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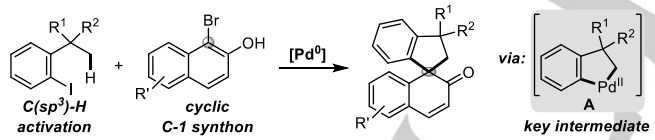
Palladium-Catalyzed Intermolecular [4+1] Spiroannulation via C(sp^3)–H Activation and Naphthol Dearomatization

Bojun Tan,[†] Lu Bai,[†] Pin Ding, Jingjing Liu, Yaoyu Wang, Xinjun Luan*

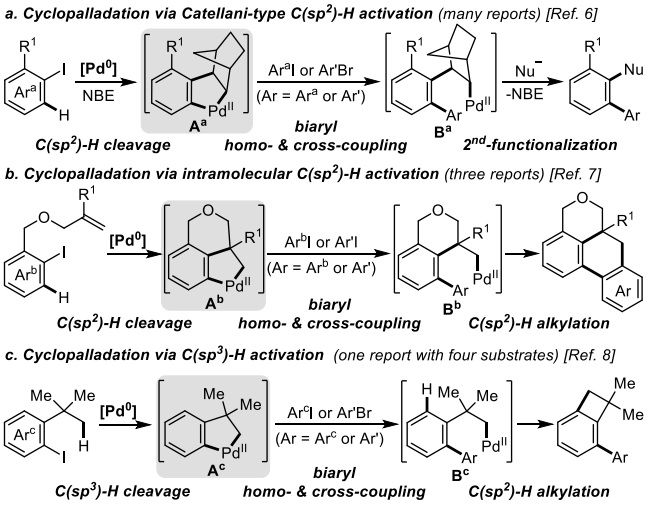
Abstract: *A novel palladium-catalyzed [4+1] spiroannulation was developed by using a C(sp^3)–H activation/naphthol dearomatization approach. This bimolecular domino reaction of two aryl halides was realized through a sequence of cyclometallation-facilitated C(sp^3)–H activation, biaryl cross-coupling, and naphthol dearomatization, thus rendering the rapid assembly of a new class of spirocyclic molecules in good yields with broad functional group tolerance. Preliminary mechanistic studies indicated that C-H cleavage is likely involved in the rate-determining step, and the five-membered palladacycle was identified as the key intermediate for the intermolecular coupling.*

Transition-metal-catalyzed dearomatization is of great interest since it allows to convert readily available aromatic feedstocks into partially saturated three-dimensional architectures.[1] From a synthetic standpoint, a cooperative strategy by combining C–H activation[2] together with arene dearomatization represents a rather economical approach to streamline chemical synthesis by enabling the use of simpler starting materials and offering novel synthetic disconnections. Consequently, several metal-catalyzed transformations within this category were recently developed by us[3] and others[4] through the incorporation of C(sp^2)–H bond activation, affording a plethora of novel molecular frameworks. In sharp contrast, the development of such processes involving the functionalization of alkane C(sp^3)–H bond, which is lack of direct interaction from the metal center,[5] is still a daunting challenge. In this context, we wish to report an unprecedented example of palladium-catalyzed [4+1] spiroannulation through a C(sp^3)–H activation/naphthol dearomatization domino process (Scheme 1).



Scheme 1. C(sp^3)–H Activation/arene dearomatization reaction (**this work**).

