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A Chemo- and Regioselective Pd(0)-Catalyzed Three-Component Spiroannulation

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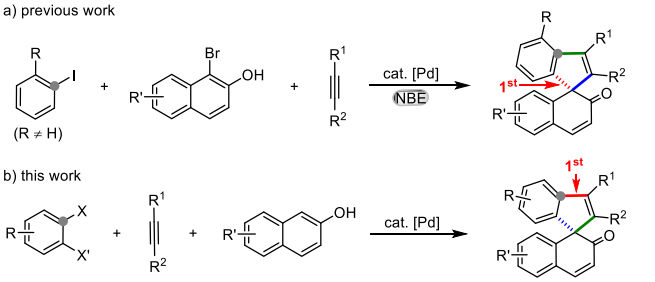
A chemo- and regioselective Pd(0)-catalyzed spiroannulation has been successfully developed. The key feature of this method is the use of readily available 1,2-dihaloarenes, alkynes and 2-naphthols for the rapid assembly of spirocarbocyclic molecules. Mechanistic studies revealed that this domino reaction proceeded through a cascade of oxidative addition to Pd(0), alkyne migratory insertion, and 2-naphthol-facilitated dearomatizing [4+1] spiroannulation.

Spirocyclic architectures containing an all-carbon quaternary center are the structural cores for a large number of functional molecules that exhibit remarkable biological or photophysical properties.[1-2] As a result, the development of new and efficient methodologies for their rapid assemblies has evoked growing interest to synthetic chemists.[3] In the past decade, transition metal-catalyzed dearomatization of phenolic derivatives has emerged as a useful approach for making spirocarbocycles.[4] It is notable that most of pioneering examples were achieved by intramolecular design,[5-6] while synthetic efficiency was largely eroded by the fact that a rather complex substrate, being often obtained by multi-step syntheses, could only lead to a single spirocyclic product. From the viewpoints of atom- and step-economy, it is highly desirable to develop intermolecular protocols for the rapid assembly of diversified spirocycles by employing different types of simple starting materials.

Clearly, one major challenge for promoting intermolecular processes via the involvement of phenol dearomatization is to control the chemoselectivity by avoiding conventional reaction pathways.[7] Therefore, two-component reactions, which might cause fewer byproducts, have been first studied. In 2013, we reported an unprecedented example of Ru(II)-catalyzed [3+2] spiroannulation of phenol-based biaryls with alkynes by using a C-H activation/dearomatization strategy.[8] Later on, it was found that such transformation could be promoted by Rh(III)- and Pd(II)-catalysis.[9-10] To further simplify the phenolic partner,



Scheme 1. Development of Three-component Dearomatizing [2+2+1] Spiroannulations.

[2+2+1] spiroannulations of 2-naphthols (or halophenols) with two equivalent of alkynes were developed by Pd(II)- and Pd(0)-catalysis, respectively.[11] By contrast, only a single example of three-component reaction, which is [2+2+1] spiroannulation of *ortho*-substituted aryl iodide, 1-bromo-2-naphthol and alkyne, was rendered by using Pd(0)/norbornene cooperative catalysis (Scheme 1a).[12] In this context, we herein disclose a new three-component reaction, which uses diverse dihaloarenes, alkynes and 2-naphthols for the rapid assembly of a wider spectrum of spirocarbocycles,[13] by simpler Pd(0)-catalysis (Scheme 1b).

Inspired by the studies of Pd(0)-catalyzed reactions with 1,2-dihaloarenes,[14] we tested the feasibility of making spirocycles with 1-bromo-2-iodobenzene (**1a**), 1,2-diphenylethyne (**2a**) and 2-naphthol (**3a**) (Table 1). Gratifyingly, it was found that an attractive [2+2+1] spiroannulation took place efficiently to give product **4a** in 90% yield with a combination of $Pd(OAc)_2$ (5.0 mol%), dppp (6.0 mol%), and K_3PO_4 (2.0 equiv.) in 1,4-dioxane at 130 °C for 16 h (entry 1). Control experiments revealed that other palladium sources like $Pd_2(dba)_3$ and $[Pd(allyl)Cl]_2$ didn't show comparable results as $Pd(OAc)_2$ (entries 2-3). Further studies by replacing the ligand with PPh_3, dppe and dppb led to decrement for the reaction efficiency (entries 4-6). Notably, the reaction was also able to proceed under simple ligand-free conditions, giving **4a** in 82% yield (entry 7). Moreover, attempt with other bases couldn't improve the reaction, and the use of Cs_2CO_3 or Na_3PO_4 shut down the process (entries 9-10). In addition, solvent screening showed that DMF and THF were applicable (entries 11-12), but not better than 1,4-dioxane, for

