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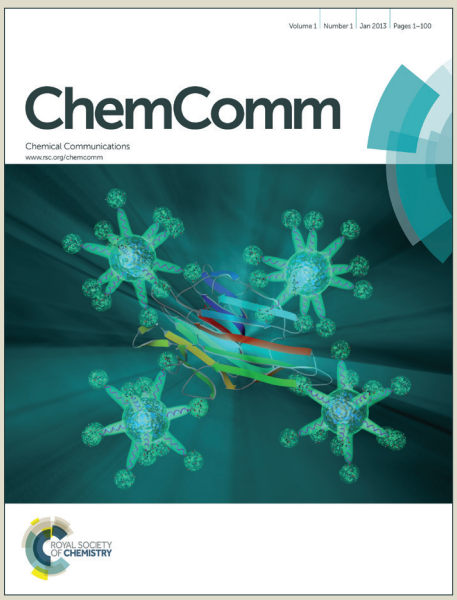

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Pd(0)-catalyzed chemoselective construction of spirocarbocycles via an alkyne insertion/β-naphthol dearomatization cascade†

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Huayu Zheng,‡ Lu Bai,‡ Jingjing Liu, Jiang Nan, Zhijun Zuo, Liu Yang, Yaoyu Wang, Xinjun Luan*

A microwave-assisted Pd(0)-catalyzed alkyne migratory insertion/β-naphthol dearomatization cascade process has been accomplished to access a variety of spirocyclic compounds bearing all-carbon quaternary stereogenic centers in high yields with excellent chemoselectivities.

Transition metal-catalyzed annulation of alkynes with readily available coupling partners has proven to be an extremely powerful strategy to access a diverse range of heterocycles and carbocycles.[1] Indeed, a great number of transition-metal-catalyzed transformations employing this approach have enabled highly efficient construction of indoles,[2] pyrroles,[3] benzofurans,[4] isoquinolines,[5] indenes,[6] polycyclic aromatic hydrocarbons,[7] and so on,[8] in a single synthetic operation. In contrast, the development of corresponding processes for the preparation of spirocarbocyclic compounds that are inaccessible by conventional cycloaddition methods has been dramatically limited.[9] In this context, we recently disclosed a Ru(II)-catalyzed oxidative annulation of alkynes with 1-aryl-2-naphthols to generate a new class of spirocyclic molecules bearing the spiro[indene-1,1'-naphthalen] skeleton.[10] Notably, this intriguing structural moiety is often present in natural products and functional materials (Fig. 1).[11]

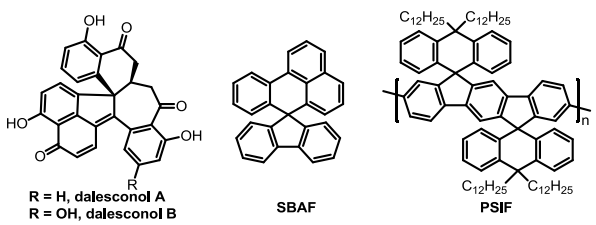
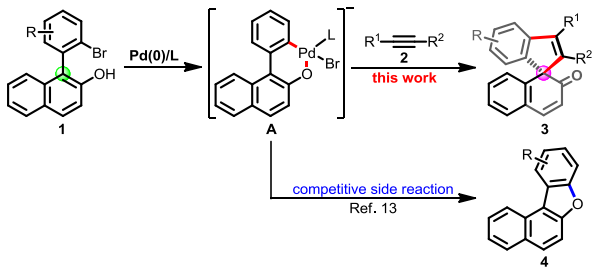


Fig. 1 Selected natural products and functional materials containing spiro[indene-1,1'-naphthalene] core structures.

