Photoredox catalyst-mediated direct regioselective phosphonylation of indoles

Zijian Zhao\textsuperscript{a,b}, Zehui Min\textsuperscript{a}, Wanhong Dong\textsuperscript{a}, Zhihong Peng\textsuperscript{a}, and Delie An\textsuperscript{a}

\textsuperscript{a}State Key Laboratory of Chemo/biosensing and Chemometrics, College of Chemistry and Chemical Engineering, Hunan University, Changsha, China; \textsuperscript{b}Huaihua University, Huaihua, China

\textbf{ABSTRACT}

An efficient hetero-cross-dehydrogenative-coupling (hetero-CDC) reaction between N-protected indoles and phosphites to 2-indolyphosphites is described. The regioselective methodology took place in the presence of photo redox catalyst Ru(bpy)\textsubscript{3}(PF\textsubscript{6})\textsubscript{2} combined with oxygen as an clean oxidant when exposed to visible light, furnishing the 2-indolyphosphites as the exclusive products in moderate to good yields with good functional group tolerance. Moreover, the phosphonylation protocol was proved by the control reaction to proceed through the radical pathway.

\textbf{GRAPHICAL ABSTRACT}

\textbf{ARTICLE HISTORY}

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\textbf{KEYWORDS}

CDC reaction; indoles; phosphonylation; photoredox catalyst; visible light

\textbf{Introduction}

Construction of the sp\textsuperscript{2} hybrid C-P bond has attracted widespread research interest not only because of its significance to organic synthesis, pharmaceutical chemistry, and nucleic acid chemistry,\textsuperscript{[1]} but also because it is used widely as ligand in transition-metal catalysts.\textsuperscript{[2]} Typically, C-P bonds have been realized by either S\textsubscript{RN1} reactions of aryl halides\textsuperscript{[3]} with Ar\textsubscript{2}P\textsuperscript{-} or transition-metal-catalyzed Arbuzov reactions.\textsuperscript{[4]} However, unstable or poisonous but high-cost preactivated substrates such as halogenated arenes,\textsuperscript{[5]} aryl borates,\textsuperscript{[6]} halophosphonates,\textsuperscript{[2]} and others\textsuperscript{[8]} were involved in the transformations.

Hetero-CDC reactions have become a direct and promising strategy for coupling two nucleophilic reagents with high step- and atom-economy and environmental sustainability.\textsuperscript{[9]} The topic has gained significant development as C(sp\textsuperscript{2})-P bond formation has been realized in the presence of various transition metal catalysts\textsuperscript{[10]} under oxidative conditions through a C-H/P-H dual activation pathway. As the first example was reported by Zhang and coworkers, hetero-arylphosphonates were obtained with the assistance of Mn (OAc)\textsubscript{3}.\textsuperscript{[11]} Moreover, indolation of phosphites has also been realized with the transition-metal-catalyzed systems, such as silver, copper, or palladium catalytic reactions.
harsh conditions, poor regioselectivity, and usage of external oxidants were unavoidable for the transformations.\textsuperscript{[12]}

It is noteworthy that the photoredox-catalyst-mediated protocols recently have been well established for the carbon-carbon\textsuperscript{[13]} and carbon-hetero\textsuperscript{[14]} bond-forming reactions in the presence of easily accessible ruthenium bipyridyl and iridium phenylpyridyl complexes. The methodology opened a promising avenue to compounds with C-P bonds in a cross-dehydrogenative fashion. Thus, possibilities for the new approaches under mild conditions or with clean oxidants were sought for the indolation of phosphites. Herein, we report the newly discovered photo-redox-catalyst-mediated reaction for the construction of C-P bonds between \textit{N}-protected indoles and phosphites.

**Discussion**

The optimization of the reaction conditions was endeavored using \textit{N}-methyl indole (1a) and dimethyl phosphate (2a) as the model substrates (Table 1). Disappointingly, FeCl$_3$, CuI, and Cu(OAc)$_2$ failed to afford the desired indolated phosphites under the oxidative conditions when combined with various oxidants such as \textit{m}-CPBA, di-\textit{tert}-butyl peroxide (DTBP), and \textit{tert}-butyl hydroperoxide (TBHP) (entries 1–4). While the utilizations of silver catalysts such as AgNO$_3$ and AgOAc were able to make the reactions happen when K$_2$S$_2$O$_8$ was used as the oxidant, but in low conversions (entries 5–8). Suprisingly, the introduction of a photoredox catalyst, Ru(bpy)$_3$(PF$_6$)$_2$, into the C-P bond-forming procedure was able to make the reaction take place with exposure to visible light, furnishing the desired indolated phosphate 3a in 79\% yield (entry 9). A trace product was provided when the reaction was conducted in a completely dark environment (entry 10).

