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Iodine/iron oxide-catalysed aerobic oxidative coupling of phosphites and alcohols *via in situ* iodophosphate formation

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The synthesis of phosphates *via* the oxidative coupling of alcohols and phosphites, catalyzed by iron(III) oxide, has been successfully achieved using elemental iodine and oxygen as oxidants. The protocol offers good to excellent yields with a broad range of substrates and remarkable environmental sustainability.

Alkyl phosphate compounds have gained significant attention in recent decades due to their versatility and broad applicability across various fields. These compounds play crucial roles in medicinal chemistry (*e.g.*, as nucleoside derivatives and prodrugs),[1] agrochemistry (*e.g.*, as pesticides and herbicides),[2] organic synthesis,[3] and the polymer industry (*e.g.*, as flame retardants and plasticizers).[4] Given their widespread utility, the synthesis of alkyl phosphates has been extensively studied, leading to the development of numerous methodologies,[5–7] although many rely on laborious procedures employing toxic starting materials. In this context, alkyl phosphates are typically accessed from halide derivatives, materials that are highly moisture-sensitive, corrosive, and generate significant halogenated waste.

More recently, catalytic phosphorylation protocols have emerged as greener alternatives; specifically, transition metal-catalysed cross-coupling reactions appeared as a powerful strategy for constructing P–O and other P–heteroatom bonds, offering a viable alternative to conventional synthetic routes.[8–10] A key advantage of this approach is the elimination of halogenated reagents, thereby improving the atom efficiency and sustainability of the process. However, these methods still commonly rely on stoichiometric amounts of peroxide oxidants, exhibit limited tolerance toward secondary alcohols, or require extended reaction times and strictly anhydrous conditions.

Inspired by recent developments,[11] we sought to explore the synthesis of alkyl phosphates by the transition metal-catalysed oxidative coupling of alcohols and phosphites. We envisioned that combining a simple iron catalyst with catalytic amounts of iodine and molecular oxygen could enable *in situ* generation of iodophosphates, providing a general route to phosphate esters without the need for halogenated starting materials. Here we report an iodine/iron oxide catalytic system that promotes the oxidative coupling of phosphites and alcohols under O_2 atmosphere, delivering a broad range of alkyl phosphates under mild conditions. The operational simplicity, use of inexpensive and non-toxic reagents, and ability to functionalise complex substrates highlight the potential of this aerobic protocol as a practical and sustainable alternative for phosphate synthesis.

Our investigation commenced with a catalyst screening using simple substrates, namely butanol and diethyl phosphite. A variety of readily available metal catalysts were evaluated, and the results are summarized in Table 1. A control experiment conducted in the absence of a catalyst confirmed its necessity for the reaction, as only small amounts of the product were detected (entry **1**, Table 1), likely formed due to the presence of iodine. Among the tested catalysts, iron oxide exhibited the optimal balance of yield and cost efficiency (entry **2**, Table 1). Notably, all iron-based catalysts proved highly effective, irrespective of their initial oxidation state (entries **3** and **4**, Table 1). Hydrated iron(III) chloride (entry **5**, Table 1) afforded a slightly lower yield, which may indicate a modest sensitivity of the system to added water. This trend was consistent with experiments in which deliberate water addition led to significant yield loss (entries **1**, **2** & **3**, Table 2).

Conducting the reaction under anhydrous conditions did not substantially improve the yield, likely due to already *in situ* formed water as a byproduct (entry **4**, Table 2). Nevertheless, the differences between the iron salts are relatively small, and should be interpreted as general trends rather than as precise activity measures. Iron(II) acetate (entry **6**, Table 1) performed

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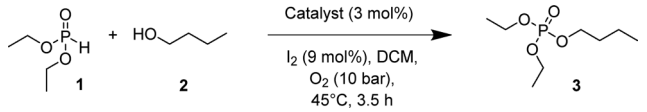
Table 1 Catalyst screening for the metal catalysed phosphorylation of alcohols[ab]



Entry	Catalyst	Yield
1	No catalyst	11%
2	Fe_2O_3	93%
3	$FeCl_2$	90%
4	$FeCl_3$	91%
5	$FeCl_3{\cdot}H_2O$	86%
6	$Fe(OAc)_2$	89%
7	Fe-Co DMC[c]	90%
8	$CuCl_2$	54% (83%)[d]
9	$Mn(OAc)_2$	34% (75%)[d]

[a] All reactions were performed in a pressurized reactor using butyl alcohol as limiting reagent (1 mmol), diethyl phosphite (2 mmol), catalyst (3 mol%), solvent (2 mL), iodine and 10 bars of oxygen at 45 °C for three and a half hours. [b] Yields of diethyl butyl phosphate were determined by ECN quantification using decane as internal standard. [c] Iron-cobalt double metal cyanide catalyst (see ref. 11). [d] 10 mol% catalyst.