Herein we describe the development of a non-oxidative version of our Ru(II)-catalyzed reaction, which was conceived to be executed by Pd(0) catalysis. This work was launched by identifying substrate **1** as the coupling partner that might undergo cyclization with alkynes involving **A** as one key intermediate. At the outset, the chemoselectivity for the prospective transformation was quite unpredictable, as one potential side reaction could occur very easily to form dibenzofuran **4**.[12] The challenge, therefore, is to find suitable conditions under which the favorable cyclization between palladacycle **A** and alkyne **2** proceeds much faster than the possible direct reductive elimination of **A**, thus providing spirocyclic **3** as the desired product. Moreover, the synthetic difficulty for accessing the spirocyclic framework in **3** was further increased due to the prerequisite dearomatization of the naphthyl ring. Remarkably, several elegant protocols of Pd(0)-catalyzed intramolecular dearomatization of *para*-substituted phenols or naphthols have been reported during the past few years.[13] However, the dearomatization of *ortho*-substituted phenol or naphthol derivatives under these reaction conditions remains a formidable challenge. To our knowledge, there is only one example of Pd(0)-catalyzed transformation in this arena, which was established by You and coworkers using an asymmetric allylic alkylation strategy.[14] In this paper, we describe the successful execution of our design, which was realized by Pd(0)-catalyzed sequential migratory insertion of the alkyne and dearomatization of α-substituted β-naphthol.

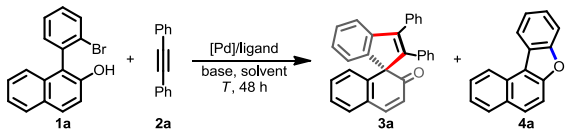


Scheme 1 Proposed Pd(0)-catalyzed one-step construction of spirocarbocycles 3 and potential challenge

The investigation commenced by using 2-naphthol **1a** and 1,2-diphenylethyne **2a** as the model substrates to optimize the reaction conditions. The experimental data are summarized in Table 1. First, with the catalytic system consisting of $Pd(OAc)_2$ (5 mol%), PPh_3 (12 mol%), and K_2CO_3 (1.0 equiv), different solvents were briefly evaluated (entries 1-5). Satisfactorily, the anticipated spirocyclic product **3a** could be obtained in 79% NMR yield in DMF, albeit with the concomitant generation of 14% unwanted byproduct **4a**. To

prevent this side reaction, other palladium sources were examined, but none of them could enhance the chemoselectivity for the desired transformation (entries 6-8). K_2CO_3 was then changed to other bases such as Na_2CO_3, Cs_2CO_3, KOAc, DBU and Et_3N. The catalytic results indicated that inorganic bases (Na_2CO_3, Cs_2CO_3 and KOAc) behaved better than organic ones (DBU and Et_3N), but they couldn't give superior results in comparison to K_2CO_3 (entries 9-13). Subsequently, various phosphine ligands and one NHC ligand were screened with the combination of $Pd(OAc)_2$ (5 mol%) and K_2CO_3 (1.0 equiv.) in DMF at 130 ℃ for 48 h (entries 14-20). Notably, IPr, Xantphos, dppe and dppp favored the formation of the desired product **3a**, while PCy_3, dppf and dppm provided compound **4a** as the major product. Based on these observations, it seemed that both steric and electronic properties of the ligands are critical for achieving the title transformation. Overall, dppp was found to be the better ligand, and was able to prevent the formation of byproduct **4a**, affording compound **3a** in quantitative yield (entry 20). Finally, to avoid the high energy cost, the harsh thermal condition (130 ℃, 48 h) was successfully switched to a microwave irradiation (135 ℃, 15 min), which was then identified as the optimal energy parameter to evaluate the reaction scope (entry 21).

Table 1 Optimization of the reaction conditions[a]