The key to success of this proposal is the involvement of an electron-rich palladacyclic intermediate **A** for enabling the cross-coupling of two electrophilic aryl halide components. In fact, this reaction design was inspired by the tremendous achievements in the area of catalytic generation of C(sp^2)–Pd^{II}–C(sp^3)-involved palladacycles (**A^a**-**A^c**) from an aryl iodide via C-H cleavage, and subsequent homo- or cross-couplings with another aryl halide (Ar^a-Ar^c or Ar'X) to generate biaryl-containing species (**B^a**-**B^c**) for further elaboration (Scheme 2).[6-8] Noteworthy, Pd/norbornene (NBE) catalysis, namely the Catellani reaction, has proven to be a powerful approach for the rapid assembly of a large number of biaryl-embraced molecules through the bisfunctionalization of aryl iodides, by taking advantage of the unique reactivity of aryl-NBE-Pd^{II} intermediate **A^a** (Scheme 2a).[6] Very recently, Lautens first illustrated that palladacycle **A^b**, which was formed through intramolecular Heck-cyclization/C(sp^2)–H activation, was able to couple with aryl iodides to furnish a variety of polycyclic products (Scheme 2b).[7,9] In contrast, catalytically bimolecular coupling of aryl halides facilitated by palladacycle **A^c** has been dramatically limited, although a number of elegant intra- and intermolecular processes have been realized on the basis of cyclopalladation of 2-*tert*-butyl aryl halides through C(sp^3)–H cleavage.[10] To our knowledge, all the known examples were disclosed in the seminal report by Dyker,[8] which are one homo-coupling with 2-iodo-*tert*-butylbenzene and three cross-couplings with electron-rich aryl bromides, affording *ortho*-arylated benzocyclobutenes in acceptable yields (Scheme 2c). In connection with our persistent interest in the development of transition-metal-catalyzed dearomatization reactions,[3,11] we postulated that using bromophenol derivatives, which possess great potential to serve as one carbon synthons via biaryl cross-coupling[12] and subsequent dearomatization,[3d] to react with in situ generated palladacycle **A^c** would lead to an unique [4+1] spiroannulation. The main issue for such a process is if σ-alkyl-Pd^{II} species **B^c** could preferentially undergo alkylative dearomatization, rather than giving rise to benzocyclobutene via C(sp^2)–H alkylation. Here, we present our efforts on this subject.



Scheme 2. Catalytic processes involving electron-rich palladacycles.

Stimulated by the aforementioned challenges, we initiated the studies by investigating the reaction of **1a** with **2a** (Table 1).

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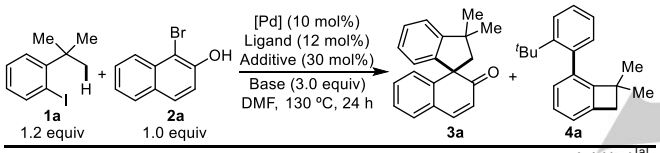
Gratifyingly, the anticipated [4+1] spiroannulation was realized by a catalytic system consisting of $Pd(OAc)_2$, PPh_3, CsOPiv, and Cs_2CO_3 in DMF at 130 °C, affording product **3a** in 34% yield (entry 1). Its structure was confirmed by X-ray crystallography.[13] Further studies revealed that the ligands had a critical impact on both reactivity and selectivity (entries 2-8). Use of more electron-rich monophosphines led to the formation of **3a** in higher yields (entries 2-3), but the efficiency was eroded by the concomitant generation of **4a** through homo-coupling of **1a**.[8] Bisphosphine ligands were applicable for this process, but no superior results were given (entries 6-8). Overall, electron-deficient P(*p*-F-C_6H_4)$_3$ turned out to be the better ligand (entry 5). Moreover, attempts by using other palladium sources and bases didn't improve the reaction (entries 9-13). Much to our delight, the use of organic phosphoric acids, which were identified as the enhancement additives for Pd-catalyzed C(sp^3)–H alkylation processes,[14] was able to greatly promote the reaction (entries 14-15). Replacing CsOPiv with $(BnO)_2PO_2H$, the yield of **3a** was increased to 83%. Additionally, it should be noted that the run with bromo-substrate **1a'** proceeded properly to give **3a** in 53% yield (entry 16).

Table 1. Optimization of the reaction conditions.

