Diselenide-Mediated Catalytic Functionalization of Hydrophosphoryl Compounds

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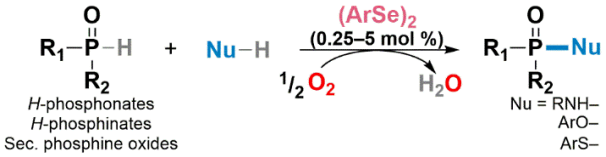
Supporting Information Placeholder

ABSTRACT: We report a diaryldiselenide catalyst for cross-dehydrogenative nucleophilic functionalization of hydrophosphoryl compounds. The proposed organocatalytic cycle closely resembles the mechanism of the Atherton–Todd reaction, with the catalyst serving as a recyclable analog of the halogenating agent employed in the named reaction. Phosphorus and selenium NMR studies reveal the existence of a P–Se bond intermediate and structural analyses indicate a stereospecific reaction.



Compounds featuring P(O)–N, P(O)–O, and P(O)–S bonds are of wide-ranging importance with applications in the development of prodrugs,[1] nonhydrolyzable phosphate analogs,[2] pesticides,[3] flame retardants,[4] and as ligands for organometallic chemistry.[5] Figure 1a illustrates three examples of compounds that feature phosphoramidate, phosphate, and phosphorothioate groups: remdesivir is an antiviral nucleotide analog which was recently authorized for emergency use to treat COVID-19 patients,[6] resorcinol bis(diphenyl phosphate) (RDP) is a flame retardant,[7] and amifostine is a chemotherapy adjuvant.[8] Conventional syntheses of P(O)–R bonds involve reactions of sensitive phosphoryl halides with appropriate nucleophiles. The Atherton–Todd reaction obviates the need to handle such sensitive precursors by forming them *in situ* from reactions of hydrophosphoryl (P(O)–H) compounds with stoichiometric halogenating agents (Figure 1b).[9] Methods for catalytic cross-dehydrogenative coupling of P(O)–H compounds with amines, thiols, and alcohols that employ peroxides[10] or electrochemical cells[11] to recycle the halogenating agents, transition metal mediated coupling,[12] as well as photocatalytic radical coupling[13] have also been described. Herein, we describe a cross-dehydrogenative method that uses simple diselenides as catalysts and oxygen from ambient air as oxidant.

This study builds on our recent efforts to recycle diaryldiselenides in the presence of P(III) reagents for amide bond formation.[14] We hypothesized that diselenides may promote dehydrogenative coupling of P(O)–H compounds with different nucleophiles. The proposed mechanism is outlined in Scheme 1. We postulated that the first step would involve the rapid reaction of $R_2P(O)$–H with diaryldiselenide to form $R_2P(O)$–SeAr intermediate accompanied by liberation of arylselenol.[15] The phosphoryl selenide would then undergo nucleophilic substitution to form $R_2P(O)$–Nu products while the liberated arylselenol reoxidizes back to diaryldiselenide in the presence of air to complete the catalytic cycle. The net reaction would be a highly atom economical reaction to form a new P–Nu bond accompanied by reduction of oxygen to water.

