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Regioselective Direct C3-Phosphorylation of *N*-Sulfonylindoles under Mild Oxidative Conditions

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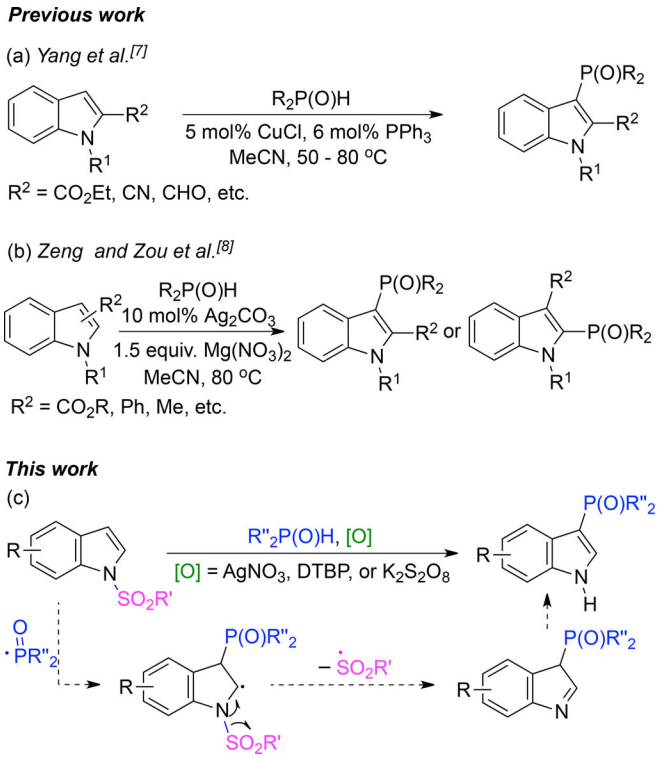
Abstract: The reactions of *N*-sulfonylindoles with H-phosphine oxides under oxidative conditions give a wide range of C-3 phosphorylated free (NH)-indoles. Several mild oxidants, such as $AgNO_3$, di-*tert*-butyl peroxide (DTBP), and $K_2S_2O_8$, can be used to promote this transformation.

Keywords: heterocycles; phosphorylation; radicals; regioselectivity; synthetic methods

Aromatic organophosphorus compounds represent an important class of chemicals in organic and organometallic chemistry,[1] materials science,[2] and medicinal chemistry.[3,4] Recently, the construction of 3-phosphoindole skeletons has received much attention due to their significant applications in pharmaceutical chemistry and transition metal catalysis.[5,6] Among all the successful strategies towards 3-phosphoindoles,[6c,7–9] transition metal-catalyzed direct C(sp^2)–H phosphorylation of indoles seems to be the most straightforward pathway. In 2014, Yang et al. reported the first Cu(I)-catalyzed cross-coupling reactions of C-2 substituted indoles with diphenylphosphine oxide and chiral (1*S*,2*S*,5*R*)-(−)-menthoxyphenylphosphinate for the synthesis of 3-phosphoindoles (Scheme 1a).[7] However, the reaction of C-2 unsubstituted *N*-methylindole with $Ph_2P(O)H$ gave only a trace amount of the desired product.[7] Very recently, Zeng and Zou et al. also developed a silver-catalyzed direct C(sp^2)–H phosphorylation of C-2 and C-3 substituted indoles with $Mg(NO_3)_2$ as additive (Scheme 1b).[8] It is notable that the reaction of unsubstituted indole with diphenylphosphine oxide took place in the presence of 2.2 equiv. of Ag_2CO_3, albeit giving a mixture of 2-phosphorylated indole and 2,3-diphosphorylated indole, which suggested that both 2- and 3-positions of indoles can be attacked by the phosphorus radical.[8,10] Therefore, it is necessary to develop a general and efficient method for regioselective C-3 phosphorylation of indoles. Moreover, by reduction with silanes, the phosphine oxides are also the key precursors of phosphine derivatives.[11]

Although indoles are known to be more susceptible to electrophilic attack at the β-position, the regioselective indole β-nucleophilic substitution was also made possible by the departure of the N-substituent as a leaving group from indolic nitrogen.[12] In addition, Zard et al. have recently discovered a desulfony-

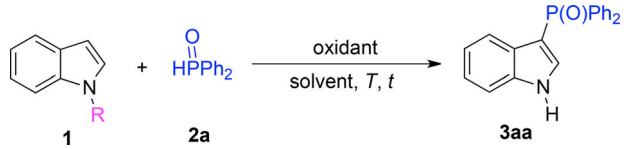


Scheme 1. C-3 Phosphorylation of indoles.

