A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition GDCh Chemie

www.angewandte.org

Accepted Article

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To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.202103395

Link to VoR: https://doi.org/10.1002/anie.202103395

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10.1002/anie.202103395

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Palladium-Catalyzed Remote C-H Phosphonylation of Indoles at the C4 and C6 Positions by a Radical Approach

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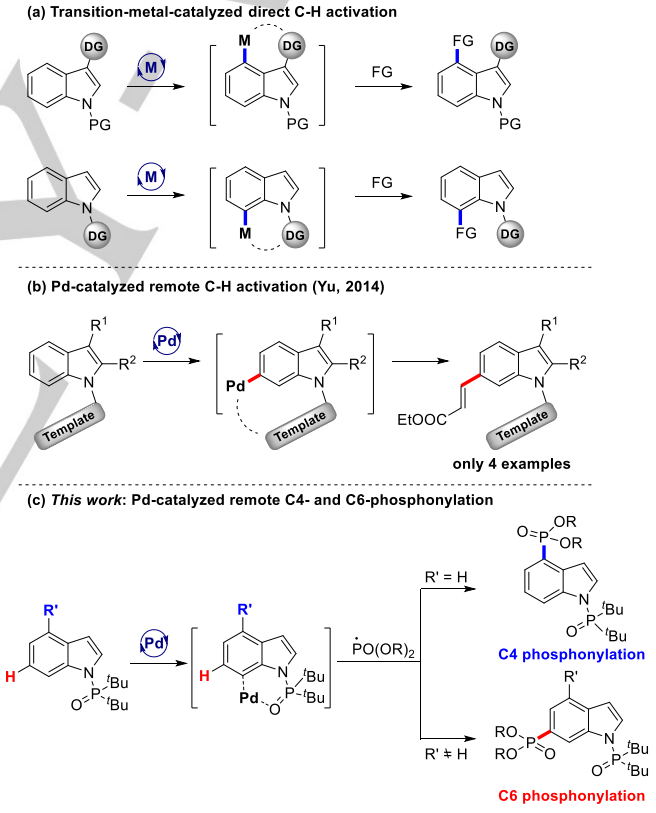
Abstract: Palladium-catalyzed direct C-H activation of indole benzenoid moiety has been achieved in the past decade. However, palladium-catalyzed remote C-H activation of indoles is really rare. Herein, we report a challenging palladium-catalyzed remote C4-H phosphonylation of indoles by a radical approach. The method provides access to a series of C4-phosphonylated indoles, including tryptophan and tryptophan-containing dipeptides, which are typically inaccessible by direct C4-H activation due to its heavy reliance on C3 directing groups. Notably, unexpected C6-phosphonylated indoles were obtained through blocking of the C4 position. The preliminary mechanistic studies indicated that the reactions may proceed via a C7-palladacycle/remote-activation process. Based on the strategy, examples of remote C4-H difluoromethylation with $BrCF_2COOEt$ are also presented, suggesting that the strategy may offer a general blueprint for other cross-couplings.

Indole scaffolds are important nitrogen-containing heterocycles owing to their ubiquity in numerous natural bioactive products, marketed drugs, pharmaceutically important compounds, and other functional molecules.[1] In recent years, the development of elegant methods to highly decorated indoles have received huge efforts. Besides traditional approaches, such as cross-couplings with prefunctionalized indoles[2] or indole ring formation involved reactions,[3] transition-metal-catalyzed regioselective direct C-H activation has been regarded as a robust and step-economical method for late-stage indole modifications.[4] However, the indole core inherently offers six distinctive C-H bond activation sites. Given the inherent reactivity of the pyrrole ring (C2-C3), selective functionalization of the benzenoid fragment (C4-C7) has remained a great challenge.[5] In the past decade, iridium, rhodium, ruthenium, and palladium-catalyzed direct C-H activation of indole benzenoid moiety has been achieved, with major contributions by the groups of Shi,[6] and Ackermann,[7] among others.[8-9] Typically, these methods utilize a specific directing group to form a six-membered metallacycle at C4 or C7 positions, allowing for subsequent oxidative addition/reductive elimination process (Scheme 1a). By contrast, palladium-catalyzed remote C-H functionalization of indoles is only known in Yu group, who reported a seminal palladium-catalyzed *meta*-C6-olefination of



Scheme 1. Regioselective C-H functionalization of indole benzenoid moiety. DG = directing group; PG = protecting group; FG = functional group.

indoles by utilizing a carefully designed U-shaped template (four examples) (Scheme 1b).[10] However, indoles with blocking groups at the pyrrole core are needed in the method to shield this part from reacting. Undoubtedly, the implicit challenge of palladium-catalyzed remote C-H activation of indoles is evident.