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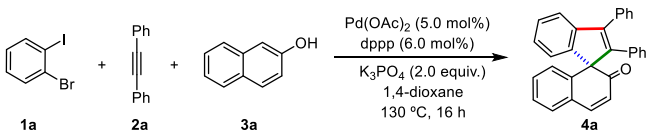
the titled [2+2+1] spiroannulation. Thereby, the reaction scope was surveyed under both conditions A and B at the same time.

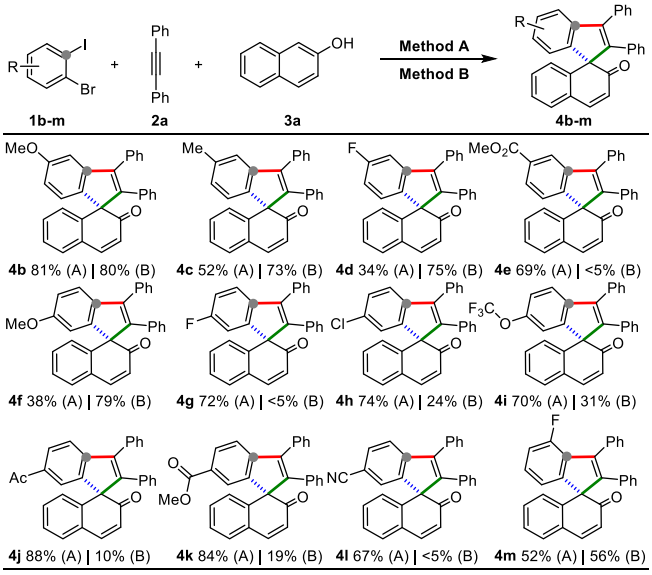
Table 1. Optimization of the reaction conditions[a]



Entry	Variation from the standard conditions	Yield (%)[b]
1[c]	None	90
2	$Pd_2(dba)_3$ instead of $Pd(OAc)_2$	0
3	$[Pd(allyl)Cl]_2$ instead of $Pd(OAc)_2$	26
4	PPh_3 instead of dppp	62
5	dppe instead of dppp	69
6	dppb instead of dppp	77
7[d]	without dppp	82
8	K_2CO_3 instead of K_3PO_4	45
9	Cs_2CO_3 instead of K_3PO_4	0
10	Na_3PO_4 instead of K_3PO_4	0
11	DMF instead of 1,4-dioxane	54
12	THF instead of 1,4-dioxane	61

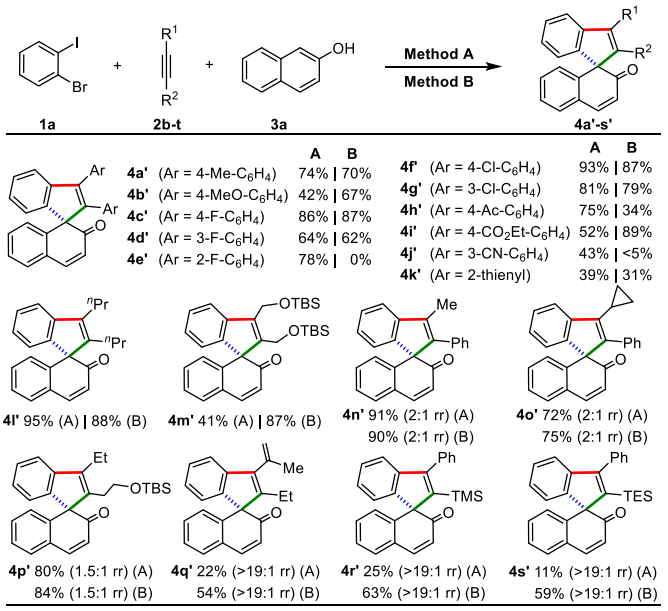
[a]0.3 mmol **1a**, 0.3 mmol **2a**, 0.2 mmol **3a**, 5.0 mol% [Pd] and 6.0 mol% L were used. [b]Isolated yield. [c]Method A. [d]Method B.