lative radical ring closure process for the formation of benzazepin-2-ones.[13] Notably, the fragmentation of the N–SO_2R bond next to a carbon radical was involved in the reaction by virtue of the correct alignment of the orbital containing the free electron with the antibonding orbital of the N–S bond.[13] Encouraged by these results, we envisaged the C-3 phosphorylation of *N*-sulfonylindoles *via* addition of the phosphoryl radical at the β-position driven by sequential cleavage of the N–SO_2R bond (Scheme 1c). Herein, we wish to disclose our findings on the regioselective formation of C-3 phosphorylated indoles through the reactions of *N*-sulfonylindoles with H-phosphine oxides under mild oxidative conditions.

According to our experience in the silver-promoted direct phosphorylation of (benzo)thiazoles,[14,15] we initially conducted the reaction of *N*-phenylsulfonylindole **1a** and diphenylphosphine oxide **2a** in the presence of 1 equiv. of AgOAc in acetonitrile at 100 °C for 25 h. To our delight, the desired C-3 phosphorylation product **3aa** was produced in 46% yield (Table 1, entry 1).[10b,16] The phenylsulfonyl group was indeed removed during the reaction as hypothesized. When Ag_2CO_3 was used instead of AgOAc, the desired product **3aa** was isolated in 56% yield (entry 2). The reaction performed in the presence of 1 equiv. of $AgNO_3$ gave **3aa** in a higher yield (73%, entry 3). Increasing the amount of **2a** to 3 equiv. led to the formation of **3aa** in 96% yield (entry 4). When the reaction was carried out at higher or lower reaction temperatures, the yield of **3aa** was reduced obviously (entry 5 and 6). In the absence of any silver salts, no phosphorylation product was observed (entry 7). The reaction also worked well without the addition of 4 Å molecular sieves, albeit affording **3aa** in diminished yield (85%, entry 8). Notably, when simple indole was treated with diphenylphosphine oxide **2a** in the presence of $AgNO_3$, the desired product **3aa** was not observed at all (entry 9). Furthermore, both *N*-tosylindole and *N*-mesylindole reacted with **2a** giving the desired product **3aa** in good yields (entry 10 and 11). Thereafter, several other oxidants, such as DTBP,[17] $(NH_4)_2S_2O_8$, $Na_2S_2O_8$, and $K_2S_2O_8$,[18] were also examined (see the Supporting Information). It was found that DTBP and $K_2S_2O_8$ could also promote the C-3 phosphorylation of **1a** with **2a** and afforded the product **3aa** in good yields (entries 12–16).

Table 1. Optimization of the reaction conditions.[a]