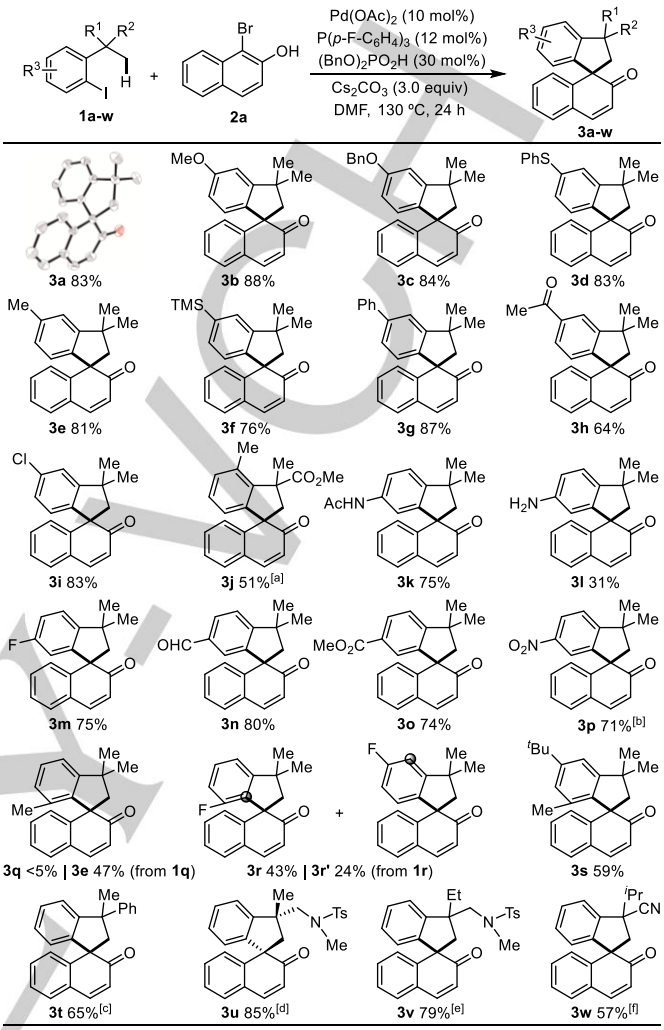


Entry	[Pd]	Ligand	Base	Additive	Yield(%)[a] 3a	4a
1	$Pd(OAc)_2$	PPh_3	Cs_2CO_3	CsOPiv	34	5
2	$Pd(OAc)_2$	PCy_3	Cs_2CO_3	CsOPiv	50	18
3	$Pd(OAc)_2$	P(*p*-Anisyl)$_3$	Cs_2CO_3	CsOPiv	42	21
4	$Pd(OAc)_2$	P(*o*-Tol)$_3$	Cs_2CO_3	CsOPiv	23	2
5	$Pd(OAc)_2$	P(*p*-F-C_6H_4)$_3$	Cs_2CO_3	CsOPiv	63	4
6	$Pd(OAc)_2$	BINAP	Cs_2CO_3	CsOPiv	49	11
7	$Pd(OAc)_2$	DPPM	Cs_2CO_3	CsOPiv	31	3
8	$Pd(OAc)_2$	DPPE	Cs_2CO_3	CsOPiv	29	5
9	$PdCl_2$	P(*p*-F-C_6H_4)$_3$	Cs_2CO_3	CsOPiv	27	15
10	$Pd_2(dba)_3$	P(*p*-F-C_6H_4)$_3$	Cs_2CO_3	CsOPiv	9	0
11	$[Pd(allyl)Cl]_2$	P(*p*-F-C_6H_4)$_3$	Cs_2CO_3	CsOPiv	31	9
12	$Pd(OAc)_2$	P(*p*-F-C_6H_4)$_3$	Na_2CO_3	CsOPiv	0	2
13	$Pd(OAc)_2$	P(*p*-F-C_6H_4)$_3$	K_2CO_3	CsOPiv	12	10
14	$Pd(OAc)_2$	P(*p*-F-C_6H_4)$_3$	Cs_2CO_3	BINA-PO_2H	72	0
15	$Pd(OAc)_2$	P(*p*-F-C_6H_4)$_3$	Cs_2CO_3	$(BnO)_2PO_2H$	83	0
16[b]	$Pd(OAc)_2$	P(*p*-F-C_6H_4)$_3$	Cs_2CO_3	$(BnO)_2PO_2H$	53	0

[a] Isolated yields. [b] **1a** was replaced by 1-bromo-2-(*tert*-butyl)benzene (**1a'**). BINA-PO_2H = 1,1'-Binaphthyl-2,2'-diyl hydrogenphosphate.

With the optimized reaction conditions in hand, the substrate scope was first explored by reacting an important number of aryl iodides (**1a-w**) with **2a**, and the results proved that this coupling partner could be varied on both the aromatic ring and the alkyl moiety, thus providing a new class of spirocyclic molecules (**3a-w**) in 31-88% yields (Table 2). With regards to the aryl ring, it can be substituted on its different positions with a wide spectrum of functional groups including electron-donating or electron-neutral methoxy (**3b**), benzyloxy (**3c**), phenylthio (**3d**), methyl (**3e**,**j**,**q**,**s**), trimethylsilyl (**3f**), acetyl amino (**3k**) and free amino (**3l)** groups, and electron-withdrawing phenyl (**3g**), acetyl (**3h**), chloro (**3i**), fluoro (**3m**,**r**,**r'**), formyl (**3n**), ester (**3o**) and nitro (**3p**) groups.

Table 2. Scope with respect to aryl iodides.



