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Cross-Hetero-Dehydrogenative Coupling Reaction of Phosphites: A Catalytic Metal-Free Phosphorylation of Amines and Alcohols

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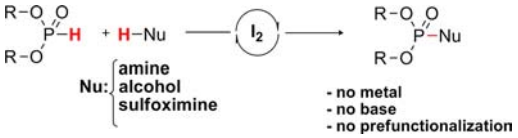
ABSTRACT



Phosphorylation of amines, alcohols, and sulfoximines are accomplished using molecular iodine as a catalyst and H_2O_2 as the sole oxidant under mild reaction conditions. This method provides an easy route for synthesizing a variety of phosphoramidates, phosphorus triesters and sulfoximine-derived phosphoramidates which are of biological importance.

Phosphoramidates and phosphate esters are structural scaffolds that are present in a variety of biologically active molecules.[1] Apart from their presence in a variety of biologically active natural products, phosphoramidates are useful pharmaceuticals (e.g., anti-HIV pro-drugs, cancer therapeutics, etc.)[2] and used as ligands[3a] in asymmetric synthesis and hydroaminoalkylation catalysis,[3b] as flame retardants,[3c] and for efficient ionization in mass spectrometric applications.[3d] Phosphorylation of amines provides an excellent protocol for the protection of amines, which are stable to Lewis acids and can be cleaved by dilute mineral acids.[4] Similarly, phosphate esters are an integral part of a variety of naturally occurring molecules, such as nucleic acids, proteins, carbohydrates, steroids, and coenzymes, and are used as pro-drugs.[5] Phosphate esters such as benzyl phosphates are employed as coupling partners in Suzuki–Miyaura cross-coupling reactions.[6] The utility of the phosphoryl group as a directing group for C–C bond-forming reactions has been well established.[7] For these reasons, the syntheses of phosphoramidate/phosphate esters are of great importance. The conventional methods for

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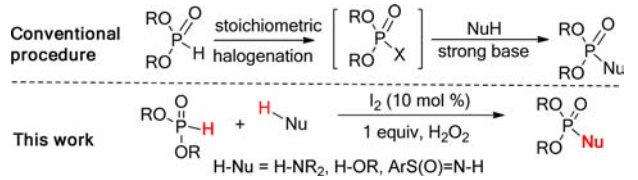
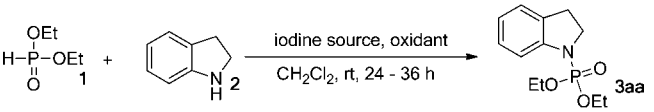
Scheme 1



the syntheses of phosphoramidate/phosphate esters largely involve treating alcohol/amine with appropriate phosphorus halides (Scheme 1).[8] Phosphorylation of alcohols has been achieved by using phosphoryl oxazolidinones in the presence of Lewis acids.[9] However, most of the methods use toxic reagents, harsh reaction conditions, and stoichiometric amount of reagents and require multistep reactions.[8] Moreover, phosphorus reagents used are more sensitive and are oxidatively and thermally unstable. For example, the classical Atherton and Todd reaction for the synthesis of phosphoramidates employs phosphites, triethylamine, and toxic CCl_4 as a solvent.[10a] The Staudinger–phosphite reaction and other such reactions require either organic azides or phosphoryl azides.[10b–d] To circumvent these problems, recently, Mizuno and co-workers reported a cross coupling of phosphites and amides (large excess) to form phosphoramidates by using Cu(II) acetate and a stoichiometric amount of base.[11] During the preparation of this manuscript, Hayes et al. reported a Cu-catalyzed cross-coupling reaction of phosphites with amines using Cu(I) iodide as the catalyst, along with stoichiometric amounts of base and 2 equiv of the amine.[12]

Cross-hetero-dehydrogenative coupling (CHDC) reactions, which do not require prefunctionalized starting materials, are emerging as highly efficient, atom economical and shorter routes for constructing C–C, C–N, C–P, and other C–heterobonds.[13] In continuation of our exploration in CDC reactions,[14] we envisioned that the Atherton–Todd-type coupling reaction could be performed using iodine as a catalyst. As a result, herein we report our recent finding on iodine-mediated phophorylations of amines and alcohols without using excess coupling partner or external base. Special techniques such as the slow addition of the phosphite (via syringe pump) are not required, and the strategy does not require metal salts.