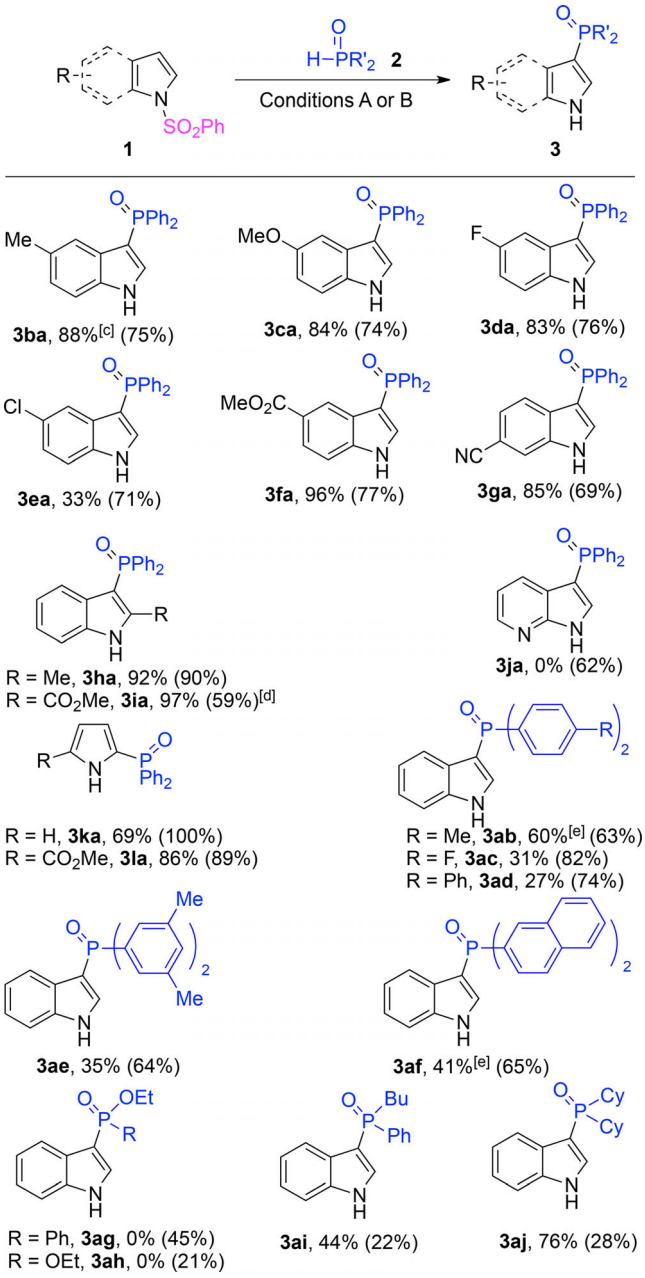
1 **2a** **3aa**

Entry	R	[O] (equiv.)	*T* [°C]	*T* [h]	Yield [%][b]
1[c]	SO_2Ph (**1a**)	AgOAc (1)	100	25	46
2[c]	SO_2Ph (**1a**)	Ag_2CO_3 (1)	100	15	56
3[c]	SO_2Ph (**1a**)	$AgNO_3$ (1)	100	15	73
4	SO_2Ph (**1a**)	$AgNO_3$ (1)	100	20	96
5	SO_2Ph (**1a**)	$AgNO_3$ (1)	80	20	59
6	SO_2Ph (**1a**)	$AgNO_3$ (1)	120	20	81
7	SO_2Ph (**1a**)	–	100	20	0
8[d]	SO_2Ph (**1a**)	$AgNO_3$ (1)	100	20	85
9	H (**1′**)	$AgNO_3$ (1)	100	20	0
10	Ts (**1a′**)	$AgNO_3$ (1)	100	20	94
11	Ms (**1a″**)	$AgNO_3$ (1)	100	20	61
12[d]	SO_2Ph (**1a**)	DTBP (3)	120	21	58
13[d]	SO_2Ph (**1a**)	DTBP (3)	140	21	73
14[d,e]	SO_2Ph (**1a**)	DTBP (3)	140	21	84
15	SO_2Ph (**1a**)	$K_2S_2O_8$ (1)	100	24	76
16	SO_2Ph (**1a**)	$K_2S_2O_8$ (2)	100	24	93

[a] *Reaction conditions:* **1** (0.2 mmol), **2a** (3 equiv.), [O], 4 Å molecular sieves (100 mg), and MeCN (3 mL) under an argon atmosphere in a sealed tube.
[b] Isolated yields.
[c] Using **2a** (2 equiv.).
[d] Without molecular sieves.
[e] Using EtOAc (3 mL).

With the optimized reaction conditions in hand, the substrate scope was examined under both $AgNO_3$- and DTBP-mediated conditions, respectively (Table 2). A series of *N*-sulfonylindoles bearing electron-donating and electron-withdrawing groups reacted with diphenylphosphine oxide affording the desired desulfonylated phosphorylation products in good yields (**3ba–3ia**). Surprisingly, the reaction of 5-chloro-1-(phenylsulfonyl)-1*H*-indole **1e** with **2a** in the presence of $AgNO_3$ gave the desired product **3ea** in only 33% yield. Both the sterically hindered 2-methyl-1-(phenylsulfonyl)-1*H*-indole **1h** and methyl 1-(phenylsulfonyl)-1*H*-indole-2-carboxylate **1i** reacted with **2a** in the presence of $AgNO_3$ or DTBP giving the corresponding products **3ha** and **3ia** in high yields. Conducting the reaction of 1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridine **1j** and **2a** in the presence of $AgNO_3$ did not afford any phosphorylation products owing to the coordinating properties of the pyridine nitrogen atom. To our delight, the reaction between **1j** and **2a** worked smoothly in the presence of 3 equiv. DTBP providing the desired product **3ja** in 62% yield. Furthermore, treatment of pyrroles **1k** and **1l**, respectively, with **2a** led to the corresponding α-phosphorylation products **3ka** and **3la** in high yields.[19] No β-phosphorylation product was observed at all. Thereafter, a range of H-phosphine oxides was examined. Under $AgNO_3$-promoted conditions, the introduction of both electron-rich and electron-deficient substituents on the phenyl ring of diarylphosphine oxides led to the formation of the desired products **3ab–3af** in varying yields (**3ab**, 60%; **3ac**, 31%, **3ad**, 27%; **3ae**, 35%; **3af**, 41%). However, the reactions performed in the presence of DTBP gave much better results (63–82%). Subsequently, the reactions of ethyl phenylphosphinate **2g** and diethyl phosphonate **2h** with *N*-