[a] dr = 1.7:1. [b] $(BnO)_2PO_2H$ was replaced by BINA-PO_2H, and DMF was replaced by toluene/DMF (4:1). [c] dr = 1:1. [d] dr = 1.4:1. [e] dr = 1.3:1. [f] dr = 3.7:1.

Notably, strong-coordinating free amine didn't hamper the [4+1] spiroannulation, albeit in lower yield of **3l**. More interestingly, the reaction with a sterically hindered substrate **1q** gave rise to **3e** in 47% yield, while the anticipated **3q** was nearly not formed. This abnormal phenomenon, which presumably arises from palladium migration through palladacycle **A** and followed by activating the C(sp^2)−H bond *ortho* to the *tert*-butyl group, is quite similar to the previous studies.[10c-d,f-g] Replacing the methyl group of **1q** with a fluoro substituent (**1r**) allowed the generation of envisioned **3r** in 43% yield, along with the formation of 24% of migration product **3r'**. The large reaction difference between **1q** and **1r** indicated that palladium migration was mainly affected by steric hindrance. To suppress the formation of such an "abnormal" regioisomer by preventing the C(sp^2)−H activation step, substrate **1s** containing an additional *tert*-butyl group was synthesized. As expected, the C(sp^3)−H/C(sp^2)−H bonds activation/naphthol dearomatization process was completely shut down, and structurally congested **3s** was obtained as the only product through an extremely challenging step of tetra-*ortho*-substituted biaryl cross-coupling.

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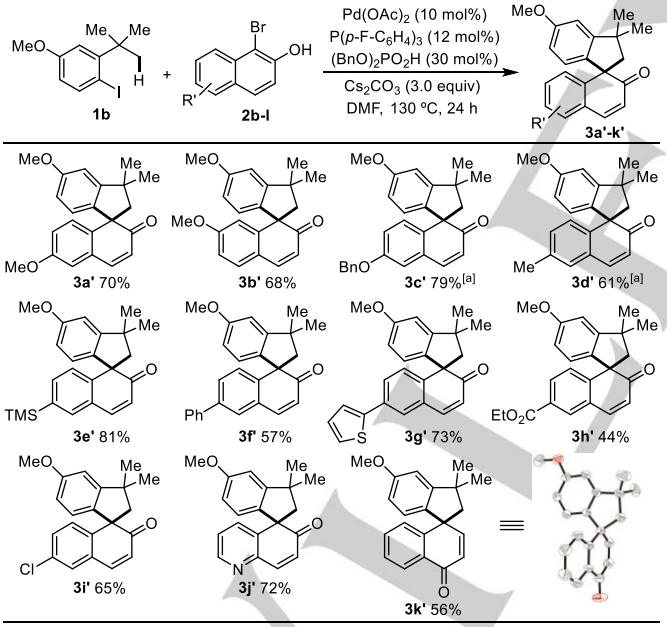
In comparison to these results, it is notable that the use of substrates (**1b-i**) bearing a *meta*-substituent to the *tert*-butyl group all delivered the anticipated products, with the palladium-migration induced regioisomers being not observed or formed at neglectable amounts. Finally, it should be mentioned that alkyl moieties (**1j,t-w**) other than *tert*-butyl group were also tolerable, with the targeted C(sp^3)−H bond functionalization all occurred at the methyl group, affording the desired products **3j** and **3t-w** in 51-85% yields with 1:1 to 3.7:1 diastereomeric ratios.

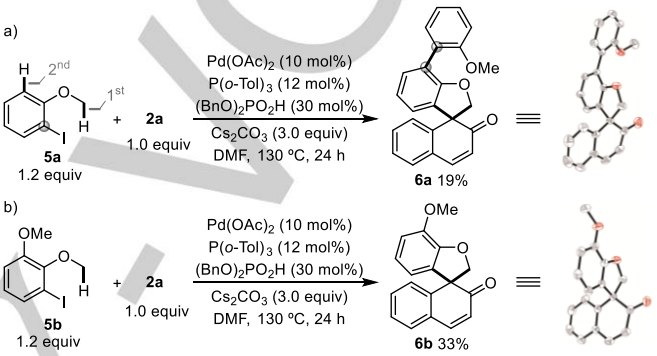
Next, we continued to survey the reaction scope with respect to the 1-bromo-2-naphthols for the [4+1] spiroannulation process (Table 3). Satisfactorily, the reactions of **2b-k** with **1b** proceeded smoothly to give their corresponding products **3a'-j'** in 44-81% yields. Notably, the naphthalene ring could be substituted with electron-donating groups such as methoxy (**3a'-b'**) and benzyloxy (**3c'**) groups, methyl (**3d'**), trimethylsilyl (**3e'**), phenyl (**3f'**) and 2-thienyl (**3g'**) groups, and electron-withdrawing groups such as ester (**3h'**) and chloro (**3i'**) groups. Notably, heterocyclic 5-bromoquinolin-6-ol (**2k**) was also tolerated, providing the desired product **3j'** in 72% yield. In particularly, it is remarkable that 4-bromonaphthalen-1-ol (**2l**) could undergo [4+1] spiroannulation with **1b** under the identical reaction conditions, leading to the formation of compound **3k'** with a different spirocyclic skeleton, which was unambiguously elucidated by X-ray crystallography.[13]

