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# An approach to spirooxindoles *via* palladium-catalyzed remote C–H activation and dual alkylation with $CH_2Br_2$†

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**A facile and efficient approach for the synthesis of spirooxindoles has been developed *via* the coupling of spirocyclic C,C-palladacycles with $CH_2Br_2$. The key spirocyclic palladacycles are generated catalytically *via* remote C–H activation. A range of spirooxindoles can be synthesized in good to excellent yields from readily available starting material.**

Spirooxindole motifs exist in many natural products and bioactive molecules.[1] Due to their biological properties, spirooxindoles are good targets for drug candidates and clinical pharmaceuticals.[2] Consequently, developing innovative methods for the synthesis of spirooxindoles and synthesizing novel spirooxindole derivatives have been the focus of organic chemists. Although a variety of approaches are available,[3] continuous efforts should still be devoted to seeking more facile and efficient reactions for the synthesis of this type of significant molecules.

Our group has been interested in palladacycles, in particular those consisting of two carbon–Pd bonds.[4] Due to their unique structures, this type of palladacycles may have novel reactivities,[5] and the two carbon–Pd bonds offer opportunities to develop new reactions, particularly for the construction of cyclic strucutres. Recently, we found that dibenzopalladacyclopentadienes derived from 2-iodobiphenyls exhibited distinct reactivities, and developed some synthetically useful reactions.[6] It should be noted that the dibenzopalladacyclopentadienes were obtained *via* C–H activation of 2-iodobiphenyls. The majority of current C–H activations rely on the use of directing groups.[7] In the formation of the dibenzopalladacyclopentadienes, the reactions were initiated by the oxidative addition of aryl iodides to Pd(0) precatalysts, which represents a complementary strategy for C–H functionalization.

Inspired by the success in dibenzopalladacyclopentadiene chemistry, we sought to explore the reactivities of other palladacycles. Recently, remote C–H activation *via* intramolecular Heck reaction attracted considerable interests.[8] This type of reactions use aryl halides bearing a tethered alkene as the substrates. The reactions are initiated by the oxidative addition of aryl halides to Pd(0) precatalyst, and the subsequent intramolecular migratory insertion forms a σ-alkyl Pd(II) intermediate. For some well-designed structures, the σ-alkyl Pd(II) species can activate C–H bonds at appropriate sites, forming spirocyclic C,C-palladacycles. In this cascade reaction, C–H bonds distal to the initial halo group are cleaved. For C–H activation reactions using directing groups, C–H bonds proximal to the directing groups are usually activated. The remote C–H activation overcomes this limitation, and represents a new strategy to expand substrate scope of C–H activation reactions. However, the reactivity of this spiropalladacyle remains underexplored. Although several intramolecular cyclization reactions of the palladacycles have been developed (Fig. 1a),[9] intermolecular reactions are rare. In 2014, the Shi group reported that the C,C-palladacyles could be captured with diaziridinone (Fig. 1b).[10a] Subsequently, García-Lopéz and Lautens reported the reaction of the palladacycles with benzynes independently (Fig. 1c).[10b,c] Most recently, the García-Lopéz group found that carbenoids could also couple with the palladacycles (Fig. 1d).[10d] Although this excellent reaction provides a novel method for the synthesis of spirooxindoles, the products were limited to those bearing two α-substituents, with one of

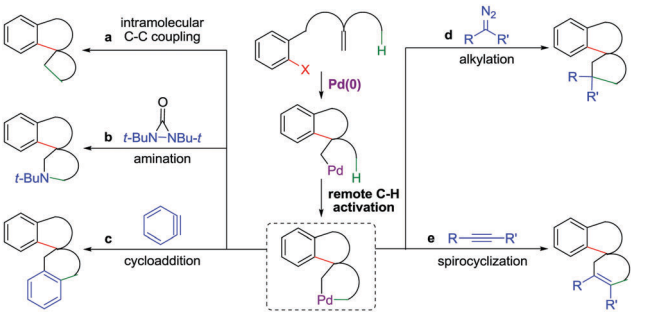


Fig. 1 Remote C–H functionalization through σ-alkyl Pd(II) intermediates.

