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FULL PAPER

Palladium-Catalyzed Phosphoryl-Carbamoylation of Alkenes: Construction of Nonbenzylic C(sp^3)–P(O)R_2 Bonds via C(sp^3)–Pd(II)–P(O)R_2 Reductive Elimination

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Abstract. We report the first example of palladium-catalyzed phosphoryl-carbamoylation of alkene-tethered carbamoyl chlorides with P(O)H compounds. Both *H*-phosphinates and secondary phosphine oxides are compatible with this reaction. DPE-Phos was used as ligand to facilitate nonbenzylic C(sp^3)–P bonds formations via C(sp^3)–Pd(II)–P reductive elimination. By using this protocol, a range of phosphorylated oxindoles and lactams were obtained in moderate to good yields.

Keywords: Carbamoyl Chlorides; Palladium; Phosphoryl-Carbamoylation; C(sp^3)–Pd(II)–P Reductive Elimination; Phosphorylated Oxindoles

Introduction

The development of new methodologies for the construction of C–P bonds have gained great attention over the years due to their omnipresence in pharmaceuticals, natural products, ligands and functional materials.[1] Accordingly, a variety of robust approaches were developed to forge C–P bonds.[2-12] Compared with the well-established C(sp^2)–P bond forming reaction,[2] the C(sp^3)–P bond forming strategy still remains limited. Apart from the traditional Michaelis–Becker and Michaelis–Arbuzov reactions,[3] the radical addition of P(O)H compounds to alkenes was recognized as an important synthetic strategy for the construction of C(sp^3)–P bond.[4] However, these methods require excess amounts of P(O)H compounds to facilitate the reaction. Moreover, oxidants were needed in most of the cases, resulting in poor tolerance of oxidizable functional groups. Therefore, it is of great significance to develop new methods for the purpose of constructing C(sp^3)–P bonds in oxidant-free conditions, aiming to noticeably reduce the waste of P(O)H compounds.

To overcome these drawbacks, the recently emerged palladium-catalyzed cross-coupling could serve as an alternative approach for the formation of C(sp^3)–P bond. In the past few years, primary developments have been achieved in benzyl–Pd(II)–P reductive elimination to form benzylphosphonates.[5-7] As depicted in Scheme 1a, Jia et al.[6] attempted to employ dearomative arylphosphorylation by palladium catalysis for indoles. The benzylic C(sp^3)–P bond was formed *via* C-Pd(II)-P reductive elimination. Very recently, Dong and co-workers[7] realized a Pd(II)-catalyzed benzylic C(sp^3)–H phosphorylation reaction between 8-methylquinolines with P(O)H compounds (Scheme 1b). However, approaches to construct nonbenzylic C(sp^3)–P bonds *via* palladium catalysis are quite rare until now. Since 2000, major breakthroughs were reported by Tanaka et al.[8] and Han et al.,[9] who constructed nonbenzylic C(sp^3)–P bonds through reductive elimination of alkyl–Pd(II)–P. It is noteworthy that utilization of 4,4,5,5-tetramethyl-1,3-dioxaphospholane2-oxide is essential to carry out this transformation. In 2019, Tong et al.[10] reported the carbophosphorylatioin of (*Z*)-1-iodo-1,6-diene with diethyl *H*-phosphonate under Pd(0) catalysis. However, the common coupling partner $HP(O)Ph_2$ did not lead to the corresponding phosphorylation product (Scheme 1c). Recently, Tang et al.[11] disclosed a Pd-catalyzed carbophosphorylation of acrylamides with secondary phosphine oxides. It was worth noting that *H*-phosphonates were not compatible with this reaction system (Scheme 1c).

Inspired by these important contributions, our attention was drawn to the use of alkene-tethered carbamoyl chlorides[13] as substrates in the phosphoryl-carbamoylation reaction. We envisioned that the relevant Pd(II) species could be captured by P(O)H compounds, followed by C(sp^3)–Pd(II)–P reductive elimination to construct C(sp^3)–P bond (Scheme 1d).