Table 3. Scope with respect to 1-bromo-2-naphthols.



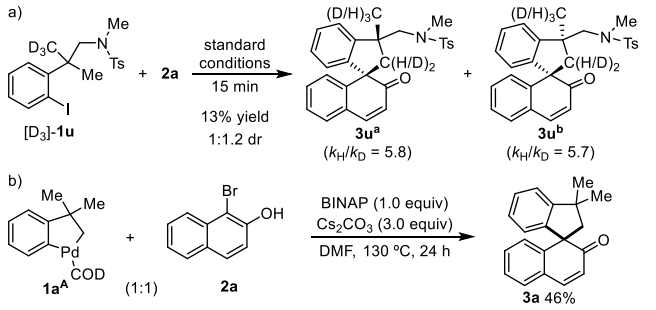
[a] P(*p*-F-C_6H_4)$_3$ was replaced by PPh_3.

Inspired by Dyker's earlier reports on the Pd(0)-catalyzed homo-coupling of 2-iodoanisoles through C-H bond activation of methoxy group,[15] we speculated that the simple 2-iodoanisoles might be able to serve as a four-atom synthon for the titled [4+1] spiroannulation. Compared to the above studies with 2-iodo-*tert*-butylbenzenes, the use of 2-iodoanisoles would be more difficult for the C-H activation step, since the swinging methoxy group is less approachable for the palladium center. Much to our delight, under similar reaction conditions, an interesting spiroannulation between 2-iodoanisole **5a** and **2a** took place to give compound **6a**[13] in 19% yield (Scheme 3a). Accordingly, such process was realized through homo-coupling of aryl iodide **5a** and followed by subsequent cross-coupling with aryl bromide **2a**, via a sequence of C(sp^3)–H activation, biaryl homo-coupling, C(sp^2)–H activation, biaryl cross-coupling, and naphthol dearomatization. Noteworthy, the use of **5b**, which contains an adjacent substituent to the methoxy group, allowed the direct bimolecular annulation with **2a** to afford anticipated **6b**[13] in 33% yield. It needs to mention that the limited efficiency of these two reactions was caused by several rather competitive homo-couplings of 2-iodoanisoles.[15]



Scheme 3. Preliminary studies based on C-H activation of methoxy group.

To gain insights into the reaction mechanism, several control experiments were carried out (Scheme 4). An intramolecular competition reaction with dimethylated [D_3]-**1u**, bearing one fully deuterated methyl group, demonstrated kinetic isotope effects for the formation of both two diastereomers (**3u^a** and **3u^b**)[13] (k_H/k_D = 5.8 & 5.7; Scheme 3a), suggesting that primary methyl C(sp^3)−H bond cleavage was most likely involved in the rate-determining step. Next, reacting the palladacyle **1a^A**, which was prepared by Cámpora's method,[16] with an equal molar amounts of BINAP[17] and **2a**, gave rise to **3a** in 46% yield (Scheme 3b), thus giving strong evidence for supporting an electron-rich palladacycle-involved mechanism for the titled transformation.



Scheme 4. Mechanistic studies.

In conclusion, we have developed an unprecedented Pd(0)-catalyzed [4+1] spiroannulation reaction, wherein two distinct aryl halides were used to construct novel spirocyclic scaffolds through a C(sp^3)−H activation/naphthol dearomatization cascade.

Remarkably, this new process, relying on the unique reactivity of electron-rich palladacycles, was featured by the cross-coupling of two different types of aryl halides, and represents a rare example of intermolecular [4+1] reactions for the rapid assembly of spirocyclic molecules from easily available feedstock. Moreover, we anticipate that this strategy will find broad utility with simple bromophenol substrates and be performed in an enantioselective manner in the future.