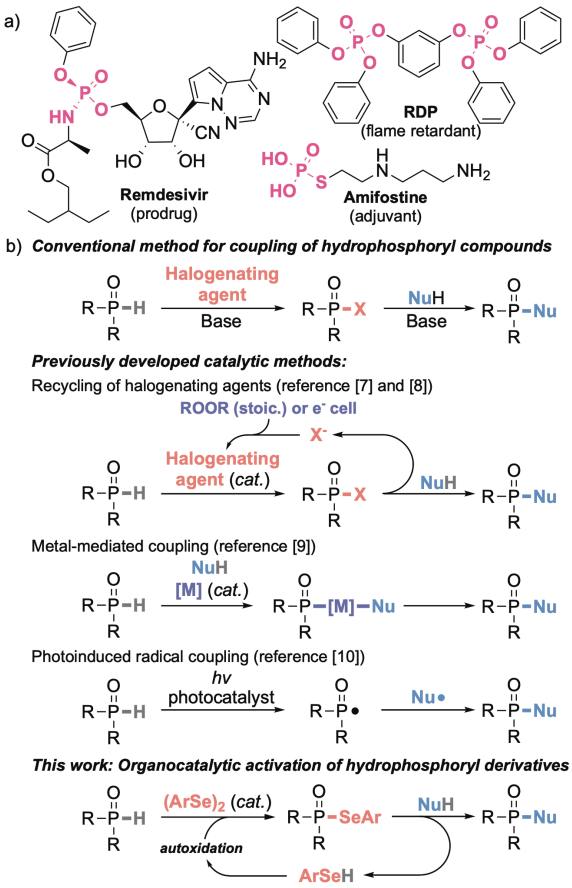
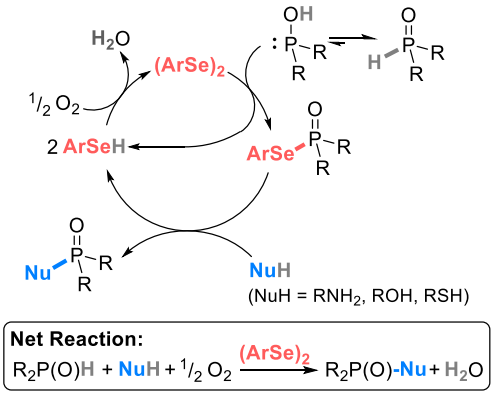


Figure 1. (a) Examples of organophosphorus compounds of interest containing P(O)–N, P(O)–O, and P(O)–S bonds. (b) Stoichiometric as well as catalytic methods to functionalize hydrophosphoryl compounds. The catalytic method reported herein requires simple diselenides and O_2 to transform hydrophosphoryl compounds into the corresponding products.

Scheme 1. Proposed mechanism for diaryldiselenide mediated dehydrogenative coupling of P(O)–H compounds and nucleophiles.



We began our investigations by screening the effectiveness of diaryldiselenides (10 mol%) for the coupling of diethylphosphite **2a** (0.05 mmol) and benzylamine **3a** (0.10 mmol) in acetonitrile at an elevated temperature (60 °C). The results revealed a qualitative correlation between electron withdrawing groups on the diaryldiselenides and the conversion rates to product (Figure 2, Figure S1–S10, and Table S3). Reaction with diphenyldiselenide (**1a**) has the slowest conversion rate with only 22% product formation after 24 h of reaction. Addition of electron withdrawing groups such as formyl (**1b**), nitro (**1c**), and trifluoromethyl (**1d**) led to a significant rate enhancement. (Dipyridyldiselenide **1e** also provided a boost over diphenyldiselenide). Bis(nitrophenyl) diselenide **1c** displays a fast initial rate but the conversion to product is accompanied by formation of byproducts and deactivation of catalyst, presumably through nucleophilic substitution on the aromatic ring. On this basis, further elaboration of the ring with nitro substituents was not pursued. We next explored fluorine substitutions to enhance the reactivity of the diselenides. Both bis(trifluoromethyl)-substituted **1g** and pentafluoro-substituted **1h** led to the completion of the model reaction within 1.5 hours. Diselenide **1f**, which has been utilized for dehydrative formation of amides[16] and esters,[17] was also found to be effective; although, a slower conversion rate was observed for **1f** than for **1g** or **1h**. No reaction was observed in the absence of diaryldiselenides.

We selected diselenides **1g** and **1h** as lead catalysts for further optimization of reaction conditions (Table 1). We found that the reaction is optimal in acetonitrile or THF. In dichloroethane, the catalyst was found to be deactivated, possibly through alkylation of selenolate. We proceeded with the reaction optimization studies in acetonitrile as the solvent. Doubling the stoichiometry of either reactants did not lead to appreciable differences in reaction time and yield: 1:1 ratio of **2a** and **3a** is sufficient to drive the reaction to completion within 1.5 hours. As expected, lowering of the reaction temperature to 20 °C from 60 °C reduced the conversion rate. We conducted a series of reactions to determine the optimal catalyst loading and were pleased to find that the reaction yield remained high with as little as 0.25 mol% diselenide **1g** (estimated turnover number = 400). In contrast, 0.25 mol% of diselenide **1h** led to only 11% product (estimated turnover number = 40).