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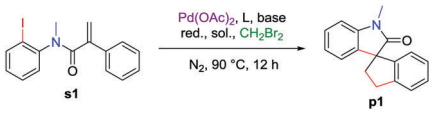
them being ester group. In addition, labile α-diazocarbonyl compounds had to be used. During the preparation of this manuscript, the Lautens group described the reaction of such spiropalladacycles with alkynes (Fig. 1e).[10e] This elegant reaction features excellent regioselectivity for unsymmetrical alkynes. Furthermore, the Zhu group proposed that the intermolecular trapping of azapalladacycles could be involved in the Pd-catalyzed heteroannulation between oximes and benzynes.[10f] On the other hand, it has been reported that $CH_2Br_2$ can react with palladacycles including dibenzopalladacyclopentadiene to form cyclic compounds.[6c,11] In these reactions, two C–C bonds were formed and a methylene group was introduced. As a very common and low-cost chemical, $CH_2Br_2$ is a desirable reagent for the development of organic reactions. We envisioned that the spirocyclic C,C-palladacycle obtained *via* the remote C–H activation could also react with $CH_2Br_2$, which would provide a new approach for the synthesis of spirooxoindoles.

We commenced our study by using acrylamide **s1** as the model substrate. Therefore, **s1** was treated with 2.0 equivalent of $CH_2Br_2$ under palladium catalysis in DMA. Whereas **s1** failed to react with $CH_2Br_2$ in the presence of $Na_2CO_3$ or $Cs_2CO_3$ as the base (Table 1, entries 1 and 3), the desired spirooxindole product **p1** was formed by using $K_2CO_3$ or $KHCO_3$ (entries 2 and 4). The yield increased to 28% by the addition of 20 mol% of $PPh_3$ (entry 5). Encouraged by this result, we sought to improve the yield by screening other phosphine ligands. The yield was further improved to 36% when P(*o*-tol)$_3$ was employed (entry 6). However, the use of other ligands including the bidentate ones led to lower yields (entries 7–10). Since the catalytic cycle was expected to start with Pd(0), we envisioned that a reductant should promote the reaction. Gratefully, although the yield remained almost unchanged in the presence of isopropyl alcohol (entry 11), it was dramatically enhanced to 79% when 2.0 equivalent of triethylamine was used (entry 12). The reaction was much less efficient in other solvents except DMF, which gave a slightly lower yield (entries 14–18). Notably, the yield was improved to 83% in the presence of TBAB (entry 19), and further promoted to 93% by using 0.5 equivalent of TBAI (entry 20).[12] After achieving the excellent yield, we turned to further optimize the reaction conditions by investigating the impact of the molar equivalents of the reagents on the reaction. First, we reduced the catalyst loading to 5 mol%. Unfortunately, the yield decreased to 83% (entry 21). The desired product was not observed when $Pd(OAc)_2$ was removed, which indicates that the reaction is a Pd-catalyzed process (entry 22). It should be noted that a yield of 87% was still obtained when 1.1 equivalent of $CH_2Br_2$ was used, which implies that the domino reaction is very efficient (entry 23). However, the yield failed to be improved even in the presence of 3.0 equivalent of $CH_2Br_2$ (entry 24). 4.0 Equivalent of $K_2CO_3$ was necessary and sufficient to afford the high yield (entries 25 and 26). Finally, the yield decreased when the amount of TEA or TBAI was reduced (entries 27 and 28).

With the optimized conditions in hand, we then explored the substrate scope of the spirooxindole-forming protocol. First, we examined the compatibility of functionalities on the phenyl groups linked to the double bonds. As shown in Scheme 1,

Table 1 Conditions survey[a]