Table 2. Scope of 1-bromo-2-iodobenzenes



First, we explored the scope of 1-bromo-2-iodobenzenes (**1**) (Table 2). Gratifyingly, by reacting **1b-m** with **2a** and **3a**, a number of spirocyclic products **4b-m** could be prepared in good yields (up to 88%) with exclusive regioselectivities (>19:1 rr for all the cases). Various substituents on the phenyl ring were well tolerated, including electron-donating methoxy (**4b**,**f**) and methyl (**4c**) groups, and electron-withdrawing groups such as a fluoro (**4d**,**g**,**m**), ester (**4e**,**k**), chloro (**4h**), trifluoromethoxy (**4i**), acetyl (**4j**) and cyano (**4l**) group. Noteworthy, all the reactions led to a single product, which was strictly controlled by the two halides in a site-specific manner. This statement was strongly supported by single-crystal X-ray crystallographic studies on **4e** and **4k**.[15] Overall, methods A and B were both efficient for dihaloarenes bearing an electron-donating group (**4b**,**c**,**f**), while it was necessary to involve the dppp ligand for reactions with electron-deficient dihaloarenes to obtain good yields for the desired products (**4e**,**g-l**).

Table 3. Scope of alkynes

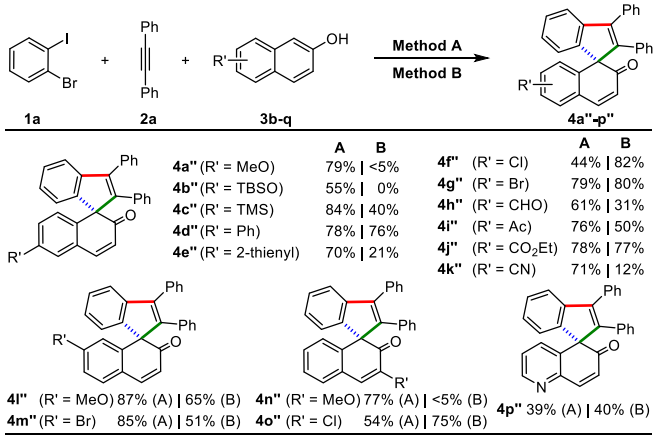


Next, we turned our attention to the scope of alkynes **2** and the experimental data are shown in Table 3. Overall, a broad range of symmetrical alkynes, bearing various aromatic, heterocyclic and aliphatic groups, underwent the titled [2+2+1] spiroannulations with **1a** and **3a** quite efficiently, affording the desired products **4a'**-**m'** in high yields. Although there was no clear trend by using different conditions, these two methods could give complementary results for certain alkynes. To unveil the potential on controlling alkyne migratory insertion, some unsymmetrical alkynes were tested. As expected, products **4n'**-**p'** could be obtained in good yields, but regioselectivities were rather low. When an alkyl/vinyl mixed alkyne was used, product **4q'** was formed as single regioisomer, with method B giving a higher yield. To our delight, the reaction with aryl/silyl mixed alkynes could also lead to products **4r'**-**s'** as single regioisomer,[15] and alkynes were installed in a steric-controlled fashion that silyl group is close to the spirocyclic center, which is consistent with literature precedents.[16]

