield (%)
1	2-F-C_6H_4	2-F-C_6H_4	**3ab**	75
2	3-F-C_6H_4	3-F-C_6H_4	**3ac**	72
3	4-Me-C_6H_4	4-Me-C_6H_4	**3ad**	53
4	4-MeO-C_6H_4	4-MeO-C_6H_4	**3ae**	48
5	4-Cl-C_6H_4	4-Cl-C_6H_4	**3af**	57
6[a]	2-thienyl	2-thienyl	**3ag**	41
7	*n*-propyl	*n*-propyl	**3ah**	62

[a]Using 10 mol % of $Pd(OAc)_2$, 4.0 equiv of **2g**, and 1.0 equiv of K_2CO_3.

To demonstrate further the utility of this [2 + 2 + 1] cycloaddition method, several alkyl−aryl mixed alkynes (**2i**−**l**) were employed. Presumably, the incorporation of two unsym-

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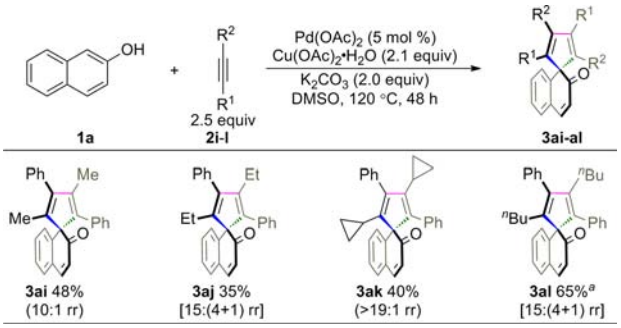
metrical alkyne units into the cyclization products might lead to three regioisomers, one of which should possess a quaternary stereogenic center, thus providing the possibility of the development of a catalytic enantioselective process. As shown in Scheme 3, the experimental results indicated that the reactions

Scheme 3. Survey of the Scope of Unsymmetrical Alkynes[a]

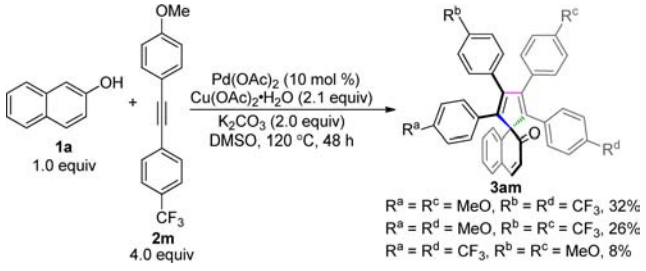


[a]Using 10 mol % of $Pd(OAc)_2$ and 4.0 equiv of **2l**, and Na_2CO_3 (1.0 equiv) to replace K_2CO_3.

with alkynes **2i**-**l** proceeded smoothly to generate the desired **3ai**-**al** in 35−65% yields with moderate to good regioselectivities. Gratifyingly, the head-to-tail product was consistently formed as the major isomer. When the alkyne was substituted with a cyclopropyl group (**2k**), the head-to-tail regioisomer was obtained as the only product. However, this method was not compatible with alkynes possessing an ester, sulfone, oxygen, nitrogen or *tert*-butyl substituent. Notably, this rare regiochemistry has previously been observed in a stoichiometric reaction between a cyclopalladated complex and two equivalents of **2i** to generate a compound bearing the spiro[4.5]deca-1,3,6,9-tetraen-8-one skeleton with three regioisomers.[18]

To reveal the structural requirements of the unsymmetrical alkynes for regioselective annulation to occur, the reaction of naphthol **1a** with alkyne **2m** that bears two sterically similar but electronically differential substituents was conducted (Scheme 4). This reaction led to a regioisomeric mixture of **3am** (4:3:1) in

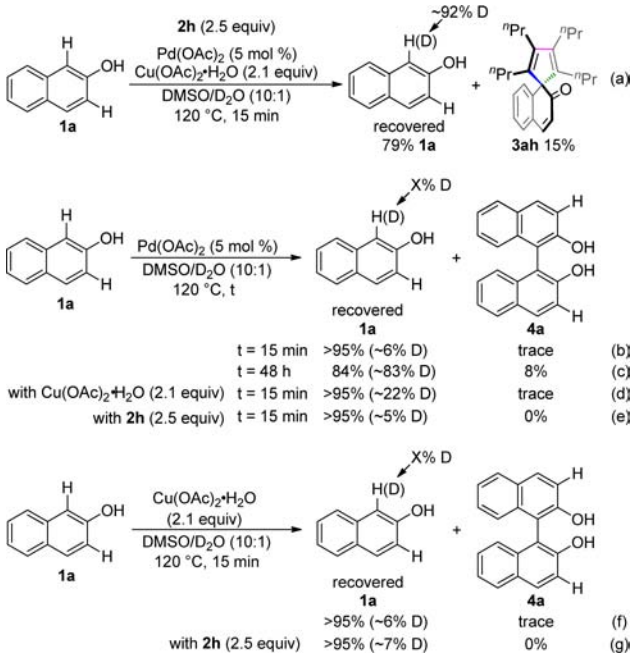
Scheme 4. Reaction Behavior of Alkyne 2m



favor of the head-to-tail and head-to-head spiro isomers. These results indicate that the insertion of one alkyne unit was highly regioselective [(32 + 26)% vs 8%], while another one was not very regioselective [(32 + 8)% vs 26%]. Based on literature precedent,[18,19] we speculated that the insertion of the first molecule of alkyne **2m** was under electronic control, with the C−C bond formation occurring preferentially at the electron-rich carbon atom of the alkyne **2m**. Given the fact that the reactions involving alkyl−aryl mixed alkynes (**2i**−**l**) were regioselective (Scheme 3), we assume that steric control most probably accounts for the regioselective insertion of the second molecule of alkyne (**2i**−**l**).