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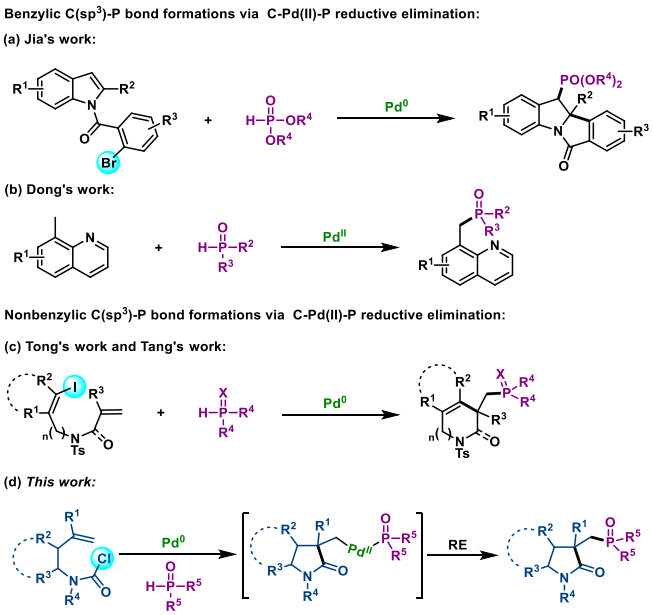


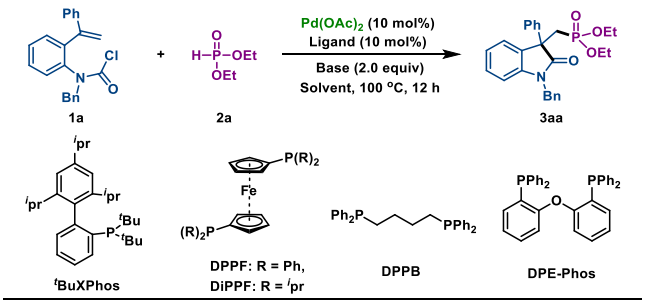
Scheme 1. C(sp^3)–P bond formations *via* C–Pd(II)–P reductive elimination.

Moreover, the corresponding β-H elimination process could be fully inhibited by the presence of R^1 substituents, avoiding the competition with the C(sp^3)–Pd(II)–P reductive elimination process. This would provide an efficient construction of the 3,3-disubstituted oxindole[14] and lactam[15] scaffolds. Thus, we developed a palladium-catalyzed phosphoryl-carbamoylation reaction of alkene-tethered carbamoyl chlorides (ATCC) with *H*-phosphinates or secondary phosphine oxides, during which a new C–C bond, a new nonbenzylic C(sp^3)–P bond, and a five-membered ring were formed in one step. It is noteworthy that the current research may be the first Heck/phosphorylation reaction system to construct a nonbenzylic C(sp^3)–P bond, which is compatible with both *H*-phosphonates and secondary phosphine oxides.

Results and Discussion

We initiated the reaction optimization of the domino phosphoryl-carbamoylation reaction by utilizing benzyl(2-(1-phenylvinyl)phenyl)carbamic chloride **1a** and diethyl *H*-phosphonate **2a**. The desired product **3aa** was obtained in 52% yield under $Pd(OAc)_2/PPh_3$ catalysis (Table 1, entry 1). Accordingly, a range of diphosphines and monophosphines were tested (Table 1, entries 2-9). As expected, a non-negligible influence of the ligand on the reaction outcome was noted, and the most efficacious ligand was DPE-Phos, with a 85% yield of the product (Table 1, entry 9). Tong group have shown that the C(sp^3)–P reductive elimination might be promoted by excess amount of phosphine ligand.[10] But in our reaction, excess amount of DPE-Phos was not necessary for this transformation (Table 1, entry 10). Other catalysts, including $PdCl_2$ and $Pd(MeCN)_2Cl_2$, were found to be less efficient than $Pd(OAc)_2$ for the above transformation (Table 1, entries 11 and 12). We then attempted to assess numerous bases, including K_2CO_3, Cs_2CO_3, NaO^{t}Bu, LiO^{t}Bu, Et_3N, as well as DBU, while no superior performance was noted in comparison with Na_2CO_3 (Table 1, entries 13-18). For the purpose of enhancing the yield, we made an effort to evaluate diverse solvents, including DMF, DCE, Toluene, CCl_4, dioxane, and DME, but better results were not shown (Table 1, entries 19-24). Reduction of the reaction temperature to 80 °C may result in decline of yield to 58%, refreshing a remarkable amount of starting materials (Table 1, entry 25). Moreover, increasing the temperature to 120 °C might result in a similar yield (Table 1, entry 26). The yield was reduced at 0.2 mmol **2a**, and it was higher at 0.4 mmol **2a** (Table 1, entry 27). Furthermore, we didn't note any remarkable changes in yield in case of elevation of **2a** loading to 3.0 equiv. (Table 1, entry 28). Eventually, we attempted to employ the following optimum conditions: $Pd(OAc)_2$ (10 mol%)/DPE-Phos (10 mol%)/Na_2CO_3 (2.0 equiv) in MeCN in N_2 atmosphere for 12 h at 100 °C.