Table 2. Synthesis of C-3 phosphorylated indoles with $AgNO_3$ or DTBP.[a,b]



[a] *Conditions A:* **1** (0.2 mmol), **2** (0.6 mmol), $AgNO_3$ (0.2 mmol), 4 Å MS (100 mg), MeCN (3 mL), 100 °C, 20 h. *Conditions B:* **1** (0.2 mmol), **2** (0.6 mmol), DTBP (0.6 mmol), EtOAc (3 mL), 140 °C, 21 h.

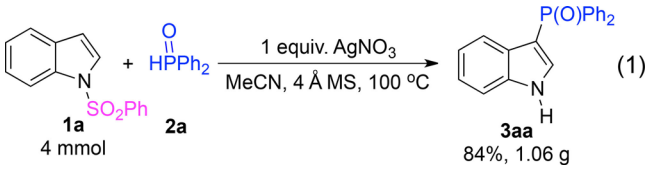
[b] Isolated yields; the yields of reactions under *conditions B* are shown in parenthesis.

[c] For 40 h.

[d] In MeCN.

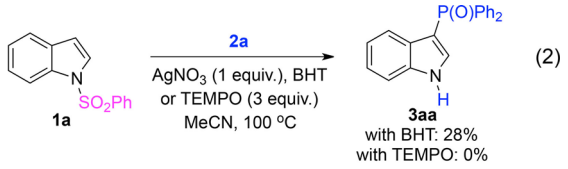
[e] For 30 h.

phenylsulfonylindole **1a** were conducted. Although no desired products were observed in the presence of $AgNO_3$, the corresponding DTBP-promoted reactions worked smoothly affording the phosphorylation product **3ag** and **3ah** in 45% and 21% yields, respectively.[20] Later, the butyl(phenyl)phosphine oxide **2i** could also react with **1a** under oxidative conditions to give the corresponding **3ai** in moderate yield. The reaction between dicyclohexylphosphine oxide **2j** and *N*-phenylsulfonylindole **1a** in the presence of $AgNO_3$ was performed leading to the formation of **3aj** in 76% yield. However, the DTBP-promoted reaction of **2j** gave only 28% yield of **3aj**. Notably, it was also found that the phosphorylation of **1a** with $Ph_2P(O)H$ in the presence of $AgNO_3$ was easily scaled up to 4 mmol scale, affording 1.06 g of **3aa** in 84% yield [Eq. (1)].



Furthermore, several reactions between different *N*-sulfonylindoles and H-phosphine oxides in the presence of $K_2S_2O_8$ were conducted. Compared with DTBP-mediated transformations, the C-3 phosphorylated indoles were obtained in similar yields (Table 3).

To investigate the mechanism of these oxidant-promoted C-3 phosphorylations of *N*-sulfonylindoles, several control experiments were performed. For the reaction of **1a** with **2a** in the presence of $AgNO_3$, the addition of BHT and TEMPO as radical scavengers both suppressed the formation of the phosphorylation product [Eq. (2)]. Moreover, for the reaction between **1a** and **2a** in the presence of DTBP in THF, besides the formation of **3aa**, S-phenyl diphenylphosphinothioate **4** was also isolated in 41% yield [Eq. (3), see also the Supporting Information].[21] These preliminary results and the good regioselectivity of the phosphorylation reactions are all consistent with the radical mechanism as we hypothesized. However, a mechanism involving the oxidation of *N*-sulfonylindole to a cation radical followed by nucleophilic addition of phosphinous acid $P(OH)R'_2$ at the 3-position cannot be excluded (see the Supporting Information).[22]