Having examined the scope of 1-bromo-2-iodobenzenes and alkynes, we investigated the tolerance of functional groups on the 2-naphthol. As shown in Table 4, a variety of substituents including electron-donating methoxy (**4a''**,**l''**,**n''**) and silyl (**4b''**-**c''**) groups, and electron-withdrawing groups such as phenyl (**4d''**), 2-thienyl (**4e''**), chloro (**4f''**,**o''**), bromo (**4g''**,**m''**), formyl (**4h''**), acetyl (**4i''**), ester (**4j''**) and cyano (**4k''**) groups could be introduced on the 3-, 6- and 7-positions of naphthyl ring. The ligand-free method B was generally applicable, but dppp was occasionally required for getting better reaction performance. It is notable that chloro-group was well tolerated under ligand-free conditions, affording the desired **4f''** and **4o''** in 82% and 75% yield, respectively. More strikingly, substrates bearing a more reactive bromo-group, which might serve as a useful

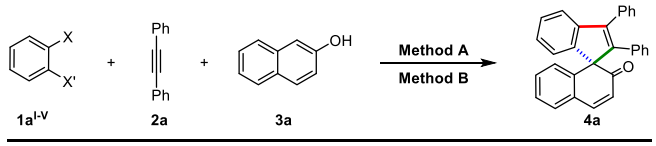
handle for further derivatization,[13c] behaved smoothly to give products **4g''** and **4m''** in high yields. In addition, it should be mentioned that heterocyclic quinolin-6-ol could participate well in the [2+2+1] spiroannulation to provide **4p''** in 40% yield.

Table 4. Scope of 2-naphthols



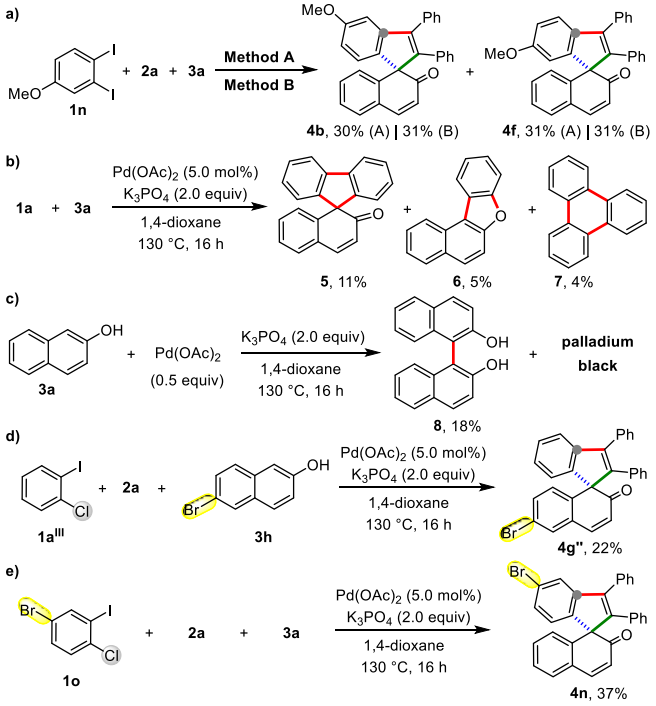
Inspired by the tolerance of additional bromo-substituent on the naphthyl ring, we tested more 1,2-dihalobenzenes for this transformation. As shown in Table 5, 1,2-diidobenzene **1a**^{I} and 1,2-dibromobenzene **1a**^{II} were well suited for the titled [2+2+1] spiroannulation, giving rise to the desired **4a** in similar yields by these two methods (entries 1-2). To our surprise, 1-chloro-2-iodobenzene **1a**^{III} and 1-chloro-2-bromobenzene **1a**^{IV}, bearing a far less reactive chloro-group, were found to be applicable as well, providing product **4a** in acceptable yields (entries 3-4). Notably, 1,2-dichlorobenzene **1a**^{V} was unreactive (entry 5), which indicated that such a domino process couldn't be triggered by the oxidative addition to aryl chloride to Pd(0).