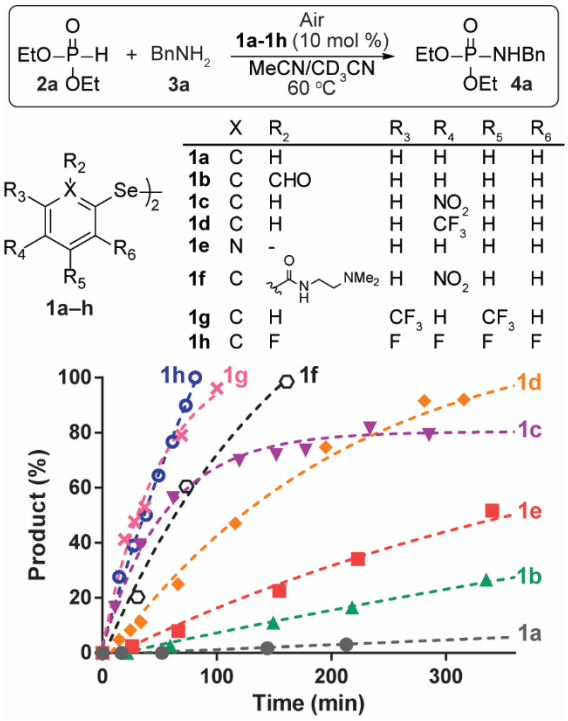


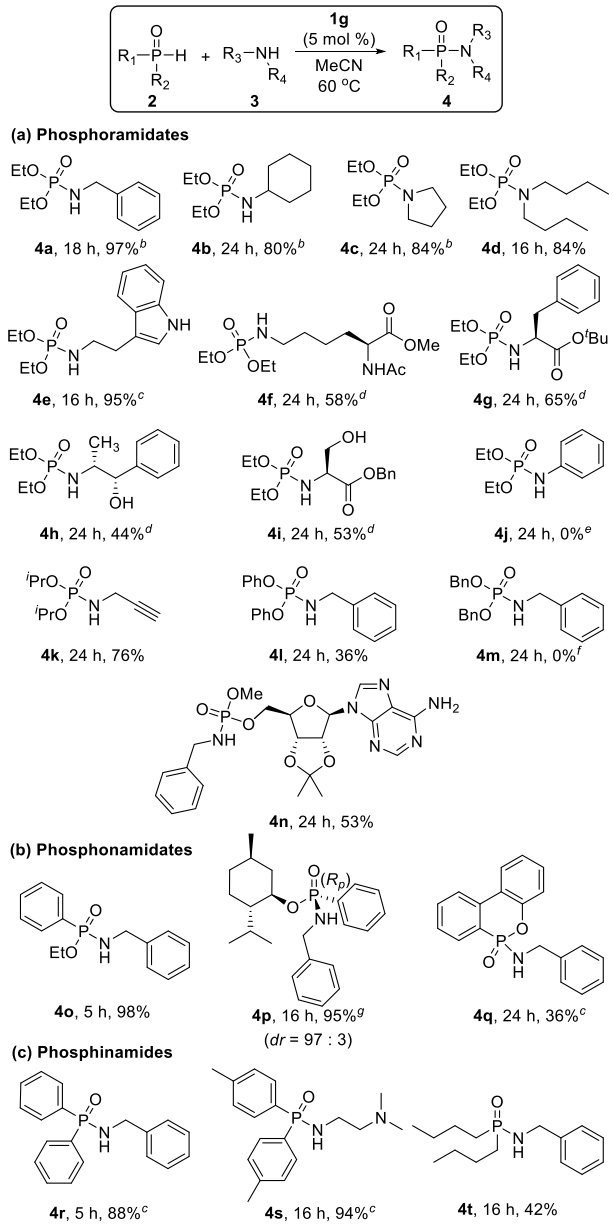
Figure 2. Design and performance of the diaryldiselenides catalysts **1a**–**1h** (10 mol%) in promoting dehydrogenative coupling of diethylphosphite **2a** (0.05 mmol) and benzylamine **3a** (0.10 mmol) to yield **4a** in MeCN (400 μL) and CD_3CN (100 μL) at 60 °C. Reaction progress was monitored by ^{31}P NMR.