Table 1. Screening Studies[a]



entry	iodine ource	oxidant	solvent	conversion[b] (%)
1	I_2 (10 mol %)	air	CH_2Cl_2	15
2	I_2 (10 mol %)	aq TBHP[c]	CH_2Cl_2	90
3	I_2 (10 mol %)	aq H_2O_2[d]	CH_2Cl_2	98
4	I_2 (5 mol %)	aq H_2O_2[d]	CH_2Cl_2	78
5	I_2 (10 mol %)	O_2	CH_2Cl_2	7
6	TBAI (10 mol %)	aq TBHP[c]	CH_2Cl_2	60
7	TBAI (10 mol %)	aq H_2O_2[d]	CH_2Cl_2	60
8	NaI (10 mol %)	aq TBHP[c]	CH_2Cl_2	83
9	NaI (10 mol %)	aq H_2O_2[d]	CH_2Cl_2	12
10	NIS (10 mol %)	aq H_2O_2[d]	CH_2Cl_2	25
11	KI (10 mol %)	aq H_2O_2[d]	CH_2Cl_2	17
12	KI (10 mol %)	aq TBHP[c]	CH_2Cl_2	17
13	NBS (10 mol %)	aq TBHP[c]	CH_2Cl_2	5
14	none	aq H_2O_2[d]	CH_2Cl_2	17
15	I_2 (10 mol %)	aq H_2O_2[d]	H_2O	20
16	I_2 (10 mol %)	aq H_2O_2[d]	EtOAc	94
17	I_2 (10 mol %)	aq H_2O_2[d]	MeCN	90

[a] Reaction conditions: **1** (0.72 mmol), **2** (0.72 mmol), solvent (2 mL), I_2 (10 mol %), H_2O_2 (1 equiv). [b] Conversions based on ^{1}H NMR data. [c] 70% solution in H_2O. [d] 50% solution in H_2O.

The screening studies were started by reacting diethyl phosphite (**1**) with indoline (**2**) in the presence of I_2 (10 mol %) and using air as a terminal oxidant, which afforded diethyl indolin-1-ylphosphonate (**3aa**) in 15% yield (entry 1, Table 1). Performing the reaction in the presence of aq TBHP or H_2O_2, resulted in the formation of product **3aa** in excellent yield (entries 2 and 3, Table 1). Reducing the amount of iodine to 5 mol % resulted in a decrease in the yield of coupled product **3aa** to 78% (entry 4, Table 1). Employing other iodine sources such as TBAI, NaI, KI, and NIS with aq TBHP or H_2O_2 for the reaction furnished low to moderate yields of **3aa** (entry 6–12, Table 1). Using *N*-bromosuccinimide (NBS) as a halogen source furnished the expected product in trace amount (entry 13, Table 1). Reaction of **1** with **2** in the absence of iodine formed the coupled product **3aa** in low yield (17%, entry 14, Table 1). Solvent screening studies revealed that CH_2Cl_2 or EtOAc or MeCN were suitable solvents for the transformation (entries 15–17). As H_2O_2 is an inexpensive and an environmentally benign