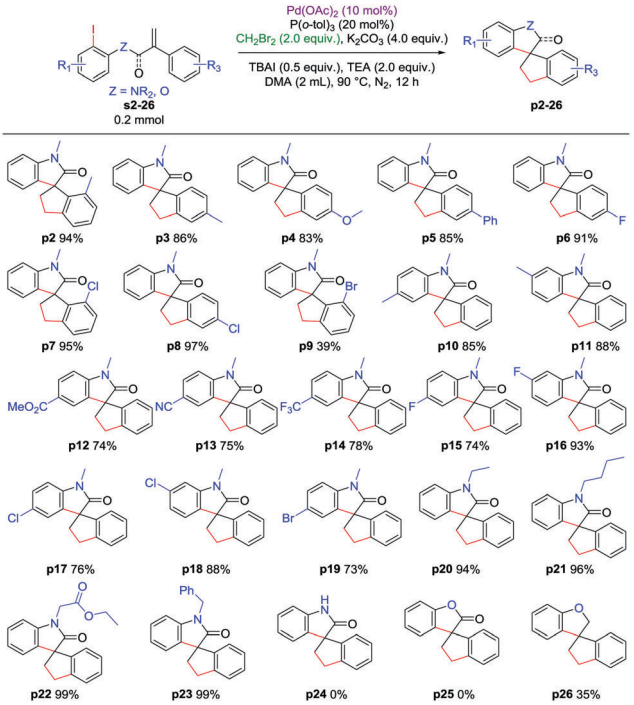

| Entry | Base | L | Red. | Sol. | Yield (%) |
|---|---|---|---|---|---|
| 1 | $Na_2CO_3$ | — | — | DMA | Trace |
| 2 | $K_2CO_3$ | — | — | DMA | 6 |
| 3 | $Cs_2CO_3$ | — | — | DMA | Trace |
| 4 | $KHCO_3$ | — | — | DMA | 5 |
| 5 | $K_2CO_3$ | $PPh_3$ | — | DMA | 28 |
| 6 | $K_2CO_3$ | P(*o*-tol)$_3$ | — | DMA | 36 |
| 7 | $K_2CO_3$ | P(*o*-MeOPh)$_3$ | — | DMA | 14 |
| 8 | $K_2CO_3$ | $PCy_3$ | — | DMA | 9 |
| 9 | $K_2CO_3$ | dppm | — | DMA | 23 |
| 10 | $K_2CO_3$ | dppe | — | DMA | 7 |
| 11 | $K_2CO_3$ | P(*o*-tol)$_3$ | IPA | DMA | 34 |
| 12 | $K_2CO_3$ | P(*o*-tol)$_3$ | TEA | DMA | 79 |
| 13 | $K_2CO_3$ | P(*o*-tol)$_3$ | DIPEA | DMA | 40 |
| 14 | $K_2CO_3$ | P(*o*-tol)$_3$ | TEA | DMF | 72 |
| 15 | $K_2CO_3$ | P(*o*-tol)$_3$ | TEA | NMP | 55 |
| 16 | $K_2CO_3$ | P(*o*-tol)$_3$ | TEA | THF | — |
| 17 | $K_2CO_3$ | P(*o*-tol)$_3$ | TEA | MeCN | 27 |
| 18 | $K_2CO_3$ | P(*o*-tol)$_3$ | TEA | Dioxane | 26 |
| 19[b] | $K_2CO_3$ | P(*o*-tol)$_3$ | TEA | DMA | 83 |
| 20[c] | $K_2CO_3$ | P(*o*-tol)$_3$ | TEA | DMA | 93 (90)[l] |
| 21[c,d] | $K_2CO_3$ | P(*o*-tol)$_3$ | TEA | DMA | 82 |
| 22[c,e] | $K_2CO_3$ | P(*o*-tol)$_3$ | TEA | DMA | — |
| 23[c,f] | $K_2CO_3$ | P(*o*-tol)$_3$ | TEA | DMA | 87 |
| 24[c,g] | $K_2CO_3$ | P(*o*-tol)$_3$ | TEA | DMA | 93 |
| 25[c,h] | $K_2CO_3$ | P(*o*-tol)$_3$ | TEA | DMA | 74 |
| 26[c,i] | $K_2CO_3$ | P(*o*-tol)$_3$ | TEA | DMA | 93 |
| 27[c,j] | $K_2CO_3$ | P(*o*-tol)$_3$ | TEA | DMA | 68 |
| 28[c,k] | $K_2CO_3$ | P(*o*-tol)$_3$ | TEA | DMA | 62 |