Table 1. Reaction Conditions Optimization [a]



Entry	Ligand	Base	Solvent	Yield (%)[b]
1[c]	PPh_3	Na_2CO_3	MeCN	52%
2[c]	P(4-F-C_6H_4)$_3$	Na_2CO_3	MeCN	46%
3[c]	P(4-MeO-C_6H_4)$_3$	Na_2CO_3	MeCN	32%
4[c]	$PCy_3.HBF_4$	Na_2CO_3	MeCN	44%
5[c]	^{t}BuXPhos	Na_2CO_3	MeCN	50%
6	DPPF	Na_2CO_3	MeCN	58%
7	DiPPF	Na_2CO_3	MeCN	59%
8	DPPB	Na_2CO_3	MeCN	52%
9	**DPE-Phos**	**Na_2CO_3**	**MeCN**	**85%**
10[d]	DPE-Phos	Na_2CO_3	MeCN	83%
11[e]	DPE-Phos	Na_2CO_3	MeCN	52%
12[f]	DPE-Phos	Na_2CO_3	MeCN	46%
13	DPE-Phos	K_2CO_3	MeCN	45%
14	DPE-Phos	Cs_2CO_3	MeCN	50%
15	DPE-Phos	NaO^{t}Bu	MeCN	41%
16	DPE-Phos	LiO^{t}Bu	MeCN	22%
17	DPE-Phos	Et_3N	MeCN	70%
18	DPE-Phos	DBU	MeCN	ND[g]
19	DPE-Phos	Na_2CO_3	DMF	ND[g]
20	DPE-Phos	Na_2CO_3	DCE	69%
21	DPE-Phos	Na_2CO_3	Toluene	51%
22	DPE-Phos	Na_2CO_3	CCl_4	ND[g]
23	DPE-Phos	Na_2CO_3	Dioxane	10%
24	DPE-Phos	Na_2CO_3	DME	12%
25[h]	DPE-Phos	Na_2CO_3	MeCN	58%
26[i]	DPE-Phos	Na_2CO_3	MeCN	82%
27[j]	DPE-Phos	Na_2CO_3	MeCN	70%
28[k]	DPE-Phos	Na_2CO_3	MeCN	84%

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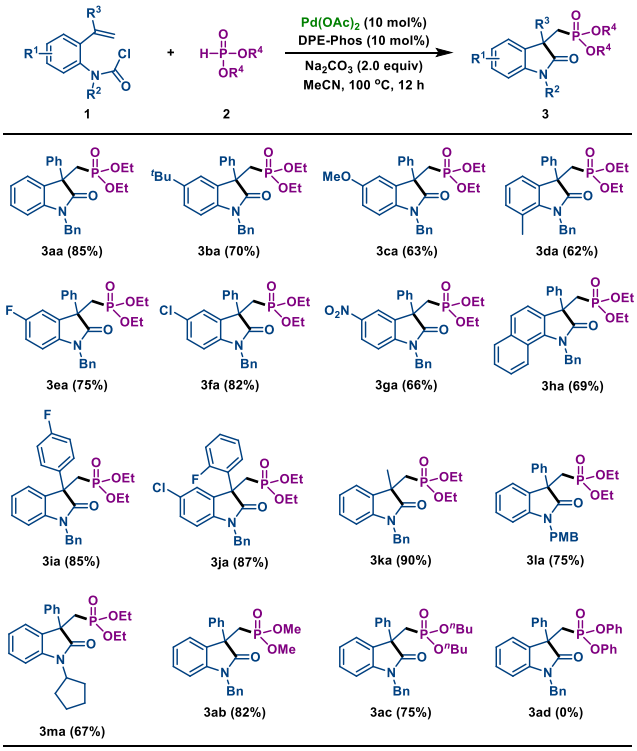
[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), $Pd(OAc)_2$, (0.02 mmol), ligand (0.02 mmol), base (0.4 mmol), solvent (2.0 mL), 12 h, 100 °C, under N_2. [b] Isolated yield. [c] Ligand (0.04 mmol) was utilized. [d] Ligand (0.06 mmol) was used. [e] $PdCl_2$ was used as catalyst. [f] $Pd(MeCN)_2Cl_2$ was used as catalyst. [g] ND = Not detected. [h] The reaction was run at 80 °C. [i] The reaction was run at 120 °C . [j] **2a** (0.2 mmol was utilized. [k] **2a** (0.6 mmol) was utilized.