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Keywords: C-H activation • dearomatization • palladacycle • domino reaction • palladium

[1] For reviews, see: a) E. P. Kündig, A. Rape, *Top. Organomet. Chem.* **2004**, *7*, 95; b) S. P. Roche, J. Porco Jr, *Angew. Chem. Int. Ed.* **2011**, *50*, 4068; *Angew. Chem*. **2011**, *123*, 4154; c) C. Zhuo, W. Zhang, S.-L. You, *Angew. Chem. Int. Ed.* **2012**, *51,* 12662; *Angew. Chem.* **2012**, *124*, 12834; d) C. Zhuo, C. Zheng, S.-L. You, *Acc. Chem. Res.* **2014**, *47*, 2558; e) W. Wu, L. Zhang, S.-L. You, *Chem. Soc. Rev.* **2016**, *45*, 1570; f) C. Zheng, S.-L. You, *Chem* **2016**, *1*, 830; f) T. Nemoto, Y. Hamada, *Synlett.* **2016**, *27*, 2301; g) O'Brien, R. J. K. Taylor, W. P. Unsworth, *Chem. Eur. J.* **2016**, *22*, 2856; h) H. Wang, X. Luan, *Org. Biomol. Chem.* **2016**, *14*, 9451; For pioneering examples, see: i) M. Bao, H. Nakamura, Y. Yamamoto, *J. Am. Chem. Soc.* **2001**, *123*, 759; j) B. M. Trost, J. Quancard, *J. Am. Chem. Soc.* **2006**, *128*, 6314; k) J. García-Fortanet, F. Kessler, S. L. Buchwald, *J. Am. Chem. Soc*. **2009**, *131*, 6676; m) Q. Wu, H. He, W. Liu, S.-L. You, *J. Am. Chem. Soc.* **2010**, *132*, 11418; n) T. Nemoto, Y. Ishige, M. Yoshida, Y. Kohno, Y. Hamada, *Org. Lett*. **2010**, *12*, 5020; o) S. Rousseaux, J. García-Fortanet, M. A. Del Aguila Sanchez, S. L. Buchwald, *J. Am. Chem. Soc*. **2011**, *133*, 9282; p) Q. Wu, W. Liu, C. Zhuo, Z. Rong, K. Ye, S.-L. You, *Angew. Chem. Int. Ed*. **2011**, *50*, 4455; *Angew. Chem.* **2011**, *123*, 4547.

[2] For a book, see: a) *C-H Activation* (Eds.: J.-Q. Yu, Z. Shi), Springer, Heidelberg, **2010**; For reviews, see: b) T. W. Lyons, M. S. Sanford, *Chem. Rev.* **2010**, *110*, 1147; c) J. Wencel-Delord, T. Dröge, F. Liu, F. Glorius, *Chem. Soc. Rev.* **2011**, *40*, 4740; d) K. M. Engle, T.-S. Mei, M. Wasa, J.-Q. Yu, *Acc. Chem. Res.* **2012**, *45*, 788; e) L. A. Ackermann, *Acc. Chem. Res.* **2014**, *47*, 281; f) G. Song, X. Li, *Acc. Chem. Res.* **2015**, *48*, 1007; g) C. Liu, J. Yuan, M. Gao, S. Tang, W. Li, R. Shi, A. Lei, *Chem. Rev.* **2015**, *115*, 12138; h) O. Daugulis, J. Roane, L. D. Tran, *Acc. Chem. Res.* **2015**, *48*, 1053; i) B. Ye, N. Cramer, *Acc. Chem. Res.* **2015**, 48, 1308; j) Z. Dong, Z. Ren, S. J. Thompson, X. Xu, G. Dong, *Chem. Rev.* **2017**, *117*, 9333.

[3] a) J. Nan, Z. Zuo, L. Luo, L. Bai, H. Zheng, Y. Yuan, J. Liu, X. Luan, Y. Wang, *J. Am. Chem. Soc*. **2013**, *135*, 17306; b) S. Gu, L. Luo, J. Liu, L. Bai, H. Zheng, Y. Wang, X. Luan, *Org. Lett.* **2014**, *16*, 6132; c) Z. Zuo, X. Yang, J. Liu, J. Nan, L. Bai, Y. Wang, X. Luan, *J. Org. Chem.* **2015**, *80*, 3349; d) Z. Zuo, H. Wang, L. Fan, J. Liu, Y. Wang, X. Luan, *Angew. Chem.* **2017**, *129*, 2811; *Angew. Chem. Int. Ed.* **2017**, *56*, 2767; e) L. Fan, J. Liu, L. Bai, Y. Wang, X. Luan, *Angew. Chem. Int. Ed.* **2017**, *56*, 14257; *Angew. Chem.* **2017**, *129*, 14445; f) L. Bai, J. Liu, W. Hu, K. Li, Y. Wang, X. Luan, *Angew. Chem. Int. Ed.* **2018**, *57*, 5151; *Angew. Chem.* **2018**, *130*, 5245.