Phosphorous-substituted heterocycles are becoming increasingly important in many applications, such as agricultural and medicinal chemistry.[11] In particular, phosphorous

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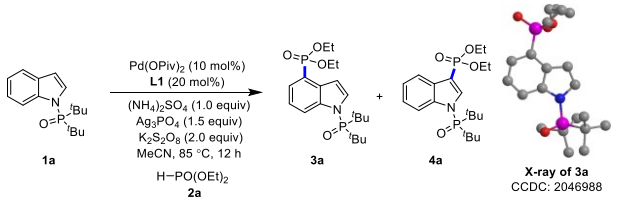
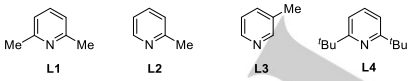
substituents can regulate important biological functions by mimicking carboxylic acid functionality in living organisms.[12] Nevertheless, to the best of our knowledge, there is still no method for the phosphonylation onto indole benzenoid core, while the catalytic systems for C2- and C3-positions are well-established.[13] In this context, selective installation of phosphorous substituents onto the benzenoid core of indoles would thus be of significant utility. Herein, we report a palladium-catalyzed remote C4-H phosphonylation of indoles with di-*tert*-butylphosphinoyl as an effective directing group (DG). Notably, unexpected C6-phosphonylated indoles were obtained through blocking of the C4 position (Scheme 1c). It is proposed to proceed via a C7-palladacycle/remote-activation process. Notable features of our strategy include i) rare palladium-catalyzed remote C-H activation, ii) versatile C4- as well as C6-phosphonylations of indoles, and iii) expedient construction of C-P bond.

Table 1. Optimization of the Remote C4-H Activation.[a]



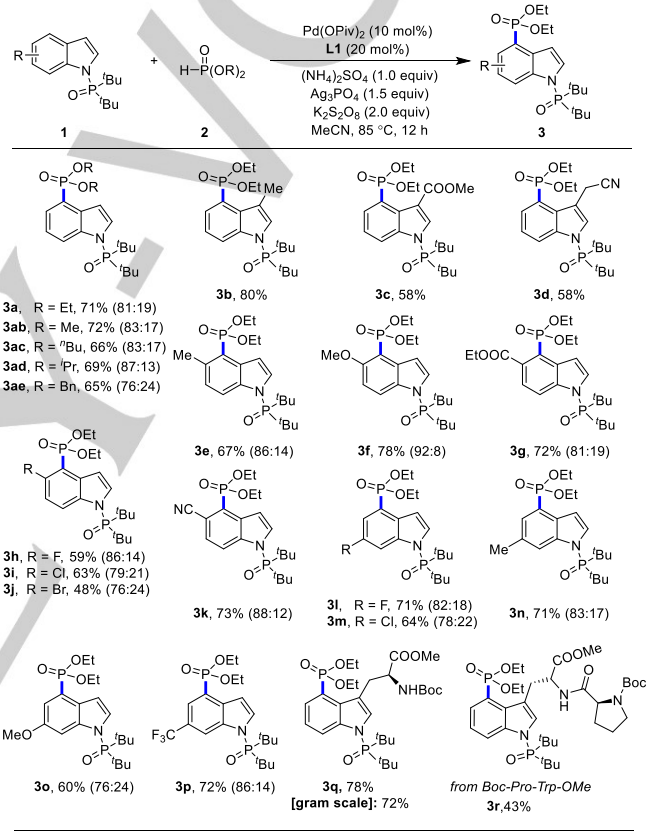
Entry	Deviation from the standard conditions	**3a** (%)	**4a** (%)
1	none	78 (71)[b]	18
2	$Pd(OAc)_2$ instead of $Pd(OPiv)_2$	48	19
3	$Pd(MeCN)_2Cl_2$ instead of $Pd(OPiv)_2$	43	24
4	L2 instead of L1	42	16
5	L3 instead of L1	65	18
6	L4 instead of L1	54	26
7	no L1	41	23
8	DMSO, DCE, dioxane, or THF	n.d.	n.d.
9	no $(NH_4)_2SO_4$	52	24
10	no Ag_3PO_4	19	13
11	no $K_2S_2O_8$	n.d.	n.d.
12	no $Pd(OPiv)_2$	8	25
13	no $Pd(OPiv)_2$, no Ag_3PO_4	3	8