[a] Reaction conditions: **s1** (0.2 mmol), $Pd(OAc)_2$ (10 mol%), L (20 mol% for monodentate ligand and 10 mol% for bidentate ligand), base (4.0 equiv.), reductant (2.0 equiv.), $CH_2Br_2$ (2.0 equiv.), solvent (2 mL). The yields were determined by $^1H$ NMR analysis of crude reaction mixture using $C_2H_2Cl_4$ as the internal standard. [b] TBAB = 0.5 equiv. [c] TBAI = 0.5 equiv. [d] $Pd(OAc)_2$ = 5 mol%. [e] No Pd. [f] $CH_2Br_2$ = 1.1 equiv. [g] $CH_2Br_2$ = 3.0 equiv. [h] $K_2CO_3$ = 3.0 equiv. [i] $K_2CO_3$ = 5.0 equiv. [j] TEA = 1.0 equiv. [k] TBAI = 0.2 equiv. [l] Isolated yield. dppm = bis(diphenylphosphino)methane, dppe = bis(diphenylphosphino)ethane, IPA = isopropanol, TEA = triethylamine, DIPEA = *N*,*N*-diisopropylethylamine, TBAB = tetrabutylammonium bromide, TBAI = tetrabutylammonium iodide.

the substrates containing an *ortho*- or *para*-methyl group were suitable, and the reactions were high-yielding (**p2–3**). The spirooxindoles bearing a methoxy or phenyl group could be synthesized in good yields (**p4–5**). The fluoro and chloro groups were well-tolerated, and the corresponding spirooxindoles were formed in excellent yields (**p6–p8**). The acrylamide bearing a bromo group was also reactive, albeit in a low yield (**p9**).

Next, we investigated the performance of acrylamides bearing different substituents on the benzene rings with the iodo group. Methyl groups at the *meta*- or *para*-position were compatible, furnishing methylated spirooxindoles in high yields (**p10–11**). The substrates containing electron-withdrawing groups, such as ester (**p12**), cyano (**p13**), and trifluoromethyl (**p14**), underwent the domino reaction smoothly. Notably, fluoro (**p15–16**), chloro (**p17–18**), and even bromo (**p19**) groups survived under the standard conditions, and the corresponding products were formed in yields ranging from 73% to 93%.

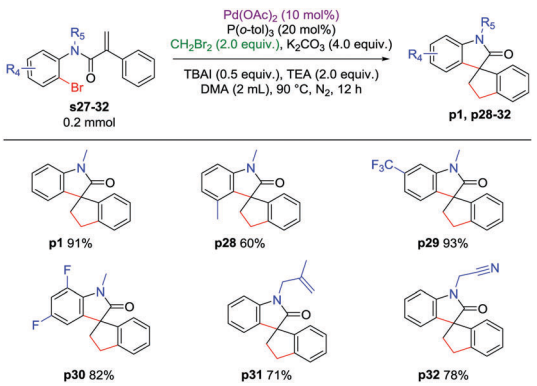
 



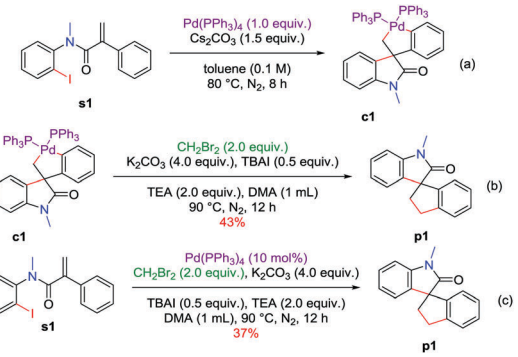

Scheme 1 Substrate scope for the reactions starting from aryl iodides.

Moreover, the reactivity of substrates containing different *N*-substituents was investigated. The reactions of the acrylamides bearing an ethyl or *n*-butyl group on the nitrogen atoms were high-yielding (**p20–21**). 2-Ethoxy-2-oxoethyl and benzyl groups were tolerated, and the spirooxindole products were formed in 99% yields (**p22–23**). The acrylamides containing no substituents on the nitrogen atom and the ester analogue were unreactive under the reaction conditions (**p24–25**). However, the substrate containing an ether linkage was suitable, although the yield was low (**p26**).