[4] For examples via C(sp^2)–H cleavage, see: a) A. Seoane, N. Casanova, N. Quiñones, J. L. Mascareñas, M. Gulías, *J. Am. Chem. Soc*. **2014**, *136*, 7607; b) S. Kujawa, D. Best, D. J. Burns, H. W. Lam, *Chem. Eur. J.* **2014**, *20*, 8599; c) J. Zheng, S.-B. Wang, C. Zheng, S.-L. You, *J. Am. Chem. Soc.* **2015**, *137*, 4880; d) X. Wang, Y. Li, T. Knecht, C. G. Daniliuc, K. N. Houk, F. Glorius, *Angew. Chem. Int. Ed.* **2018**, *57*, 5520; *Angew. Chem.* **2018**, *130*, 5618; For examples with acidic C(sp^3)–H bond cleavage, see: e) H. Zhang, R. Hu, N. Liu, S. Li, S. Yang, *Org. Lett.* **2016**, *18*, 28; f) S. Gao, Z. Wu, X. Fang, A. Lin, H. Yao, *Org. Lett.* **2016**, *18*, 3906.

[5] For reviews, see: a) R. Jazzar, J. Hitce, A. Renaudat, J. Sofack-Kreutzer, O. Baudoin, *Chem. Eur. J.* **2010**, *16*, 2654; b) H. Li, B.-J. Li, Z.-J. Shi, *Catal. Sci. Technol.* **2011**, *1*, 191; c) O. Baudoin, *Chem. Soc. Rev.* **2011**, *40*, 4902; d) Z. Huang, H. N. Lim, F. Mo, M. C. Young, G. Dong, *Chem. Soc. Rev.* **2015**, *44*, 7764; d) G. He, B. Wang, W. A. Nack, G. Chen, *Acc. Chem. Res.* **2016**, *49*, 635; e) J. H, M. Was, K. S. L. Chan, Q. Shao, J.-Q. Yu, *Chem. Rev*. **2017**, *117*, 8754; f) O. Baudoin, *Acc. Chem. Res.* **2017**, *50*, 1114; g) J. C. K. Chu, T. Rovis, *Angew. Chem. Int. Ed.* **2018**, *57*, 62; *Angew. Chem.* **2018**, *130*, 64.

[6] For reviews, see: a) M. Catellani, *Top. Organomet. Chem.* **2005**, *14*, 21; b) M. Catellani, E. Motti, N. Della Ca', *Acc. Chem. Res.* **2008**, *41,* 1512; c) A. Martins, B. Mariampillai, M. Lautens, *Top. Curr. Chem.* **2010**, *292*, 1; d) J. Ye, M. Lautens, *Nat. Chem.* **2015**, *7*, 863; e) N. Della Ca', M. Fontana, E. Motti, M. Catellani, *Acc. Chem. Res.* **2016**, *49,* 1389.

[7] a) M. Sickert, H. Weinstabl, B. Peters, X. Hou, M. Lautens, *Angew. Chem. Int. Ed*. **2014**, *53*, 5147; *Angew. Chem.* **2014**, *126*, 5247; b) H. He, W. Wang, X. Yu, J. Huang, L. Jian, H. Fu, X. Zheng, H. Chen, R. Li, *Eur. J. Org. Chem.* **2016**, 5616; c) X. Luo, Y. Xu, G. Xiao, W. Liu, C. Qian, G. Deng, J. Song, Y. Liang, C. Yang, *Org. Lett*. **2018**, *20*, 2997.

[8] G. Dyker, *Angew. Chem. Int. Ed. Engl*. **1994**, *33*, 103; *Angew. Chem.* **1994**, *106*, 117.

[9] For related examples, see: a) Q. Huang, A. Fazio, G. Dai, M. Campo, R. C. Larock, *J. Am. Chem. Soc.* **2004**, *126*, 7460; b) T. Piou, L.Neuville, J. Zhu, *Angew. Chem. Int. Ed*. **2012**, *51*, 11561; *Angew. Chem.* **2012**, *124*, 11729; c) T. Piou, A. Bunescu, Q. Wang, L.Neuville, J. Zhu, *Angew. Chem. Int. Ed*. **2013**, *52*, 12385; *Angew. Chem.* **2013**, *125*, 12611.