Table 2 Effect of water on the iron oxide-catalysed coupling of phosphites and alcohols[ab]

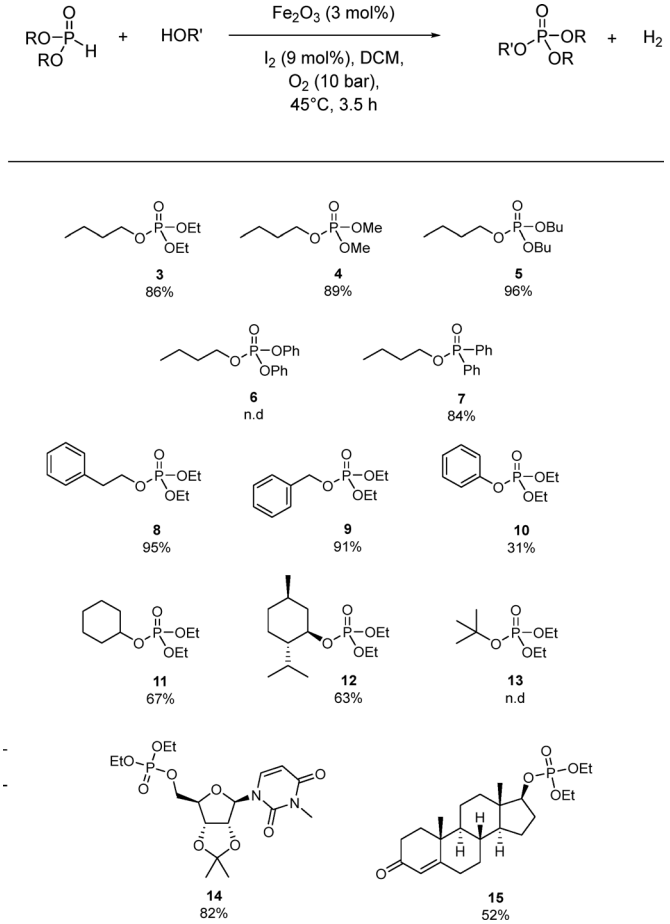
Entry	Amount of water added	Yield of 3
1	1 mmol	72%
2	2 mmol	56%
3	10 mmol	n.d
4	Anhydrous	95%

[a] All reactions were performed in a pressurized reactor using butyl alcohol as limiting reagent (1 mmol), diethyl phosphite (2 mmol), Fe_2O_3 (3 mol%), DCM (2 mL), iodine and 10 bars of oxygen at 45 °C for three and a half hours. [b] Yields of diethyl butyl phosphate were determined by the ECN quantification using decane as internal standard.

comparably to its chloride counterpart, indicating minimal ligand influence on phosphate formation. Similarly, iron–cobalt double metal cyanide, a heterogeneous catalyst with an open framework structure[12] (entry 7, Table 1) facilitated the transformation, although the site isolation of Fe in a Fe–N≡C–Co network did not seem to improve the yield.

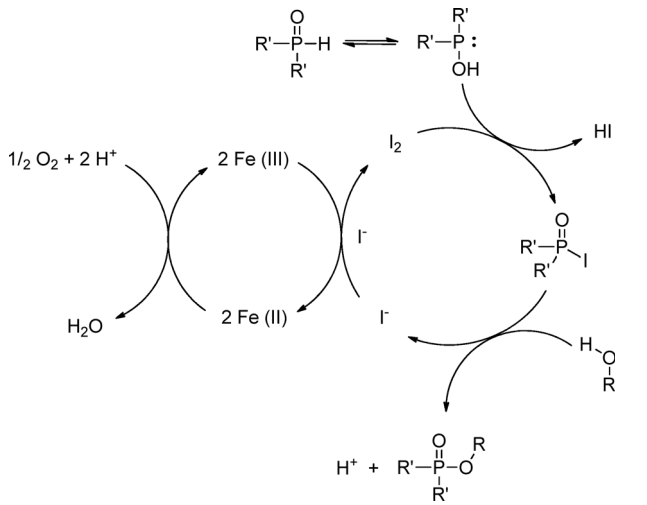
Other metal catalysts, including copper chloride and manganese acetate (entries **8** & **9**, Table 1), proved less effective, yielding the product in only 54% and 34% yield, respectively. While increasing catalyst concentration improved their performance, neither surpassed the efficiency of iron-based systems. Further optimization revealed that reducing the iron catalyst loading below 3 mol% significantly diminished the yield, whereas exceeding this threshold provided no additional benefit (entries 1 and 2, Table S1). Iodine was found to be essential for the reaction, as its omission completely suppressed product formation (entry 3, Table S1), ruling out a purely metal-mediated cross-dehydrogenative coupling mechanism. The optimal iodine loading was determined to be 9 mol%, as further reduction negatively impacted the yield (entry 4, Table S1) (Table 3).