[a] Conditions: **1a** (0.1 mmol), **2a** (3.0 equiv), $Pd(OPiv)_2$ (10 mol%), **L1** (20 mol%), $(NH_4)_2SO_4$ (1.0 equiv), Ag_3PO_4 (1.5 equiv), and $K_2S_2O_8$ (2.0 equiv) in MeCN (1 mL), under Ar at 85 ℃ for 12 h, and the yields of **3a** and **4a** were determined by NMR using CH_2Br_2 as the internal standard. n.d. = not detected. [b] Isolated yield.

The investigation into the remote functionalization of indole derivatives began by applying a variety of *N*-substituted indoles (**1a-1af**) with diethyl phosphite **2a** (Table S1 in the Supporting Information). And the reaction of **1a** yielded a mixture of C4- and C3-phosphonylated products, whereas other DGs were not effective for the reaction, including pyrimidine that showed good reactivity in ruthenium-catalyzed remote C6-H activation of indoles.[14] Inspired by those results, we became interested in investigating the remote C4-phosphonylation of di-*tert*-butyl(1*H*-indol-1-yl) phosphine oxide **1a** with diethyl phosphite **2a**. After extensive evaluation of the reaction conditions, the best results were obtained with a combination of $Pd(OPiv)_2$ and **L1**, Ag_3PO_4, $K_2S_2O_8$ as co-oxidants, and $(NH_4)_2SO_4$ as an additive in MeCN within 12 h at 85 ℃ (Table 1, entry 1). And the structure of **3a** was further confirmed via single-crystal X-ray crystallography.[15] Other Pd sources were less efficient for this reaction (Table 1, entries 2-3). Further screening revealed that ligand had an influence on both regioselectivity and conversion (Table 1, entries 4-7). In addition, changing the solvent from MeCN to dimethyl sulfoxide, dichloroethane, dioxane and tetrahydrofuran failed to generate any phosphonylated products (Table 1, entry 8). The control experiments revealed that the cooperation between Ag_3PO_4 and $K_2S_2O_8$ was essential for this transformation (Table 1, entries 10-11). Also, $Pd(OPiv)_2$ plays an important role in switching selectivity to obtain 4-phosphonylated product **3a** as the major regioisomer (Table 1, entries 12-13).

Table 2. Scope for the C4-Selective Phosphonylation.[a]



[a] Conditions: **1** (0.1 mmol), **2** (3.0 equiv), $Pd(OPiv)_2$ (10 mol%), **L1** (20 mol%), $(NH_4)_2SO_4$ (1.0 equiv), Ag_3PO_4 (1.5 equiv), and $K_2S_2O_8$ (2.0 equiv) in MeCN (1 mL), under Ar at 85 ℃ for 12 h. Isolated yield. Values in parentheses indicate the C4:C3 ratios, which were determined by NMR using CH_2Br_2 as the internal standard.

With the best conditions in hand, we examined the scope of this remote C4-H phosphonylation (Table 2). Initially, a variety of phosphonates were examined with **1a**, delivering the corresponding products **3a**-**3ae** in 65-72% yields with good C4 selectivity. Subsequently, the scope of the indole substrates was explored using **2a** as the coupling partner. Indoles bearing electron-donating substituents including methyl and methoxy at the C3, C5, and C6 positions underwent facile phosphonylation affording the corresponding products **3b**, **3e, 3f, 3n,** and **3o** in 60-80% yields, where methoxy functional group at C5 enhanced the regioselectivity to 92:8. The halogen-containing motifs were well-tolerated in the C4-phosphonylation (**3h-3j** and **3l-3m**). Indoles substrates containing electron-deficient substituents such as