[10] a) O. Baudoin, A. Herrbach, F. Guéritte, *Angew. Chem. Int. Ed.* **2003**, *42*, 5736; *Angew. Chem.* **2003**, *115*, 5914; b) T. E. Barder, S. D. Walker, J. R. Martinelli, S. L. Buchwald, *J. Am. Chem. Soc.* **2005**, *127*, 4685; c) M. Chaumontet, R. Piccardi, N. Audic, J. Hitce, J.-L. Peglion, E. Clot, O. Baudoin, *J. Am. Chem. Soc.* **2008**, *130*, 15157; d) S. Rousseaux, M. Davi, J. Sofack-Kreutzer, C. Pierre, C. E. Kefalidis, E. Clot, K. Fagnou, O. Baudoin, *J. Am. Chem. Soc.* **2010**, *132*, 10706; e) Á. Gutiérrez-Bonet, F. Juliá-Hernández, B. de Luis, R. Martin, *J. Am. Chem. Soc.* **2016**, *138*, 6384; f) Z. Wu, D. Ma, B. Zhou, X. Ji, X. Ma, X. Wang, Y. Zhang, *Angew. Chem. Int. Ed*. **2017**, *56*, 12288; *Angew. Chem.* **2017**, *129*, 12456; g) A. Lu, X. Ji, B. Zhou, Z. Wu, Y. Zhang, *Angew. Chem. Int. Ed*. **2018**, *57*, 3233; *Angew. Chem.* **2018**, *130*, 3287; h) J. Yan, H. Li, X. Liu, J. Shi, X. Wang, Z.-J. Shi, *Angew. Chem. Int. Ed.* **2014**, *53*, 4945; *Angew. Chem.* **2014**, *126*, 5045.

[11] a) L. Yang, H. Zheng, L. Luo, J. Nan, J. Liu, Y. Wang, X. Luan, *J. Am. Chem. Soc*. **2015**, *137*, 4876; b) L. Bai, Y. Yuan, J. Liu, J. Wu, L. Han, H. Wang, Y. Wang, X. Luan, *Angew. Chem. Int. Ed.* **2016**, *55*, 6946; *Angew. Chem.* **2016**, *128*, 7060.

[12] E. Motti, F. Faccini, I. Ferrari, M. Catellani, R. Ferraccioli, *Org. Lett.* **2006**, *8*, 3967.

[13] CCDC 1878029 (**3a**), 1878030 (**3k'**), 1878031 (**6a**), 1878033 (**6b**), 1878034 (**3u**[a]) and 1878035 (**3u**[b]) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

[14] a) S. Zhang, G. He, W. A. Nack, Y. Zhao, Q. Li, G. Chen, *J. Am. Chem. Soc.* **2013**, *135*, 2124; b) S. Zhang, Q. Li, G. He, W. A. Nack, G. Chen, *J. Am. Chem. Soc.* **2015**, *137*, 531.

[15] a) G. Dyker, *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1023. b) G. Dyker, *Chem. Ber.* **1994**, *127*, 739.

[16] J. Cámpora, J. A. López, P. Palma, D. del Río, E. Carmona, *Inorg. Chem.* **2001**, *40*, 4116.

[17] BINAP gave higher yield for the formation of **3a**.

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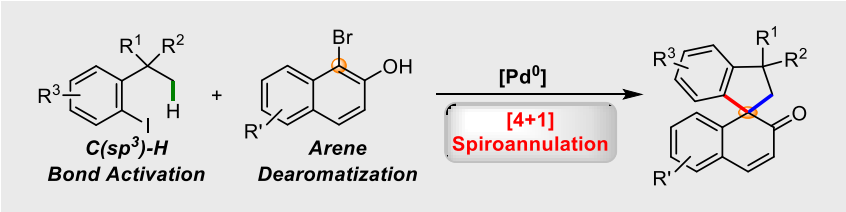

An unprecedented palladium-catalyzed [4+1] spiroannulation of two types of aryl halides has been developed for the rapid construction of a new class of spirocyclic frameworks. This intermolecular domino process was realized through a sequence of C(sp^3)-H cleavage, unsymmetrical biaryl coupling, and naphthol dearomatization.

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