Table 3 Reaction scope[ab]



[a] All reactions were performed in a pressurized reactor using alcohol as limiting reagent (1 mmol), phosphite (2 mmol), Fe_2O_3 (3 mol%), solvent (2 mL), iodine and 10 bars of oxygen at 45 °C for three and a half hours. [b] Isolated yields after purification of crude reaction by flash column chromatography.

With our best catalyst defined, substrate scope studies were carried out, essentially revealing that primary alcohols are more easily coupled with phosphites than secondary and tertiary alcohols, presumably due to steric constraints, with *tert*-butanol being entirely unreactive with diethyl phosphite (**13**). Phenol exhibited poor reactivity relative to aliphatic alcohols, likely due to its reduced nucleophilicity stemming from aromaticity and acidity (**10**). This trend was further illustrated by comparing phosphates **8**, **9**, and **10**, where elongation of the carbon chain enhanced nucleophilicity and, consequently, yield. Secondary alcohols still afforded noteworthy yields (*e.g.*, phosphates **11** and **12**, 67% and 63%, respectively). Variations in phosphite ester substituents had minimal impact on yield (*cf.* compounds **4** and **5**); however, diphenyl phosphite (see **6**) failed to react due to rapid degradation, with the starting material undergoing rapid hydrolysis under the reaction conditions. In contrast, non-hydrolysable substituents, as in phosphine oxide **7**, permitted successful coupling. Notably, the reaction tolerated a range of functional groups, as demonstrated by the



Scheme 1 Proposed Fe–I_2 catalysed oxidative cross-coupling of phosphites and alcohols.

formation of phosphates **14** and **15** from protected uridine nucleoside and testosterone, underscoring the method's potential for pharmaceutical applications.

Based on our data, we propose a plausible pathway in which the metal centre alternates between two oxidation states (Scheme 1). The initial step likely involves spontaneous iodination of the phosphite, evidenced by the loss of colour of the iodine solution. The resulting iodophosphate then would react with the alcohol to form the desired phosphate, releasing protons and iodide ions. These species subsequently participate in a redox cycle, regenerating iodine and producing water, with iron cycling between oxidation states and molecular oxygen serving as the terminal oxidant.

Notably, when a control experiment was conducted using stoichiometric iodine in the absence of both iron and oxygen under comparable conditions, the reaction afforded a significantly diminished yield (68%, entry 14, Table S1). Increased formation of iodinated side products, such as the corresponding alkyl iodide, was observed, arising from competitive iodination of the alcohol substrate. This behaviour can be attributed to the higher concentration of HI generated when iodine is used stoichiometrically, which favours off-pathway reactions rather than productive oxidation toward the desired phosphate. These findings show that iodine alone is insufficient to drive the reaction to completion.

To the best of our knowledge, this is the first report of an iron catalyst being used in combination with catalytic amounts of iodine to achieve the *in situ* formation of an iodophosphate intermediate for the synthesis of alkyl phosphates. Complementary methodologies exist in literature, such as the approach described by Prabhu *et al.*,[13] in which iodine is used catalytically along with stoichiometric amounts of an oxidant, specifically H_2O_2, to generate trialkyl phosphates. However, we believe our method offers significant advantages, particularly in achieving higher yields with secondary alcohols and avoiding the need for stoichiometric external oxidants. Instead, we utilize catalytic amounts of an iron catalyst with molecular oxygen as the terminal oxidant. Moreover, the aforementioned protocol requires a higher excess of the limiting reagent (3 equivalents *vs.* 2 equivalents in our method) and significantly longer reaction times (18 hours *vs.* 3.5 hours in our procedure). Another related method is reported by Han *et al.*,[14,15] where $Fe(acac)_3$ and a base are employed to couple phosphites and alcohols, proceeding *via* a fundamentally different and more complex mechanism that does not involve aerobic oxidative coupling. Instead, their reaction pathway involves the initial iron-catalysed dehydrogenation of alcohols to aldehydes. This makes our approach mechanistically distinct and operationally simpler.

We have developed an efficient iron-catalysed oxidative cross-coupling method for the synthesis of alkyl phosphates and phosphine oxides. This protocol employs oxygen as the terminal oxidant, generating water as the sole byproduct, and thus offers a more sustainable and environmentally friendly alternative to existing methods. The reaction is operationally straightforward, avoids hazardous reagents, and does not require strict exclusion of moisture or air. Furthermore, the use of mild conditions and inexpensive iron oxide makes this strategy attractive and practical for the synthesis of alkyl phosphates.

Conflicts of interest

There are no conflicts to declare.

Data availability

The corresponding data of this study is available within the paper and the supplementary information (SI). Any additional raw data files needed are available from the corresponding author upon reasonable request. Supplementary information is available. See DOI: https://doi.org/10.1039/d5cc05139h.

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