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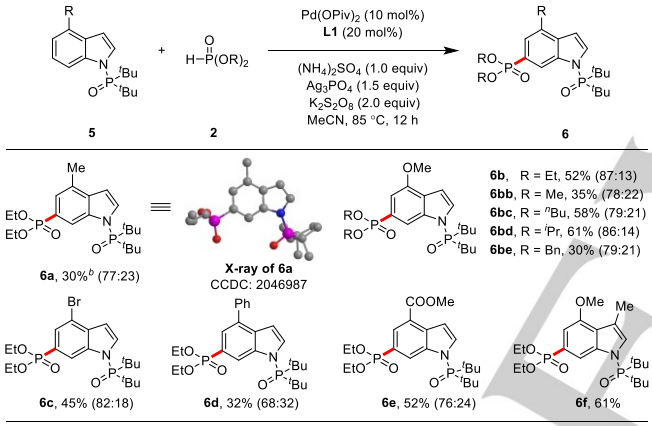
ester, cyanomethyl, cyano and trifluoromethyl were converted in 58-73% yields with good C4 selectivity (**3c-3d**, **3g**, **3k,** and **3p**). Notably, C5-substituted indoles that exert steric effect to C4 position were also converted in good efficiency. More importantly, tryptophan (Trp) and Trp-containing dipeptides reacted smoothly at the C4 position, providing **3q** and **3r** in 78% and 43% yield respectively.

Remote reactivity at C6 of an indole has been only sparingly observed.[10,14,16] Unexpectedly, C6-phosphonylated indoles **6** were obtained through blocking of the C4 position under the same standard conditions, albeit with a slightly lower regioselectivity and conversion (Table 3). Both electron-donating (**6a**, **6b, 6d,** and **6f**) and electron-deficient (**6c** and **6e**) substituents were converted to the corresponding C6-phosphonylated products in 30-61% yields. Moreover, different P(O)H compounds were well-tolerated, affording the desired products **6bb-6be** in satisfied yields with good C6-selectivity. Additionally, the 3-methyl-4-methoxy disubstituted indole was also transformed to the corresponding product **6f** in 61% yield. And the molecular structure could be verified by X-ray crystallography of **6a**.[15]

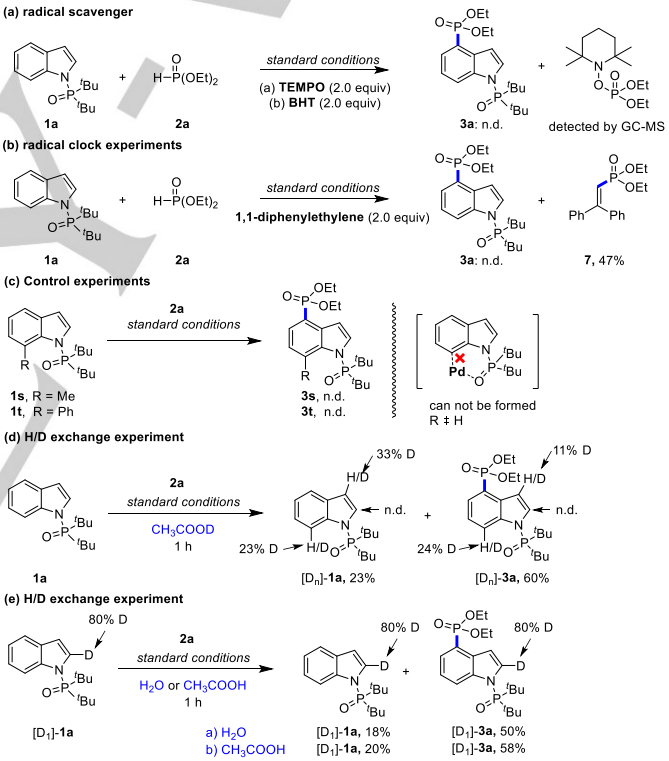
Table 3. Scope for the C6-Selective Phosphonylation.[a]



[a] Conditions: **5** (0.1 mmol), **2** (3.0 equiv), Pd(OPiv)$_2$ (10 mol%), **L1** (20 mol%), $(NH_4)_2SO_4$ (1.0 equiv), Ag_3PO_4 (1.5 equiv), and $K_2S_2O_8$ (2.0 equiv) in MeCN (1 mL), under Ar at 85 ℃ for 12 h. Isolated yield. Values in parentheses indicate the C6:C3 ratios, which were determined by NMR using CH_2Br_2 as the internal standard. [b] Using Pd(OAc)$_2$ (10 mol%), **L3** (20 mol%).