Aryl bromides were also reactive enough to undergo the cascade reaction. As shown in Scheme 2, the bromo analogue **s27** had similar reactivity to **s1**, furnishing the spirooxindole product **p1** in 91% yield. The substrate scope with the respect of bromides was also explored. The presence of a methyl group *ortho*- to the bromide resulted in a much lower yield, probably




Scheme 2 Substrate scope for the reactions starting from aryl bromides.

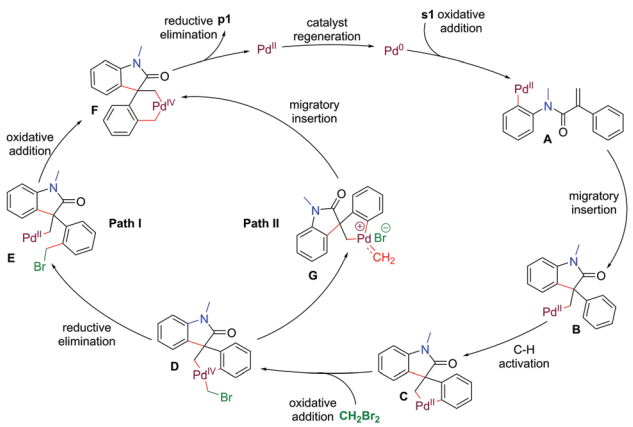



Scheme 3 Mechanistic studies.

due to steric encumbrance (**p28**). The trifluoromethyl group almost had no impact on the reaction (**p29**), and substrate **s30**, containing two fluoro groups also reacted with $CH_2Br_2$ in a good yield. 2-Methylallyl and cyanomethyl groups on the nitrogen atoms of acrylamides **s31** and **s32** were tolerated, affording product **p31** and **p32** in moderate yields. It should be mentioned that one of the intramolecular cyclization reactions of spiropalladacycles also formed spirooxindoles as the final products.[9d]

To investigate if the reactions proceeded *via* palladacycles as the intermediate, we prepared complex **c1** starting from **s1** and $Pd(PPh_3)_4$ (Scheme 3).[10c] When palladacycle **c1** that contains two $PPh_3$ ligands was subjected to the standard conditions, spirooxindoles **p1** was formed, albeit in a low yield. The low yield could result from the negative effect of the $PPh_3$ on the reaction. To prove this assumption, the reaction of **s1** and $CH_2Br_2$ was carried out using $Pd(PPh_3)_4$ as the catalyst, and it was found that the yield decreased dramatically to 37%. These experimental results indicate that $PPh_3$ could suppress the formation of the spirooxindole product, and also provide evidences to support that the palladacycle acted as the key intermediate in the reaction.

On the basis of the above experimental results and the previous reports,[10,11b] a tentative mechanism was proposed as shown in Scheme 4. The catalytic cycle starts with the oxidative addition of the halide to Pd(0) to form Pd(II) species **A**, which is




Scheme 4 Proposed mechanism.

followed by intramolecular migratory insertion to give σ-alkyl Pd(II) species **B**. The subsequent intramolecular C–H activation furnishes palladacycle **C**. **C** may undergo oxidative addition of $CH_2Br_2$ to form Pd(IV) complex **D**. The reductive elimination and intramolecular oxidative addition yield six-membered palladacycle **F** (path I). **F** could also be formed *via* a carbene complex **G** (path II).[11b] The reductive elimination of **F** generates final product **p1** and release Pd(II), which is reduced to Pd(0) to close the catalytic cycle.

In conclusion, we have developed a facile and efficient approach for the synthesis of spirooxindoles through Pd-catalyzed cascade reactions. In this reaction, the key spirocyclic C,C-palladacycles, which were generated *via* remote C–H activation, coupled with $CH_2Br_2$, and two new C–C bonds were formed. A range of spirooxindoles can be synthesized in good to excellent yields from simple starting materials.

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## Conflicts of interest

There are no conflicts to declare.

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