We then assessed the substrate scope of ATCC **1** and *H*-phosphonates **2** in this method, and the outcomes are listed in Table 2. Diverse ATCC, bearing either electron-donating groups or electron-withdrawing groups, smoothly underwent phosphoryl-carbamoylation reactions with diethyl *H*-phosphonate **2a**, delivering phosphinonyloxindoles **3aa**-**3ga** (62%-85%). Functional groups such as methoxyl, fluoro, chloro and nitro groups, which are useful in further synthetic transformations, were all well tolerated under the current conditions. The desired product **3ka** was obtained in 90% yield. *p*-Methoxybenzyl (**1l**) and cyclopentyl groups (**1m**) were tolerated, providing the corresponding products **3ma** and **3la** in 67% and 75% yields, respectively. Additionally, the reaction could also extended to other *H*-phosphonates. Dimethyl and dibutyl *H*-phosphonates could appropriately react with **1a** to attain the products **3ab** and **3ac** in satisfactory yields. Nevertheless, it was found that the reaction was inefficacious with diphenyl *H*-phosphonate (**3ad**).

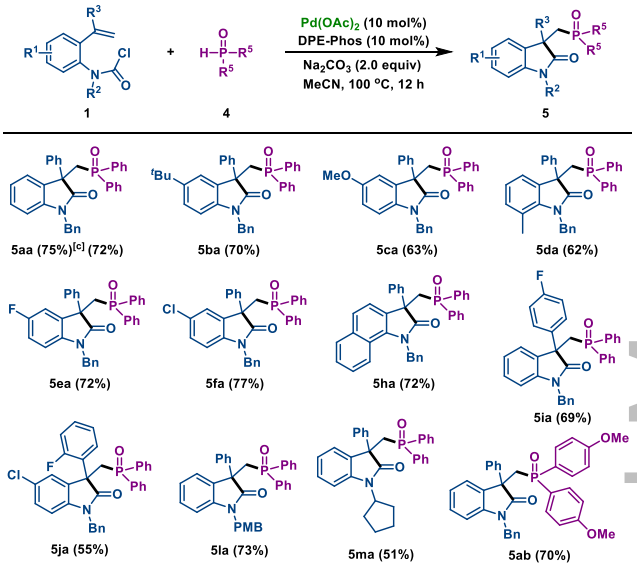
Table 2. Reaction scope of ATCC with *H*-phosphonates[a],[b]



[a] Reaction conditions: **1** (0.2 mmol), **2** (0.4 mmol), $Pd(OAc)_2$ (10 mol%), DPE-Phos (10 mol%), Na_2CO_3 (0.4 mmol) in 2.0 mL of MeCN at 100 °C under N_2 atmosphere for 12 h. [b] Isolated yield.

With respect to other P(O)H compounds, we attempted to utilize diarylphosphine oxides (Table 3). To our delight, $HP(O)Ph_2$ **4a** indeed reacted well with alkene-tethered carbamoyl chlorides **1** under the standard conditions, leading to phosphoryl-carbamoylation product **5aa** in 75% yield. However, **5aa** was extremely difficult to be purify because its polarity was similar to untreated $HP(O)Ph_2$. When the $HP(O)Ph_2$ loading was reduced to 1.0 equiv., we observed a similar yield, and purification was possible. As shown in Table 3, most of the ATCC **1** reacted well with $HP(O)Ph_2$ **4a**, providing the target phosphoryl-carbamoylation products **5** in moderate to good yields. Fortunately, except $HP(O)Ph_2$, $HP(O)(4\text{-}OMe\text{-}C_6H_4)_2$ **4b** was also suitable for the reaction and the corresponding product **5ab** was obtained in 70% yield.