Table 5. Scope of 1,2-Dihalobenzenes



Entry	1a^{I-V}	X	X'	Yield(%) of **4a** A | B
1	**1a**^{I}	I	I	74% | 78%
2	**1a**^{II}	Br	Br	43% | 44%
3	**1a**^{III}	I	Cl	58% | 47%
4	**1a**^{IV}	Br	Cl	40% | 8%
5	**1a**^{V}	Cl	Cl	0% | 0%

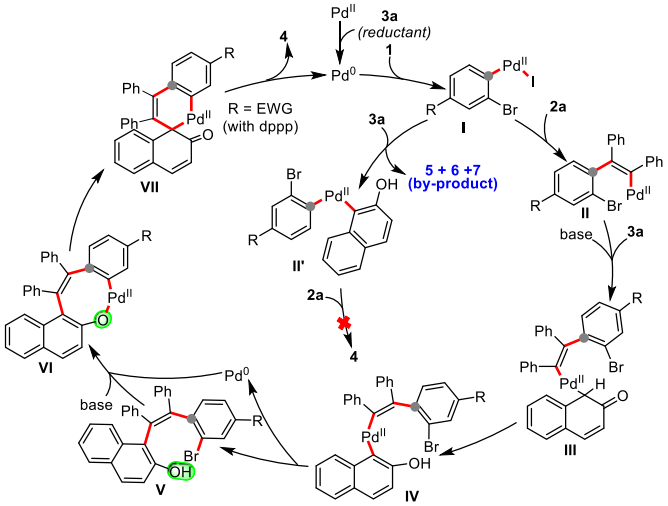
To shed light on the reaction mechanism, a series of control experiments were performed (Scheme 2). When compound **1n** was reacted with **2a** and **3a** under both the two conditions, 1:1 mixtures of products **4b** and **4f** were obtained (Scheme 2a), indicating that the methoxyl group of **1n** didn't affect its initial oxidative addition of C–I bond to Pd(0) and couldn't contribute to controlling the regiochemistry. So it is believed that the excellent regiochemistry for 1-bromo-2-iodobenzenes (**1b-m**) was just controlled by the position of two halides. Thereby, the reaction should be triggered from aryl iodide, and proceed via migratory insertion of alkyne **2**. Notably, a control run with **1a** and **3a** led to dehalogenated products **5-7**, which were not found in the standard reaction with **1a**, **2a** and **3a** (Scheme 2b). This outcome implied: i) alkyne **2** reacted more preferentially than naphthol **3** towards the aryl-Pd(II) species that was *in situ* generated from **1**; ii) naphthol **3** should be the reductant for producing Pd(0)-catalyst and formally reduced products **5** and **7**. Next, **3a** was mixed with $Pd(OAc)_2$, leading to dinaphthol **8** in 18% yield and expected active Pd(0)-species (Scheme 2c).[17] Remarkably, when **1a**^{III} was combined with **2a** and **3h**, the titled [2+2+1] spiroannulation proceeded to give **4g''** in 22% yield (Scheme 2d). Moreover, the reaction with **1o**, which contains one more bromo-group in comparison to **1a**^{III}, took place to afford **4n** in 37% yield (Scheme 2e). These results indicated that aryl chloride reacted smoothly in the presence of a generally more active bromo-functionality being involved at different partners. Presumably, such a unique reactivity was possibly enabled by intramolecularly directed activation of C–Cl bond to accelerate its oxidative addition.



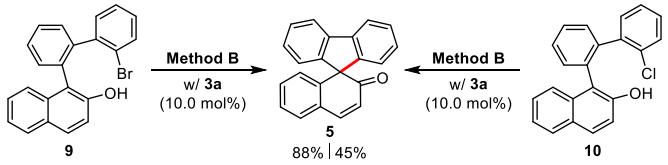
Scheme 2. Mechanistic studies

Based on the above results and prior reports,[8-12] a plausible reaction pathway for the formation of product **4** is shown in Scheme 3. First, active Pd(0)-catalyst is generated by reduction of $Pd(OAc)_2$ with naphthol **3a**. Afterwards, oxidative addition occurs at the more active iodo-site of 1-bromo-2-iodobenzene (**1**) to give arylpalladium species **I**. At this stage, two reaction modes might be considered: a) coordination and migratory insertion of alkyne **2a** provides intermediate **II**; b) electrophilic palladation of **3a** takes place to generate **II'**. According to the regiochemistry for **1**, the first mode is reasonable while the second one could be excluded. Subsequently, intermediate **II** undergoes electrophilic palladation with naphthol **3a**, followed by tautomerization and reductive elimination to deliver **V**. At the same time, active Pd(0)-catalyst is regenerated. Next, it is assumed that the hydroxyl group would direct Pd(0)-species to facilitate regioselective oxidative addition of aryl halide **V**. The intermediate **VI** then undergoes dearomative ring-contraction