Table 1. Optimization of reaction conditions[a]

	2a (mmol)	**3a** (mmol)	catalysts (mol%)	solvents	conversion (%)[b]
1	0.05	0.10	**1g**, 10%	MeCN	96% (1.5 h)
2				Dioxane	89% (6 h)
3				THF	96% (1.5 h)
4				DCE	21% (24 h)
5				Toluene	90% (3 h)
6	0.10	0.05	**1g**, 10%	MeCN	99% (1.5 h)
7	0.05	0.05	**1g**, 10%		99% (1.5 h)
8[c]			**1g**, 10%		95% (45 h)[c]
9			**1g**, 5.0%		99% (3 h)
10			**1g**, 2.5%		94% (7 h)
11			**1g**, 1.0%		97% (16h)
12			**1g**, 0.50%		94% (30 h)
13			**1g**, 0.25%		93% (48 h)
14			**1h**, 0.25%		11% (48 h)

[a]Reaction conditions: **2a**, **3a**, and catalyst in solvent (500 μL) at 60 °C under ambient air. [b]Conversion was monitored by ^{31}P NMR. Time when the reaction was last monitored was provided in the parentheses. [c]Reaction was conducted at room temperature

Scheme 2. Substrate scope of P(O)–H compounds and amine nucleophiles[a]



[a]Reaction condition: P(O)–H compound (0.50 mmol), amine (0.55 mmol), and diselenide **1g** (5 mol%) were stirred in MeCN (2.5 mL) at 60 °C for the indicated time period in the presence of ambient air; see Supporting Information Table S1 for detailed condition of each reaction. [b]Only 1 mol% of **1g** was used. [c]Reaction was conducted in THF (2.5 mL) instead. [d]HCl salt of the corresponding amine was converted *in situ* into its free form by addition of equimolar triethylamine (0.55 mol). [e]MS and ^{31}P NMR indicated the formation of tetraethyl pyrophosphate instead. [f]Catalyst deactivated. [g]The corresponding starting material has diastereomeric ratio (R_p/S_p) of 98:2.

We explored the utility of catalyst **1g** for the reaction of P(O)–H compounds (1.0 eq) with different amines (1.1 eq) at a practical 0.5 mmol reaction scale (Scheme 2 and Table S1). Reaction of diethylphosphite with primary aliphatic amines (benzylamine, cyclohexylamine, and tryptamine) and secondary amines (pyrrolidine and dibutylamine) required 1 mol% **1g** for high yields of their corresponding products (**4a**–**4e**). More complex amines necessitated 5 mol% catalyst. Catalyst **1g** can tolerate amines bearing a diversity of functional groups, including esters (to yield the corresponding product **4f**, **4g** and **4i**), amide (**4f**), alkyne (**4k**), and unprotected purine base (**4n**). In the presence of unprotected alcohol, the more nucleophilic amine was preferentially phosphorylated (see products **4h** and **4i**). Unsurprisingly, aromatic amines (**4j**) proved to be poor nucleophilic partners. In cases with less reactive partners, tetraethylpyrophosphate (TEPP) was found to be the common side product (*vide infra*). Detailed reaction conditions, including structures of the starting materials, are provided in the Supporting Information, Table S1.