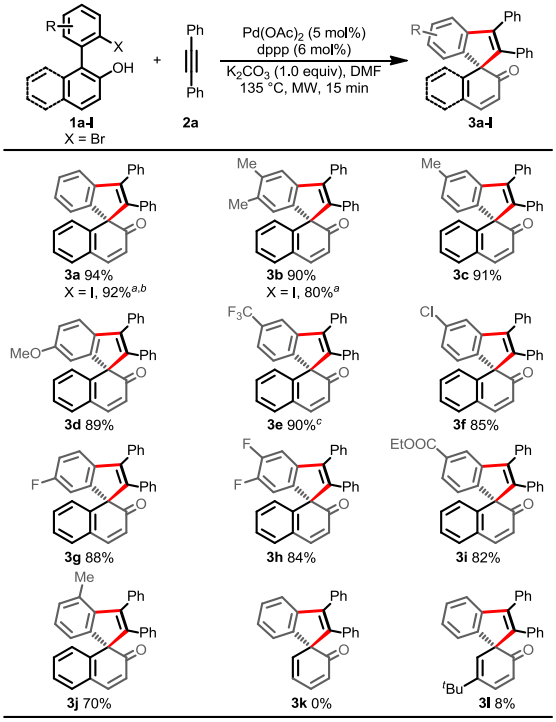
1a 2a 3a 4a

entry	[Pd]	Ligand	base	solvent	T (℃)	conv. (%) (**3a**/**4a**)[b]
1	$Pd(OAc)_2$	PPh_3	K_2CO_3	THF	60	3 (0:3)
2	$Pd(OAc)_2$	PPh_3	K_2CO_3	MeCN	80	5 (0:5)
3	$Pd(OAc)_2$	PPh_3	K_2CO_3	DME	100	19 (13:6)
4	$Pd(OAc)_2$	PPh_3	K_2CO_3	toluene	100	33 (26:7)
5	$Pd(OAc)_2$	PPh_3	K_2CO_3	DMF	130	93 (79:14)
6	$Pd(dba)_2$	PPh_3	K_2CO_3	DMF	130	93 (49:44)
7	$PdCl_2$	PPh_3	K_2CO_3	DMF	130	30 (21:9)
8	$[Pd(allyl)Cl]_2$	PPh_3	K_2CO_3	DMF	130	60 (45:15)
9	$Pd(OAc)_2$	PPh_3	Na_2CO_3	DMF	130	83 (66:17)
10	$Pd(OAc)_2$	PPh_3	Cs_2CO_3	DMF	130	94 (64:30)
11	$Pd(OAc)_2$	PPh_3	KOAc	DMF	130	85 (68:17)
12	$Pd(OAc)_2$	PPh_3	DBU	DMF	130	90 (45:45)
13	$Pd(OAc)_2$	PPh_3	Et_3N	DMF	130	49 (33:16)
14	$Pd(OAc)_2$	PCy_3	K_2CO_3	DMF	130	92 (17:75)
15[c]	$Pd(OAc)_2$	IPr	K_2CO_3	DMF	130	85 (68:17)
16[c]	$Pd(OAc)_2$	xantphos	K_2CO_3	DMF	130	90 (68:22)
17[c]	$Pd(OAc)_2$	dppf	K_2CO_3	DMF	130	85 (29:56)
18[c]	$Pd(OAc)_2$	dppm	K_2CO_3	DMF	130	88 (15:73)
19[c]	$Pd(OAc)_2$	dppe	K_2CO_3	DMF	130	89 (78:11)
20[c]	$Pd(OAc)_2$	dppp	K_2CO_3	DMF	130	99 (99:0)
21[c,d]	$Pd(OAc)_2$	dppp	K_2CO_3	DMF	135	94[e] (97:2)

[a]0.2 mmol of **1a**, 0.3 mmol of **2a**, 5.0 mol% of [Pd], 12.0 mol% of PPh_3, and 0.2 mmol of base. [b]Determined by ^1H NMR analysis. [c]6 mol% of ligand was used to replace PPh_3. [d]Microwave, 15 min. [e]Isolated yield.

Under the optimal reaction conditions, we first examined the reaction scope with regard to the naphthol coupling partner. As shown in Table 2, a variety of naphthol derivatives (**1a-j**) reacted smoothly with **2a** to generate a broad range of spirocyclic compounds **3a-j** in high yields (70-94%) with excellent chemoselectivities. Satisfactorily, various substituents on the 4- or 5-position of the phenyl ring were well tolerated in the reaction, including an electron-neutral group such as a methyl group (**3b-c**), an electron-donating group (EDG) such as a methoxy group (**3d**), and electron-withdrawing groups (EWGs) such as trifluoromethyl (**3e**), chloro (**3f**), fluoro (**3g-h**), and ester (**3i**) groups. Moreover, it should be noted that the chlorine-containing substrate **1f** underwent envisioned annulation without decomposition to afford compound **3f**, in which the variable chlorine group could serve as a highly valuable synthetic handle for further functionalization. Accordingly, the more active aryl iodides often react preferentially in Pd(0)-catalyzed O-arylation of phenol derivatives.[15] Under the original reaction conditions, iodo-substrates **1a'** and **1b'** mainly occurred via an intramolecular cyclization pathway to give dibenzofurans **4a** and **4b** as the major products respectively. To overcome this limitation, one equivalent of $^nBu_4NCl$, which was used in the Larock's protocol,[2b] was quickly recognized as the additive, and the desired products **3a** and **3b** were then obtained in high yields (92% and 80%), which are comparable to the reaction performance of their bromo-counterparts (94% and 90%). In sharp contrast to our prior Ru(II)-catalyzed oxidative approach,[10] this new Pd(0)-catalyzed transformation has enabled a great example for expanding the naphthol scope. When substrate **1j** was used, the synthetically challenging compound **3j**, which was not able to be accessed via Ru(II)-method,[10] was successfully prepared in 70% yield. In the end, the phenol substrates (**1k-l**) were also attempted for the desired transformation, and one (**1k**) was totally ineffective, while another one (**1k**) was able to give an encouraging yield (8%) of the anticipated product **3l**.