With the optimal conditions in hand, the scope and limitations of the substrates were evaluated as summarized in Table 2. Gratifyingly, \textit{N}-tert-butyl indole 1b reacted with dimethyl phosphate 2a, offering the desired product 3b in 76\% yield (entry 2). \textit{N}-Benzyl

| Entry | Catalyst | Oxidant | Solvent | Temp. (°C) | Yield (\%)$^a$ |
|-------|----------|---------|---------|------------|---------------|
| 1     | FeCl$_3$ | \textit{m}-CPBA | DCE | 70 | n.d. |
| 2     | CuI      | TBHP    | DCE | 70 | n.d. |
| 3     | Cu(OAc)$_2$ | DTBP | DCE | 70 | n.d. |
| 4     | Cu(OAc)$_2$ | TBHP | DCE | 70 | n.d. |
| 5     | AgNO$_3$ | K$_2$S$_2$O$_8$ | DCE | 70 | 28 |
| 6     | AgNO$_3$ | K$_2$S$_2$O$_8$ | DMSO | 70 | 32 |
| 7     | AgNO$_3$ | K$_2$S$_2$O$_8$ | DMF | 70 | 42 |
| 8     | AgOAc    | K$_2$S$_2$O$_8$ | DMF | 70 | 38 |
| 9     | Ru(bpy)$_3$(PF$_6$)$_2$ | O$_2$ | DCM | r.t. | 79 |
| 10    | Ru(bpy)$_3$(PF$_6$)$_2$ | O$_2$ | DCM | r.t. | Trace$^d$ |

\textsuperscript{a}Conditions: 1a (0.3 mmol), 2a (0.36 mmol), cat. 10 mol\%, oxidant (2.0 equivalent), solvent (3 mL) for 10 h.

\textsuperscript{b}Isolated yields.

\textsuperscript{c}5 mol\% of catalyst was used.

\textsuperscript{d}The result was obtained in the dark.
indole 1c coupled with 2a successfully, giving the N-benzyl-2-phosphonylated indole (3c) in 81% yield (entry 3). In a similar fashion, N-protected indoles with electron-rich and electron-poor benzyl groups such as 4-methyl (1d), 4-fluoro (1e), 4-chloro (1f), 4-bromo (1g), 4-cyanobenzyl (1h), and benzyl and 2-naphthylmethyl (1i) substituted indoles reacted with 2a smoothly, furnishing the desired products 3d–3i in yields ranging from 74% to 81% (entries 4–9). N-Aryl indoles also underwent the indolation reaction with 2a successfully. For example, N-(4-methylphenyl)- (3j) and N-(4-methoxyphenyl)- (3k) 2-phosphonylated indoles were obtained in moderate to good yields, 72% and 80% respectively (entries 10 and 11). With the benzyl group as the protecting group of indoles,

Table 2. Substrate scope of the one-pot protocol.\(^a\)

|        | R\(^1\) | R\(^2\) | R\(^3\) | 3      | Yield (%)\(^b\) |
|--------|---------|---------|---------|--------|-----------------|
| 1      | H       | Me      | Me      | 3a     | 79              |
| 2      | H       | n-Bu    | Me      | 3b     | 76              |
| 3      | H       | Benzyl  | Me      | 3c     | 81              |
| 4      | H       | 4-Methylbenzyl | Me | 3d     | 75              |
| 5      | H       | 4-Fluorobenzyl | Me | 3e     | 78              |
| 6      | H       | 4-Chlorobenzyl | Me | 3f     | 74              |
| 7      | H       | 4-Bromobenzyl | Me | 3g     | 78              |
| 8      | H       | 4-Cyanobenzyl | Me | 3h     | 81              |
| 9      | H       | 2-Naphthylmethyl | Me | 3i     | 80              |
| 10     | H       | 4-Methylphenyl | Me | 3j     | 72              |
| 11     | H       | 4-Methoxyphenyl | Me | 3k     | 80              |
| 12     | H       | Benzyl   | Et      | 3l     | 76              |
| 13     | H       | Benzyl   | i-Pr    | 3m     | 82              |
| 14     | H       | Benzyl   | n-Bu    | 3n     | 80              |
| 15     | S-CN    | Benzyl   | Me      | 3o     | 80              |
| 16     | S-CN    | Benzyl   | Et      | 3p     | 82              |
| 17     | S-CN    | Benzyl   | i-Pr    | 3q     | 79              |
| 18     | S-CN    | Benzyl   | n-Bu    | 3r     | 78              |

\(^a\)Conditions: 1 (0.5 mmol), 2 (0.6 mmol), Ru(bpy)\(_3\)(PF\(_6\))\(_2\) (5 mol%) in DCM (5.0 mL) at room temperature for 10 h.