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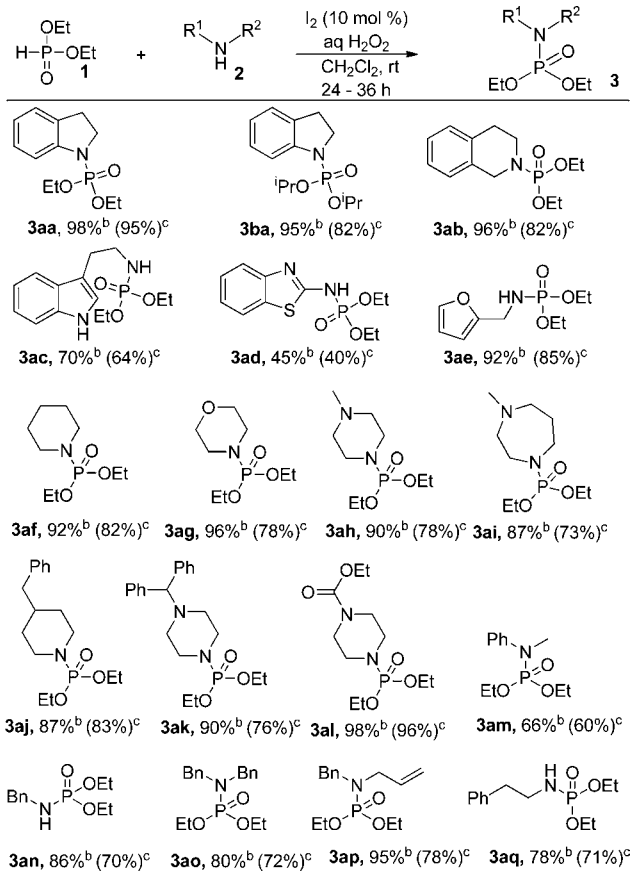
Scheme 2. Scope of the Reaction: Phosphorylation of Amines[a]



[a] Reaction conditions: **1** (0.72 mmol), **2** (0.72 mmol), solvent (2 mL), I_2 (10 mol %), H_2O_2 (1 equiv). [b] Conversions based on ^{1}H NMR data. [c] Isolated yields.

oxidant, further studies were performed using H_2O_2 as a terminal oxidant.

Having established the optimal reaction conditions, the scope of the coupling reaction was studied using a variety of primary and secondary amines and dialkyl phosphite. Thus, indoline **2a**, a cyclic aromatic secondary amine, in a reaction with diethyl and diisopropyl *H*-phosphite, furnished the coupled products **3aa** and **3ba** in excellent yields (98% and 95%, respectively, Scheme 2). 1,2,3,4-Tetrahydroisoquinoline reacted well with diethyl *H*-phosphite to give the coupled product (**3ab**) in excellent yield (96%).[16a] Heterocyclic amine derivatives such as tryptamine, 2-aminobenzothiazole, and furfurylamine afforded the coupled products **3ac**, **3ad**, and **3ae** in good to moderate yields (70%, 45%, and 92%, respectively). In the reaction of tryptamine with diethyl *H*-phosphite, a selective formation of the *N*−*P* bond with aliphatic amine in the presence of the aromatic amine is worth noting. Sterically encumbered aliphatic cyclic secondary amines such as piperidine, morpholine, *N*-methylpiperazine, *N*-methylhomopiperazine, 4-benzylpiperidne, 1-benzhydrylpiperazine, and ethyl piperazine-1-carboxylate underwent a smooth reaction with diethyl *H*-phosphite to furnish coupled products **3af**, **3ag**, **3ah**, **3ai**, **3aj**, **3ak**, and **3al** in good to excellent yields (87−98%, Scheme 2). Interestingly, in the reaction of tertiary amines such as *N*-methylpiperazine and *N*-methylhomopiperazine, the corresponding phosphoramidates were formed, and the corresponding *N*-oxides were not obtained, which are usually expected when they are treated with H_2O_2.[15d] This observation suggests that the iodine gets oxidized preferentially over the amine. In the case of ethyl piperazine-1-carboxylate, the carbamate moiety was unaffected, thus showing tolerance of carbamate moiety under the reaction conditions. Reaction of *N*-methylaniline with diethyl *H*-phosphite furnished the coupled product **3am** in 66% yield.[16b] Benzylamine, dibenzylamine, *N*-allylbenzylamine, and phenylethylamine underwent a smooth phosphorylation to furnish the coupled products **3an**, **3ao**, **3ap**, and **3aq** in good yields (78−95%).