Table 2 Survey of the scope of the naphthol coupling partner

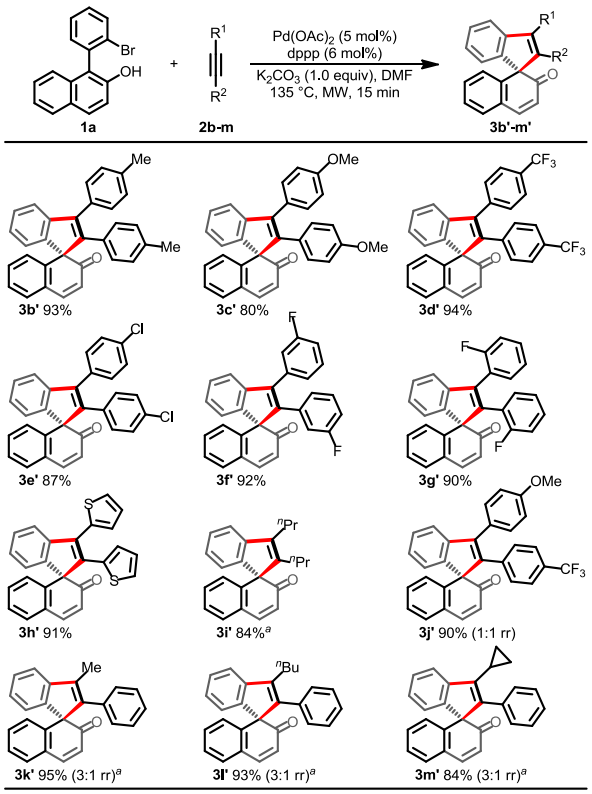


[a]1.0 equiv of $^nBu_4NCl$ was added. [b]2.0 equiv of K_2CO_3 was used. [c]3.0 equiv of **2a** was used.

Next, we evaluated the reaction performance of a variety of alkynes bearing different substituents by using this new protocol. As shown in Table 3, the Pd(0)-catalyzed alkyne insertion/β-naphthol dearomatization tandem process proceeded smoothly with various symmetrical alkynes. Annulation of 2-naphthol **1a** with 4-methylphenyl-substituted alkyne **2b** or electron-rich 4-methoxyphenyl-substituted alkyne **2c** produced the spirocyclic **3b'** and **3c'** in 93% and 80% yields, respectively. Similarly, the electron-

poor alkynes that are substituted with EWGs such as trifluoromethyl (**2d**), chloro (**2e**), and fluoro (**2f** and **2g**) groups at the *p*-, *m*-, or *o*-position of the aromatic ring underwent effective annulations with substrate **1a** (87-94% yields for **3d'-g'**). Notably, the potentially removable chlorine substituent in **2e** remained intact under the Pd(0) catalysis conditions. Moreover, heterocyclic **2h** could adapt to this reaction as well, resulting in **3h'** in 91% yield. Due to the lack of conjugation, the dialkyl-substituted **2i** reacted sluggishly under the optimized conditions. However, the successful preparation of **3i'** in good yield (84%) was simply managed by using three equivalents of **2i**. Meanwhile, several unsymmetrical alkynes **2j-m** were also employed to study the regioselectivity for this new method.[16] The experimental results indicated that the insertion of alkyne **2j** with two sterically similar but electronically differential substituents was not selective, while the reactions involving alkyl-aryl mixed alkynes **2k-m** could be obtained with moderate regioselectivities (3:1) by giving the same major regioisomer as the prior report.[10]

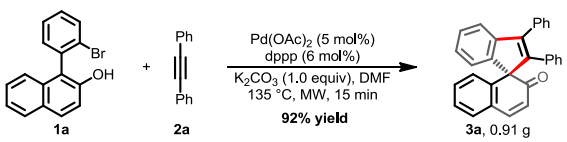
Table 3 Survey of the scope of the alkynes coupling partner



[a]3.0 equiv. of alkyne was used.