Given the unique features of the unprecedented palladium-catalyzed remote C4/C6-H activation, various experiments were conducted to elucidate the reaction mechanism (Scheme 2). The reaction was completely inhibited when the radical scavenger TEMPO or BHT was added under the standard conditions. As expected, the TEMPO-trapped compound was observed. (Scheme 2a). The radical scavenger 1,1-diphenylethylene trapped ·PO(OEt)$_2$ directly to generate **7** in 47% yield (Scheme 2b). These results showed that the reaction proceeded via a radical pathway. In addition, the intermolecular competition experiment indicated that electron-rich indole substrates reacted preferentially (Scheme S4 in the Supporting Information).

Subsequently, methyl and phenyl functional groups in C7 position did not yield C4-phosphonylated products, and the only material obtained was the recovered starting materials (Scheme 2c). These results suggested that the key intermediate may not be formed with a blocking group in C7 position. Also, the reaction between **1a** and **2a** was performed in the presence of D_2O (Scheme S5 in the Supporting Information). However, no incorporated deuterium was observed at C7 position**,** presumably because H-atom in C7 was transferred to the O-atom in Lewis basic phosphinoyl DG in concerted metalation-deprotonation process (CMD). As expected on the basis of this hypothesis, 23% [D$_n$]-**1a** and 60% [D$_n$]-**3a** were isolated in the presence of CH_3COOD (10.0 equiv) (Scheme 2d). Deuterium was incorporated into the C7 position in significant quantities (23%, 24%), while there was no deuterium at C2. Also, when [D$_1$]-**1a** was treated with **2a** in the presence of H_2O or CH_3COOH (10.0 equiv), no deuterium loss was observed (Scheme 2e). This highlights that the reaction is most likely not accessed through C2 insertion as observed in Frost's work,[14] but through a C7-cyclometalation/remote-activation pathway. Furthermore, intermolecular kinetic experiments with substrates **1a** and [D$_4$]-**1a** suggested that C-H cleavage is not kinetically relevant (Scheme S8 in the Supporting Information). In good agreement with this finding, detailed kinetic experiments unraveled a zero-order dependence of the reaction rate on **1a** and Pd(OPiv)$_2$, but a first-order dependence was observed for the concentration of **2a** (Scheme S9 in the Supporting Information).



Scheme 2. Mechanistic Experiments.

Although the detailed mechanism of the reaction remains unclear, we propose a tentative catalytic cycle for the remote phosphonylation of **1a** and **5a** (Scheme 3).[14,17-19] Phosphonate-assisted cyclometalation at C7 occurs from the active palladium complex **A**, while H-atom at the C7 position was transferred to the O-atom in phosphinoyl DG, delivering the six-membered palladacycle **C**. The newly formed radical then attacks the palladacycle at the *para*-position to the C-Pd bond, while the C6-H was activated with blocking groups at C4 position, leading to species **D** or **D'**. Subsequently, single-electron transfer (SET) occurs from the complex **D** or **D'** to the persulfate ion, followed by

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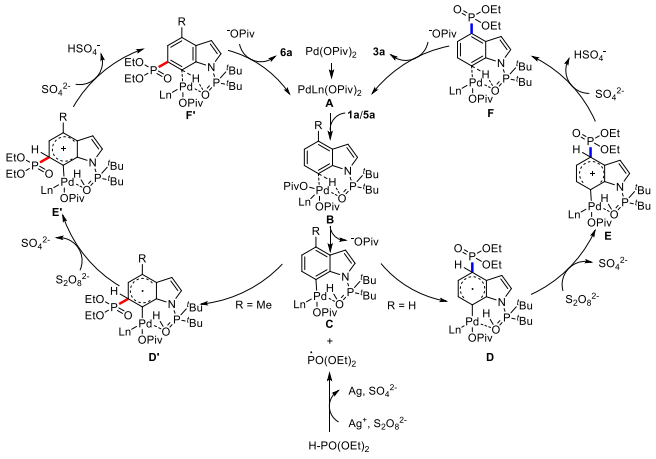
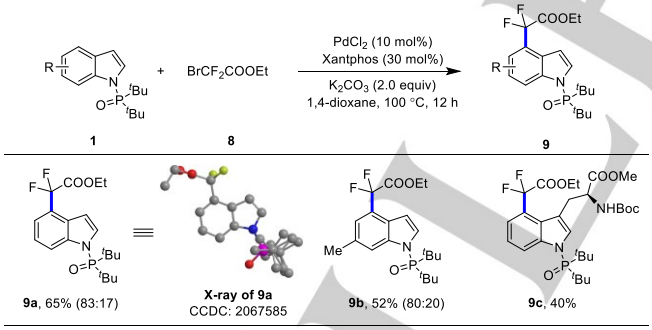
the subsequent rearomatization. Finaly, the desired product **3a** or **6a** is delivered by reprotonation, which simutaneously regenerates the catalytically active palladium(II) complex **A**.