to give spirocyclic **VII**. Finally, reductive elimination takes place to form product **4**. Although plausible intermediate **V** was not isolated, control runs with analogue **9** and its Cl-counterpart **10** were able to give dearomative spiroannulation product **5** in reasonable yields (Scheme 4). These results clearly supported the above proposed reaction pathway. In addition, based on the behavior of electron-deficient substrates (**1e**,**g-k**) by using the methods A and B, it is believed that dppp should be more helpful for promoting the reductive elimination from **VII** to **4**, thus enhancing the yield of corresponding products (**4e**,**g-k**).



Scheme 3. Proposed mechanism



Scheme 4. Control experiments with **9** and **10**.

In summary, we have developed a novel Pd(0)-catalyzed dearomative [2+2+1] spiroannulation reaction, which offers an unprecedented pathway for the rapid assembly of spirocyclic molecules from three rather simple chemical feedstocks in an intermolecular manner. Remarkably, the regiochemistry of this domino transformation, with respect to both 1,2-dihaloarene and alkyne coupling partners, could be selectively controlled by the precise variation of their structures.

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Conflicts of interest

There are no conflicts to declare.

Notes and references

1 (a) J. A. Marshall, S. F. Brady and N. H. Andersen, The Chemistry of Spiro[4.5]decane Sesquiterpenes. In Fortschritte der Chemie Organischer Naturstoffe; Springer-Verlag: New York, 1974; (b) S. Quideau, In Modern Arene Chemistry; Astruc, D., Ed.; Wiley-VCH, Weinheim, Germany, 2002; p 539.

2 For two recent examples, see: (a) Z. Zhou, S. Xie, X. Chen, Y. Tu, J. Xiang, J. Wang, Z. He, Z. Zeng and B. Z. Tang, *J. Am. Chem. Soc.*, 2019, **141**, 9803; (b) R. P. Kaiser, D. Nečas, T. Cadart, R. Gyepes, I. Císařová, J. Mosinger, L. Pospíšil and M. Kotora, *Angew. Chem. Int. Ed.*, 2019, **58**, 17169.

3 For reviews, see: (a) V. A. D'yakonov, O. A. Trapeznikova, A. Meijere, U. M. Dzhemilev, *Chem. Rev.*, 2014, **114**, 5775; (b) A. Ding, M. Meazza, H. Guo, J. W. Yang and R. Rios, *Chem. Soc. Rev.*, 2018, **47**, 5946.

4 For reviews, see: (a) C. Zhuo, W. Zhang, and S. You, *Angew. Chem. Int. Ed.*, 2012, **51**, 12662; (b) C. Zhuo, C. Zheng and S. You, *Acc. Chem. Res.*, 2014, **47**, 2558; (c) T. Nemoto and Y. Hamada, *Synlett*, 2016, **27**, 2301; (d) W. Wu, L. Zhang and S. You, *Chem. Soc. Rev.*, 2016, **45**, 1570; (e) W. Sun, G. Li, L. Hong and R. Wang, *Org. Biomol. Chem.*, 2016, **14**, 2164; (f) C. Zheng and S. You, *Chem.*, 2016, **1**, 830.

5 For pioneering examples, see: (a) T. Nemoto, Y. Ishige, M. Yoshida, Y. Kohno and Y. Hamada, *Org. Lett.,* 2010, **12**, 5020; (b) S. Rousseaux, J. García-Fortanet, M. A. Del Aguila Sanchez and S. L. Buchwald, *J. Am. Chem. Soc.*, 2011, **133,** 9282; (c) Q. Wu, W. Liu, C. Zhuo, Z. Rong, K. Ye and S. You, *Angew. Chem. Int. Ed.*, 2011, **50**, 4455.