To gain insight into the mechanism, the experiment with D_2O as solvent for the reaction of **1a** with **2h** was first studied (Scheme 5a), and dramatic deuteration (~92% D) was observed on the 1-

Scheme 5. Deuteration Experiments



position of recovered 2-naphthol. This outcome indicated that the scrambling of H/D was fast and reversible under the reaction conditions. Next, a series of control experiments were conducted (Scheme 5b−g). The results suggested that both $Pd(OAc)_2$ and $Cu(OAc)_2$ be able to promote the scrambling of H/D (Scheme 5b and 5f), with their combination showing the superior activity (~22% D) (Scheme 5d). Notably, the anticipated deuteration could be further increased to 83% D with $Pd(OAc)_2$ after 48 h (Scheme 5c). In addition, the suspectable enhancing effect of alkyne **2h** for the cleavage of C−H bond with $Pd(OAc)_2$ or $Cu(OAc)_2$ were not observed (Scheme 5e,g).

On the basis of the above results and literature reports,[2,4,11,13] a plausible mechanism is proposed (Scheme 6, top). We speculate that the catalytic cycle originates from the generation of dearomatized C-bound palladium enolate **6** via tautomerization of phenoxide species **5**. Alkyne coordination followed by carbopalladation then affords a six-membered palladacycle **7**, whereupon base-assisted rearomatization of quinone-ring yields **8**. Next, coordination and subsequent migratory insertion of the second molecule of alkyne **2** provides a strained eight-membered palladacycle **9**, which then undergoes a unique ring contraction process to give the dearomatized intermediate **10**. Finally, reductive elimination takes place to deliver the spirocyclic product **3** and concomitantly regenerates $Pd(OAc)_2$ to complete the cycle. In addition, we assumed that the steric repulsion between R^1 and the naphthyl ring in **8** and **9** played an important role in hampering the reductive elimination to form the unwanted **11**[20] and **12**.

Taking palladium enolate **6** as the key intermediate, a possible pathway for the formation of 1,1-bi-2-naphthol **4a** is also outlined (Scheme 6, bottom). The acetate ligand in **6** is replaced with **1a** to generate **13**, followed by reductive elimination and

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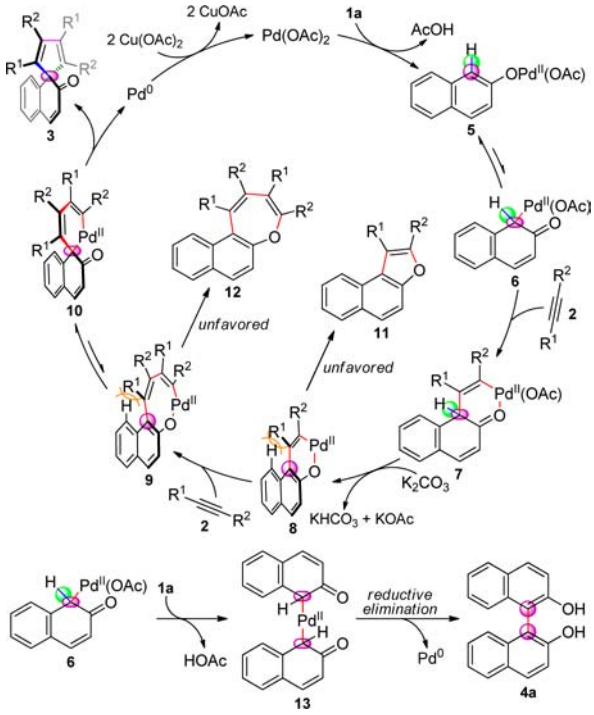
Scheme 6. Proposed Mechanism



tautomerization to produce **4a**. Notably, anticipated palladium black was observed on the reaction vessel.

In summary, we have developed a novel palladium-catalyzed [2 + 2 + 1] oxidative annulation of simple 2-naphthols with alkynes. This reaction was rendered by the joint C−H functionalization and naphthyl ring dearomatization occurring at the 1-position of 2-naphthols. Compared with the previous reports,[11,13] this new method is more economical and allows the one-step synthesis of analogous spirocyclic compounds from readily available starting materials.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

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Notes

The authors declare no competing financial interest.

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(20) A trace amount of **11** was occasionally observed in the crude reaction mixture. Presumably, it was formed via intermediate **8**, which should be generated by the tautomerization of **7**.