Table 3. Reaction scope of ATCC with diarylphosphine oxides[a],[b]



[a] Reaction conditions: **1** (0.2 mmol), **4** (0.2 mmol), $Pd(OAc)_2$ (10 mol%), DPE-Phos (10 mol%), Na_2CO_3 (0.4 mmol) in 2.0 mL of MeCN at 100 °C under N_2 atmosphere for 12 h. [b] Isolated yield. [c] 2.0 equiv of **4** was used.

It is noteworthy that this methodology could be further applied to the synthesis of phosphorylated bicyclic lactams **7**. As shown in Table 4, cyclobutane-fused, cyclopentane-fused and cyclohexane-fused lactams **7aa**-**7ca** were formed as a single diastereomer in 45%-72% yields. Moreover, this reaction is tolerant toward heterocycle. Indeed, piperidine-fused lactam **7da** was also obtained as a single diastereomer in 77% yield.

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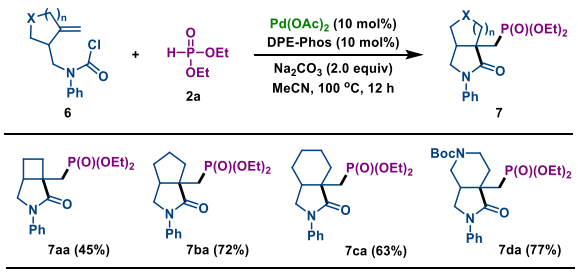
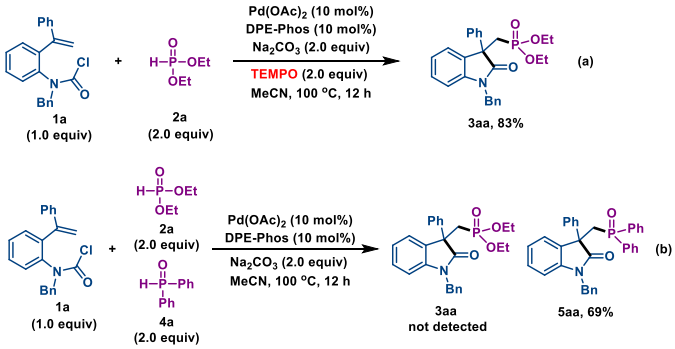
Table 4. The synthesis of phosphorylated bicyclic lactams[a],[b]



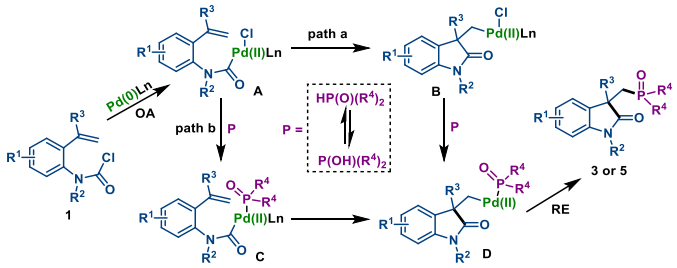
[a] Reaction conditions: **6** (0.2 mmol), **2a** (0.4 mmol), $Pd(OAc)_2$ (10 mol%), DPE-Phos (10 mol%), Na_2CO_3 (0.4 mmol) in 2.0 mL of MeCN under N_2 atmosphere at 100 °C for 12 h. [b] Isolated yield.

In order to rule out transition-metal-promoted radical process of P(O)H compounds,[4] **1a** was reacted with diethyl *H*-phosphonate under the standard conditions in the presence of TEMPO (2.0 equiv). Indeed, the radical scavenger did not negatively affect the reaction, and compound **3aa** was isolated in 83% (Scheme 2a). This result indicated that the radical process did not occur under our optimized conditions. Moreover, according to the experimental results of intermolecular competition between $HP(O)(OEt)_2$ and $HP(O)Ph_2$, the reactivity of $HP(O)Ph_2$ was higher compared to $HP(O)(OEt)_2$ (Scheme 2b).[4c]



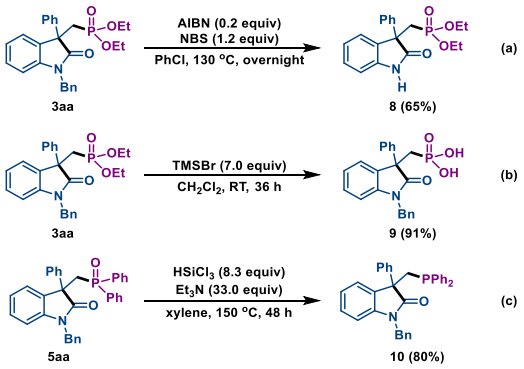
Scheme 2. Control experiments.