6 For examples, see: (a) A. Rudolph, P. H. Bos, A. Meetsma, A. Minnaard and B. L. Feringa, *Angew. Chem., Int. Ed.,* 2011, **50,** 5834; (b) T. Nemoto, Z. Zhao, T. Yokosaka, Y. Suzuki, R. Wu and Y. Hamada, *Angew. Chem. Int. Ed.*, 2013, **52**, 2217; (c) M. J. James, J. D. Cuthbertson, P. O'Brien, R. J. K. Taylor and W. P. Unsworth, *Angew. Chem. Int. Ed.,* 2015, **54,** 1; (d) R. Xu, P. Yang and S. You, *Chem. Commun.,* 2017, **53,** 7553.

7 For examples, see: (a) Y. Suzuki, T. Nemoto, K. Kakugawa, A. Hamajima, Y. Hamada, *Org. Lett.*, 2012, **14**, 2350; (b) Q. Xu, L. Dai and S. You, *Org. Lett.*, 2012, **14**, 2579.

8 J. Nan, Z. Zuo, L. Luo, L. Bai, H. Zheng, Y. Yuan, J. Liu, X. Luan and Y. Wang, *J. Am. Chem. Soc.*, 2013, **135**, 17306.

9 (a) A. Seoane, N. Casanova, N. Quiñones, J. L. Mascareñas and 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. Wang, C. Zheng and S. You, *J. Am. Chem. Soc.*, 2015, **137**, 4880.

10 L. Han, H. Wang and X. Luan, *Org. Chem. Front.*, 2018, **5**, 2453.

11 (a) S. Gu, L. Luo, J. Liu, L. Bai, H. Zheng, Y. Wang and X. Luan, *Org. Lett.*, 2014, **16**, 6132; (b) L. Bai, Y. Yuan, J. Liu, J. Wu, L. Han, H. Wang, Y. Wang and X. Luan, *Angew. Chem. Int. Ed.*, 2016, **55**, 6946.

12 Z. Zuo, H. Wang, L. Fan, J. Liu, Y. Wang and X. Luan, *Angew. Chem. Int. Ed.*, 2017, **56**, 2767.

13 For applications of spirocarbocycles, see: (a) G. B. Jones, Y. Lin, Z. Xiao, L. Kappen and I. H. Goldberg, *Bioorg. Med. Chem.*, 2007, **15**, 784; (b) Y. Zhang, H. Ge, W. Zhao, H. Dong, Q. Xu, S. Li, J. Li, J. Zhang, Y. Song and R. Tan, *Angew. Chem. Int. Ed.*, 2008, **47**, 5823; (c) H. Wang, Y. Liu, W. Hu, W. Xu, P. Wang, Y. Wang and Luan, X. *Org. Electron.*, 2018, **61**, 376.

14 (a) J. Barluenga, A. Jiménez-Aquino, F. Aznar and C. Valdés, *J. Am. Chem. Soc.*, 2009, **131**, 4031; (b) T. Liu, C. Xing and Q. Hu, *Angew. Chem. Int. Ed.*, 2010, **49**, 2909.

15 CCDC 1978474 (**4e**), 1978473 (**4k**) and 1978475 (**4s'**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystal-lographic Data Centre.

16 For an early example, see: R. C. Larock, E. K. Yum, M. J. Doty and K. K. C. Sham, *J. Org. Chem.,* 1995, **60**, 3270.

17 No related dinaphthols were formed, when **3b**, **3c** and **3o** were respectively mixed with $Pd(OAc)_2$ under the same conditions. So the formation of corresponding **4a''**, **4b''** and **4n''** couldn't be enabled by the ligand-free method B.

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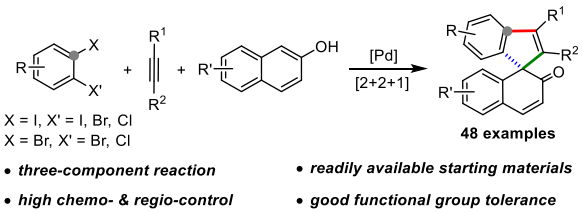

A novel Pd(0)-catalyzed three-component [2+2+1] dearomatizing reaction for the highly chemo- and regio-selective assembly of spirocarbocycles is described.