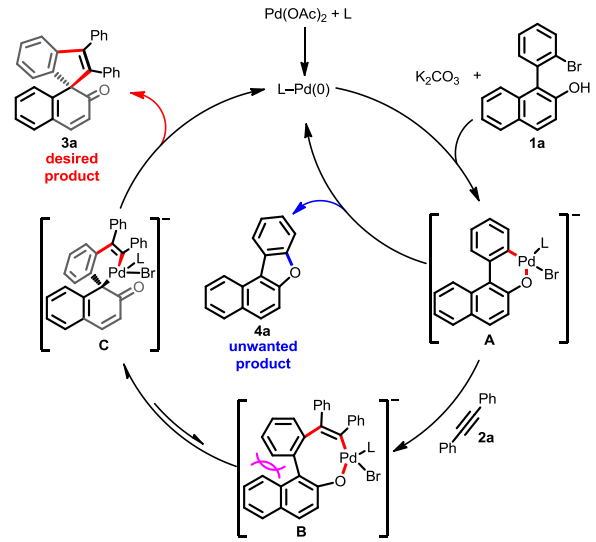
Notably, the above reactions could also work quite well under the thermal conditions (see: Table 1, entry 20), and the experimental results are given in the ESI (Tables S1 and S2).

To evaluate the practicality of this microwave assisted method, a large-scale experiment was conducted with **1a** and **2a**, and the desired product **3a** (0.91 g) was obtained in 92% yield (Scheme 2).



Scheme 2 Gram-scale preparation of **3a**

Based on the catalytic cycles put forth for previous related processes,[2b,6a,17-18] a plausible mechanism was proposed for this unprecedented transformation (Scheme 2). Initial oxidative addition of aryl bromide to zerovalent palladium occurs to afford arylpalladium bromide, followed by deprotonation of the acidic proton of 2-naphthol by potassium carbonate, thus enabling the intramolecular cyclization to access a six-membered palladacycle **A**. Subsequently, coordination and migratory insertion of the alkyne **2a** with intermediate **A** to form an eight-membered palladacycle **B**, which then undergoes a ring contraction to give a spirocyclic intermediate **C** by release the ring strain and steric repulsion of intermediate **B**. Finally, reductive elimination of the spirocyclic intermediate **C** takes place to provide spirocyclic compound **3a** and concomitantly regenerate the Pd(0) catalyst to complete the catalytic cycle. It should be mentioned that the direct reductive elimination of intermediate **A** to generate dibenzofuran **4a**, which is a known pathway in the literature,[13] was also observed during our optimization process. However, careful control of the reaction conditions could prevent its concomitant formation. Additionally, the possible seven-membered oxepine byproduct was never observed in this study, we assumed that the steric repulsion between the phenyl and naphthyl rings of intermediate **B** played an important role on preventing the direct reductive elimination of **B**.[18]



Scheme 3 Proposed mechanism

Conclusions

In summary, we have developed a novel Pd(0)-catalyzed vinylative dearomatization reaction of β-naphthols with internal alkynes to access a class of valuable spirocyclic compounds. This new approach was successfully implemented by avoiding stoichiometric $Cu(OAc)_2$ oxidant, and it represents a highly competitive alternative to the previous Ru(II)-catalyzed oxidative approach. More importantly, this Pd(0)-catalyzed transformation has gained significant progress for expanding the naphthol scope in comparison to the Ru(II)-method.

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Notes and references

Key Laboratory of Synthetic and Natural Functional Molecular Chemistry of the Ministry of Education, College of Chemistry & Materials Science, Northwest University, Xi'an 710069, China.
E-mail: xluan@nwu.edu.cn

† Electronic Supplementary Information (ESI) available: Experimental details and spectroscopic data. See DOI: 10.1039/c000000x/

‡ H. Zheng and L. Bai contributed equally to this work.

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