With respect to these findings and previous reports,[5-12] we propose the reaction mechanism depicted in Scheme 3. Formation of the mentioned reaction, as displayed in path a of Scheme 3, was noteworthy in form of Pd(0)'s oxidative addition to ATCC to finalize Pd(II) intermediate **A**, followed by insertion of alkene for producing alkyl–Pd(II) intermediate **B**. After substitution of ligand with $HP(O)(R^4)_2$ or $P(OH)(R^4)_2$, conversion of **B** into the alkyl–Pd(II)–P intermediate **D** was undertaken, which may be also produced by intermediate **C** (Scheme 3, path b).[10] Eventually, **D** received C–Pd(II)–P reductive elimination to deliver phosphinonyloxindoles **3** or **5**.



Scheme 3. Proposed mechanism.

We made an effort to investigate the applicability of the prepared phosphinonyloxindoles, in which a number of transformations were undertaken. As shown in Scheme 4, successful deprotection of **3aa** was noted feasible with the aid of AIBN/NBS reagent for attaining *N*-unprotected phosphinonyloxindoles **8** in 65% yield (Scheme 4a).[16] With exposure of **3aa** to TMSBr in DCM, the corresponding phosphoric acid **9** was obtained in 91% yield (Scheme 4b).[10] The corresponding trivalent phosphine product **10** could be attained in a yield of 80%, providing a method for the construction of bulky phosphine ligands with a 3,3-disubstituted oxindoles motif (Scheme 4c).[17]



Scheme 4. Transformations of phosphinonyloxindoles.

Conclusion

We developed a Heck/phosphorylation reaction system to construct nonbenzylic $C(sp^3)$–P bond, which is compatible with both *H*-phosphonates and secondary phosphine oxides, allowing for straightforward and efficient construction of numerous phosphorylated oxindoles and lactams in good to excellent yields. DPE-Phos was used as ligand to facilitate $C(sp^3)$–Pd(II)–P reductive elimination to form nonbenzylic $C(sp^3)$–P bonds. Further studies will be aimed at the development of new methodologies to synthesize functionalized oxindoles and lactams and will be reported in due course.

Experimental Section

General Procedure for the Synthesis of Phosphinonyloxindoles 3:

In a 38 mL sealed tube, the mixture of **1** (0.20 mmol), **2** (0.40 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), DPE-Phos (10.8 mg, 0.02 mmol), Na_2CO_3 (42.4 mg, 0.40 mmol) were dissolved in anhydrous MeCN (2 mL). Then, N_2 was used to purge the tube three times, followed by PTEF cap sealing. The reaction mixture was heated to 100 °C for 12 h. After the reaction, it was cooled down to room temperature. We then eliminated the solvents at reduced pressure, and it was followed by residue purification by column chromatography (CC) on silica gel (EtOAc/Petroleum Ether), giving rise to products **3**.

General Procedure for the Synthesis of Phosphinonyloxindoles 5:

In a 38 mL sealed tube, the mixture of **1** (0.20 mmol), **4** (0.20 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), DPE-Phos (10.8 mg, 0.02 mmol), Na_2CO_3 (42.4 mg, 0.40 mmol) were dissolved in anhydrous MeCN (2 mL). Then, N_2 was used to purge the tube three times, followed by PTEF cap sealing. The reaction mixture was heated to 100 °C for 12 h. After the reaction, it was cooled down to room temperature. We then eliminated the solvents at reduced pressure, and it was followed by residue purification by column chromatography (CC) on silica gel (EtOAc/Petroleum Ether), giving rise to products **5**.

General Procedure for the Synthesis of Phosphorylated Bicyclic Lactams 7:

In a 38 mL sealed tube, the mixture of **6** (0.20 mmol), **2a** (0.40 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), DPE-Phos (10.8 mg, 0.02 mmol), Na_2CO_3 (42.4 mg, 0.40 mmol) were dissolved in anhydrous MeCN (2 mL). The subsequent procedures were the same as those for the synthesis of phosphinonyloxindoles, giving rise to products **7**.

For a detailed description of the synthesis of starting materials and final products, see the Supporting Information.

Acknowledgements

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FULL PAPER

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