After successful phosphorylation of amines with phosphite, we turned our attention toward the phosphorylation of alcohol. The phosphorylation of alcohols can lead to phosphate esters, which have a vast diversity in their applications. With the intention of installing of phosphate ester functional group, the reaction of benzyl alcohol with diethyl *H*-phosphite was performed under similar reaction conditions to those that have been adopted for the synthesis of phospharamidates. However, this reaction resulted in the formation of phosphate ester **5aj** in poor yield (40%). Nevertheless, this problem was circumvented by using 3 equiv of alcohol under solvent-free reaction conditions to obtain the phosphate ester in almost quantitative yield.

The optimized reaction conditions were applied to the phosphorylation of an array of primary alcohols, which furnished phosphorylated alcohols **5aa**, **5ab**, **5ac**, **5ad**, and **5ae** in excellent yields (97−98%, Scheme 3). Phosphorylation of branched chain alcohols such as isobutyl alcohol and citronellol afforded the coupled products **5af** and **5ag** in excellent to good yields. Allyl and propargyl alcohols were phosphorylated smoothly to furnish the phosphate esters **5ah** and **5ai** in excellent yields (98% and 95%, respectively). Treatment of benzyl alcohol and phenethyl alcohol with diethyl *H*- phosphite furnished the products **5aj** and **5ak** in good yields. Our attempt to study the selectivity in phosphorylation of amine and alcohol led to the phosphorylation of the amine functional group in the presence of alcohol to form **5al** in moderate yield. The more nucleophilic amine is easily susceptible to phosphorylation in the presence of the alcohol functional group. Under the optimal reaction conditions, 4-nitrocinnamyl alcohol furnished a mixture of phosphorylated product **5am** along with 4-nitrocinnamaldehyde (**6**) in almost 1:1 ratio (50% yield). The phosphorylation of secondary alcohols such as isopropyl alcohol proceeded smoothly to

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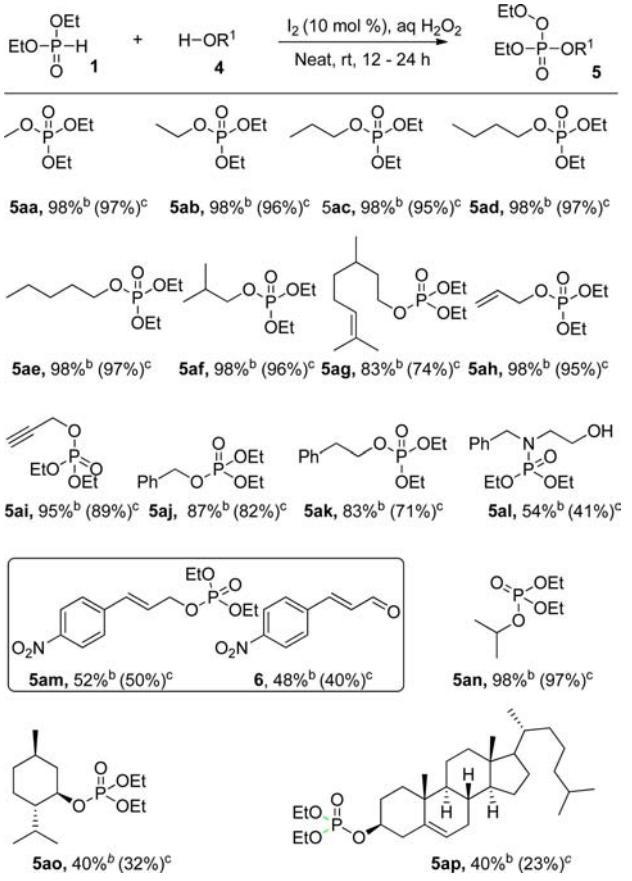
(16) (a) The reaction of tetrahydroquinoline under the optimal conditions resulted in the formation of a mixture of coupled product and quinoline in a 1:5 ratio (determined by GCMS analysis). (b) The reaction of aniline under the optimal conditions resulted in the formation of a mixture of coupled product, nitrobenzene, and a diphenylazo compound in a 1:1:1 ratio (determined by GCMS analysis).