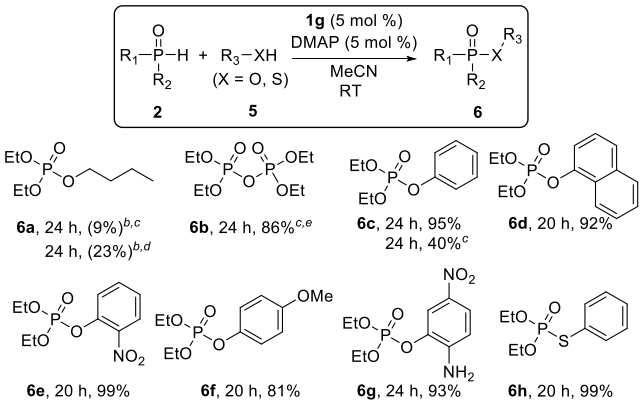
We next explored the potential of diselenide **1g** to catalyze coupling of a diverse set of *H*–phosphonates. Dialkyl phosphites provided good to excellent yields of the corresponding phosphoramidate products (**4a**–**4k**, and **4n**), while the hydrolytically prone diphenylphosphites afforded a lower yield of product **4l**. No product (**4m**) formation was observed with dibenzylphosphite—we hypothesize that the selenoate undergoes nucleophilic substitution reaction at the benzylic position of the phosphite, thereby deactivating the catalyst.

We also evaluated the potential of diselenide **1g** to functionalize *H*-phosphinates[18] and secondary phosphine oxides[19] with amines to form phosphonamidates and phosphinamides, respectively (Scheme 2b–c and Table S1). Reaction of alkyl phenylphosphinates and diarylphosphine oxides with primary amines led to high yields of products **4o**–**p** and **4r**–**s**, respectively. 9,10-dihydro-9-oxy-10-phosphaphenanthrene-10-oxide, which contains aryloxy group, provided low yield of the product **4q** likely due to the susceptibility of this phosphine oxide to hydrolysis. Low reaction yield (**4t**) was also observed with dibutylphosphine oxide, presumably due to its propensity to oxidize and disproportionate.[20]

Reactions of amino alcohols with *H*-phosphonates (see products **4h** and **4i**) suggest that alcohols are poor nucleophile partners. Indeed, attempts at condensing *n*-butanol with diethylphosphite led to unreacted starting materials, as monitored by ^{31}P NMR. Addition of DMAP as a base and co-catalyst to the reaction mixture marginally enhanced the yield (9%) of the desired product **6a**; however, these conditions also led to the conversion of the diethylphosphite starting material into TEPP (**6b**) from reaction with water produced during the catalytic cycle.[9b, 21]

Reactions with nucleophiles weaker than water, i.e. aniline and aliphatic alcohols, will potentially be accompanied by formation of pyrophosphate. In accordance with this hypothesis, we found that treatment of diethylphosphite with 5 mol% **1g** and 5 mol% DMAP in anhydrous acetonitrile at 60 °C afforded TEPP (**6b**) in 86% yield. Conversely, phenols reacted efficiently with diethylphosphite in the presence of 5 mol% **1g** and 5 mol% DMAP to provide their corresponding phosphate esters **6c**–**g** as major products (Scheme 3 and Table S2). Formation of TEPP can be compensated for in these cases by addition of excess (1.5 eq) phosphite. High yield of product **6c** was obtained from reaction between diethylphosphite and phenol at room temperature. We also explored the reactivity of various substituted phenols. Reaction with 1-naphthol, 2-nitrophenol, 4-methoxyphenol, and 2-amino-5-nitrophenol resulted in high yields of the corresponding products (**6d**–**6g**), demonstrating that variability in electronic properties and position of substituents are reasonably tolerated. Thiophenol also reacted to form phosphorothioate **6h** in near quantitative yield.

Scheme 3. Substrate scope of alcohol nucleophiles[a]



[a]Reaction condition: Diethylphosphite (0.75 mmol), alcohol (0.50 mmol), DMAP (5 mol%), and **1g** (5 mol%) were stirred in MeCN at room temperature in the presence of ambient air; see Supporting Information Table S2 for detailed condition of each reaction. [b]NMR yield as determined by ^{31}P NMR; product was not isolated. [c]Reaction was conducted at 60 °C. [d]Three equivalent of BuOH was used. [e]No nucleophile was added into the reaction.