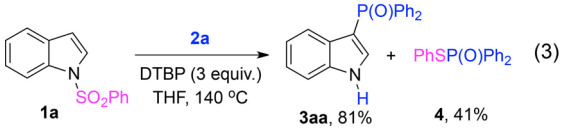
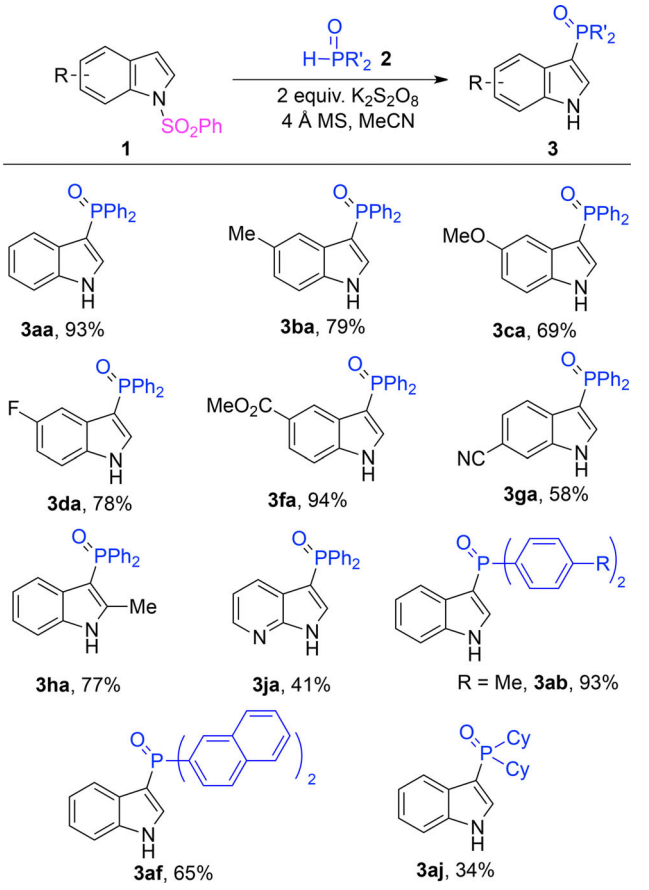


Table 3. $K_2S_2O_8$-promoted phosphorylation of *N*-sulfonylindoles with H-phosphine oxides.[a,b]



[a] *Reaction conditions:* **1** (0.2 mmol), **2** (0.6 mmol), $K_2S_2O_8$ (0.4 mmol), 4 Å MS (100 mg), MeCN (3 mL), 100 °C, 24 h.

[b] Isolated yields.

In conclusion, we have developed an efficient general approach for the synthesis of 3-phosphoindoles starting from *N*-sulfonylindoles and H-phosphine oxides. Several simple oxidants, such as $AgNO_3$, DTBP, and $K_2S_2O_8$, could be used to promote the reaction. Further investigations on the detailed mechanism, scope and applications of this method are underway in our laboratory.

Experimental Section

General Procedure for $AgNO_3$- or $K_2S_2O_8$-Meditated C-3 Phosphorylation of *N*-Sulfonylindoles

To a 25-mL tube, *N*-sulfonylindole **1** (0.2 mmol), $AgNO_3$ (0.2 mmol) or $K_2S_2O_8$ (0.4 mmol), 4 Å MS (100 mg), and acetonitrile (3.0 mL) were added under an argon atmosphere. After the reaction mixture had been stirred at room temperature for about two minutes, H-phosphine oxide **2** (0.6 mmol) was added. Then the tube was sealed with a Teflon-lined cap, and the reaction mixture was stirred at 100 °C for 20 or 24 hours. After cooling the reaction mixture to room temperature, it was quickly filtered through a short column (2 cm) of silica gel to remove the 4 Å MS and salt. Subsequently, the filtrate was washed with saturated $NaHCO_3$ and extracted with dichloromethane. The combined extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 1:1 to 1:3; acetone) to afford the product **3**.

General Procedure for DTBP-Meditated C-3 Phosphorylation of *N*-Sulfonylindoles

To a 25-mL tube, *N*-sulfonylindole **1** (0.2 mmol), ethyl acetate (3 mL), H-phosphine oxide **2** (0.6 mmol), and DTBP (0.6 mmol) were added under an argon atmosphere. Then the tube was sealed with a Teflon-lined cap, and the reaction mixture was stirred at 140 °C for 21 hours. Subsequently, the reaction was quenched with saturated $NaHCO_3$ and extracted with dichloromethane. The combined extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 1:1 to 1:3; acetone) to afford the product **3**.

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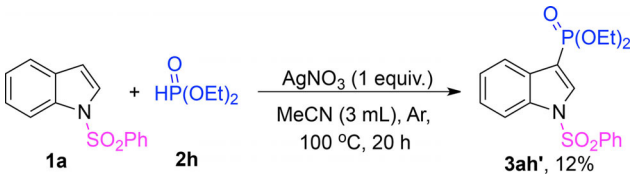
[19] CCDC 1510627 contains the supplementary crystallographic data for compound **3la** in this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif. See also the Supporting Information.

[20] For the reaction between diethyl phosphonate **2h** and **1a** in the presence of $AgNO_3$, the direct C–H phosphorylation product **3ah′** was isolated in 12% yield.



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