afford the coupled product **5an** in excellent yield (98%). Cyclic secondary alcohols such as menthol and cholesterol under the optimal conditions gave the coupled products **5ao** and **5ap** in moderate yields. However, tertiary butyl alcohol and phenol failed to furnish the coupled product under the optimal reaction conditions.

Scheme 3. Scope of the Reaction: Phosphorylation of Alcohols[a]



[a] Reaction conditions: **1** (0.72 mmol), **4** (2.17 mmol), I_2 (10 mol %), H_2O_2 (1 equiv). [b] Conversions based on ^{1}H NMR data. [c] Isolated yields.

This versatile method for successful phosphorylation of amines and alcohols to obtain a wide range of phosphoramidates and phosphate esters has led to an investigation to examine the scope of phosphorylation of sulfoximines, which are potential insecticides.[17] Therefore, we performed a preliminary study on phosphorylation of sulfoximines under optimal conditions that have been adopted for amines and alcohols. Thus, subjecting (*S*-methylsulfonimidoyl)-benzene with dimethyl, diethyl, and diphenyl *H*-phosphites furnished the coupled products **8ca**, **8aa**, and **8da** in moderate yields (Scheme 4).

Based on the earlier study by Atherton and Todd and literature precedence regarding an I_2/H_2O_2 catalytic system,[15a−c] we propose the following mechanism:

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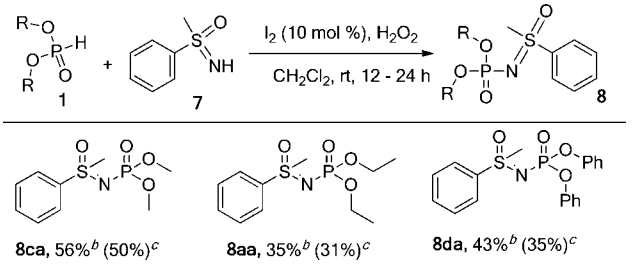
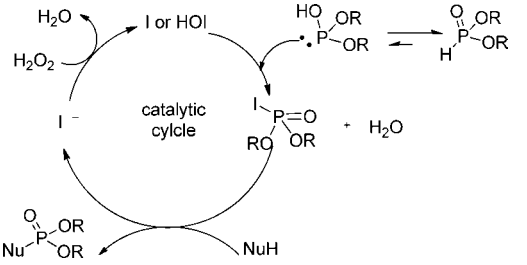
Scheme 4. Phosphorylation of Sulfoximines[a]



[a] Reaction conditions: **1** (0.72 mmol), **2** (0.72 mmol), solvent (2 mL), I_2 (10 mol %), H_2O_2 (1 equiv). [b] Conversions based on ^{1}H NMR data. [c] Isolated yields.

Scheme 5. Tentative Mechanism



Iodine reacts with H_2O_2 to form hypoiodous acid followed by in situ electrophilic iodination of dialkyl *H*-phosphite to give phosphoryl iodide. This further undergoes nucleophilic substitution reaction to afford the corresponding cross-hetero-dehydrogenative coupled product (Scheme 5).

Iodine-mediated phosphorylation reactions to synthesize phosphoramidates/phosphate esters have been developed under very mild, efficient, and environmentally benign conditions. This catalytic system was found to be effective and compatible with a wide variety of primary/secondary amines, primary/secondary/cinnamyl/allyl/propargyl alcohols, and sulfoximines. A variety of useful phosphoramidates and phosphate triesters can be synthesized using this environmentally benign procedure.

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Supporting Information Available. Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org

The authors declare no competing financial interest.