\(^b\)Isolated yields.

Figure 1. XRD analysis of 3f (thermal ellipsoids are drawn at 30% probability).
different functional groups were tested on the phosphites. In the same way, diethyl- (2\text{I})
, di-iso-propyl- (2\text{m}), and di-n-butyl- (2\text{n}) phosphites reacted with N-protected indole 1\text{c}
 successfully, offering the corresponding products 3\text{l}–3\text{n} in yields ranging from 76\% to
82\% (entries 12–14). In a similar manner, N-benzyl-2-phosponylated-5-nitri l indoles
3\text{o}–3\text{r} were obtained in 78–82\% yields (entries 15–18).

As shown in Figure 1, structure of the product 3\text{f} was unequivocally determined by
the analysis of x-ray diffraction (XRD).\[^{[15]}\] The results of the analysis showed that the
indolation reaction took place exclusively on the C2 position of substituted indoles.

Based on our previously reported mechanism investigations, a plausible mechanism for
the present hetero-CDC protocol was proposed, as illustrated in Scheme 1.

With the assistance of the photoredox catalyst, a radical cation intermediate I formed in
the addition of visible light from dimethyl phosphite 2\text{a}, which made a easily in situ
generation of another radical cation intermediate II. The intermediate I or II coupled with
N-substituted indole 1\text{c} on the C(2)–C(3) double bond, forming a new intermediate III,
which was able to afford the desired product 3 in the presence of the molecular oxygen
with a release of H2O. Then, with the assistance of the molecular oxygen, the catalyst
was reoxidized for the completion of the catalytic cycle.

Furthermore, the control reaction was conducted with the addition of 2,2,6,6-
tetramethyl piperidine 1-oxide (TEMPO), and the yield of 3\text{a} dropped dramatically to
18\%. The results indicated the visible-light-mediated CDC reaction proceeds likely
through the radical pathway.

**Conclusions**

In summary, we have disclosed an efficient and practical method for the formation of
2-phosponylated indoles in the presence of commercially available photoredox ruthenium
catalyst. The newly developed system furnishes the desired products in moderate to good
yields, exhibiting good functional group tolerance. It offers promising access for the
construction of the C-P bond-containing compounds.
Experimental

General procedure for the synthesis of 2-phosphonylated indoles 3

A Schlenk tube (25 mL) equipped with a magnetic bar was loaded with the N-substituted indole (0.5 mmol), Ru(bpy)$_2$(PF$_6$)$_2$ (5 mol%), and dimethyl phosphite (0.6 mmol), and dichloromethane (DCM, 5 mL) was added. The resulting solution was stirred with exposure to visible light (fluorescent lamp) at room temperature for ca. 10 h when indole was consumed, as checked by thin-layer chromatography (TLC). Then the mixture was filtered through a short celite pad and washed with DCM ($\times 3$). The filtrate was concentrated, and the oily crude product was purified by column chromatography using silica gel as stationary phase and a mixture of n-hexane and ethyl acetate as eluent to give the indolated phosphites 3.

Spectral data of dimethyl (1-methyl-1H-indol-2-yl) phosphonate (3a)

Yellowish oil, yield: 79%. $^1$H NMR (400 MHz, CDCl$_3$) δ (ppm) = 7.61 (dd, $J = 8.0$, 0.9 Hz, 1H), 7.34–7.26 (m, 2H), 7.12 (d, $J = 4.5$ Hz, 1H), 7.11–7.06 (m, 1H), 3.87 (d, $J = 9.2$ Hz, 3H), 3.74 (d, $J = 11.4$ Hz, 6H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ (ppm) = 140.6, 140.5, 127.0, 126.9, 126.1, 125.2, 124.0, 122.6, 120.8, 115.1, 114.9, 110.5, 110.4, 53.57, 53.51, 32.2. $^{31}$P NMR (162 MHz, CDCl$_3$) δ (ppm) 13.1; IR (neat) ν (cm$^{-1}$) = 2955, 2080, 1504, 1461, 1209, 1312, 1243, 1027, 899, 825; MS (EI) $m/z$ (%): 89.1 (13), 130.1 (24), 144.1 (45), 192.0 (20), 206.1 (25), 239.1 (100); HRMS (EI) calcd for [M$^+$]: 239.0711, found 239.0711.

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[15] For more details about the crystal, see CCDC No. 1426144.