Scheme 3. Proposed catalytic cycle.

The strategy should also be adapted to other cross-couplings. To illustrate this point, $BrCF_2COOEt$ **8**, the common coupling partner in ruthenium catalyzed *meta*/*para*-C-H activation,[18-19] was subjected to the strategy (Table 4). The difluoromethylation products **9a**-**9c** were obtained with the *in situ* formation palladium(0) complex from $PdCl_2$ and Xantphos in dioxane. And the structure of **9a** was confirmed by X-ray crystallography analysis.[15] Unfortunately, difluoromethylation at C6 position failed with the C4-substituted indole substrates **5** under the optimized standard conditions.

Table 4. Remote C4-Difluoromethylation of Indoles.[a]



[a] Conditions: **1** (0.1 mmol), **8** (3.0 equiv), $PdCl_2$ (10 mol%), Xantphos (30 mol%), and K_2CO_3 (2.0 equiv) in 1,4-dioxane (1 mL), under Ar at 100 ℃ for 12 h. Isolated yield. Values in parentheses indicate the C4:C3 ratios, which were determined by NMR using CH_2Br_2 as the internal standard.

In summary, we have reported the first palladium-catalyzed remote C-H phosphonylation of indole motifs at C4 and C6 positions, which likely proceeds through a C7-palladacycle/remote-activation process. The steric/electronic property of the phophinoyl DG plays an important role in selectivity-controlling. Examples of remote C4-H difluoromethylation with $BrCF_2COOEt$ are also presented, suggesting that the strategy may offer a general blueprint for other cross-couplings. Studies on the mechanistic investigations as well as new cross coupling reactions are currently ongoing in our laboratory.

Acknowledgements

This work was supported by the Funded by National Program for Support of Top-notch Young Professionals, Fund of Taishan scholar project, Shandong Provincial Natural Science Foundation for Distinguished Young Scholars (JQ201722), Qingdao Science and Technology Benefit People Demonstration Guide Special Project (20-3-4-20-nsh), Fundamental Research Funds of Shandong University (2020GN033), and Haiyan Sui and Xiaoju Li from Shandong University Core Facilities for Life and Environmental Sciences for their help with the NMR.

Keywords: phosphonylation • C-H activation • indoles • palladium • regioselectivity

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10.1002/anie.202103395

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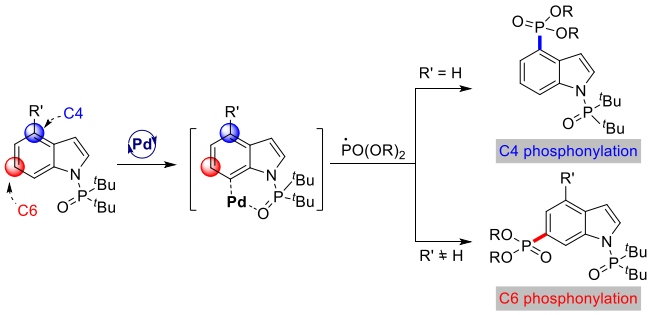

Pd-catalyzed remote C-H activation: A palladium-catalyzed remote phosphonylation for the indole C4- and C6-positions was achieved by a radical approach. The preliminary mechanistic studies indicated that the reactions may proceed via a C7-palladacycle/remote-activation process.