We probed the mechanistic underpinnings of the catalyzed reaction by analyzing the stereochemistry of the phosphorus center. We prepared diastereomerically enriched (R_P)–menthyl phenylphosphinate (**2p**, 98:2 *dr*) and treated it with benzylamine (Figure 3a). Evaluation of the resulting product **4p** by chiral HPLC showed that the reaction proceeded in stereospecific fashion (97:3 *dr*). The same reaction with less enriched **2p** (58:42 *dr*) led to a similar outcome. X-ray spectroscopy analysis showed that the major diastereomer of **4p** is in R_P conformation (Figure 3b), indicating an overall inversion of stereochemistry on the phosphorus center during the reaction.[22] We conducted proton-coupled ^{31}P and ^{77}Se NMR studies to identify potential intermediates guiding this reaction outcome (Figures 3c–d, and S11–S12). When **2p** and stoichiometric **1g** were mixed in CD_3CN, a new resonance appeared immediately downfield of starting materials (34.9 ppm) in ^{31}P NMR (Figure 3c). ^{77}Se NMR spectrum of the same mixture showed a doublet with coupling constant magnitude (J_{SeP} = –385 Hz) equivalent to the heteronuclear coupling observed in ^{31}P NMR (Figure 3d). These coupling constants are consistent with the formation of a P–Se bond in phosphonoselenoate **7p** intermediate.[23] Addition of benzylamine into this reaction mixture caused the appearance of a new resonance at 20.5 ppm in keeping with the formation of phosphonamidate **4p**. The formation of phosphonoselenoates from diselenides and *H*-phosphinates is known to proceed stereospecifically with retention of configuration.[15a] On the basis of the above experiments and literature precedents, we deduce that inversion of stereochemistry occurs during nucleophilic substitution of amine on the phosphorus center.

In conclusion, we describe a diselenide organocatalyst for nucleophilic functionalization of hydrophosphoryl compounds. The mechanism of the organocatalytic reaction resembles that of the Atherton–Todd reaction with the diaryldiselenide representing a recyclable substitute for halogenating agents. This atom-economical reaction provides efficient route for the synthesis of pharrmaceuticals and other important compounds that contain phosphoramidate, phosphonamidate, phosphinamide, phosphate, and phosphorothioate groups. The aryl group of the diselenide provides opportunities for further modifications to optimize the catalyst, including for asymmetric synthesis of phosphorus compounds.

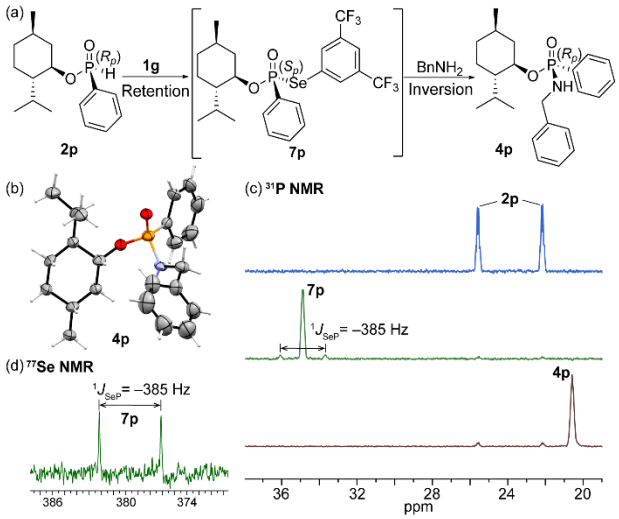


Figure 3. (a) Results from ^{31}P NMR experiments implicate the stereospecific formation of phosphonoselenoate intermediate **7q**. The retention of configuration in the first step is expected based on prior studies.[15a] (b) Crystal structure of **4p** (ellipsoids at 50% probability level) showing an R_P configuration.[22] (c) Proton-coupled ^{31}P NMR spectra showing the evolution of starting material **2p** (top) to intermediate **7p** (middle) to product **4p** (bottom). (d) ^{77}Se NMR spectra of intermediate **7p** showing coupling constant equivalent to that of ^{31}P NMR ($^1J_{SeP}$ = –385 Hz).

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Synthesis and characterization of catalysts, reaction screening, and mechanistic studies (PDF)

X-ray crystallographic data for **4p** (CCDC 2007666)

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Notes

The authors declare no competing financial interest.

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