Metal-Free, NIS-Induced Regioselective Iodophosphoryloxylation of Alkenes with P(O)-OH bonds

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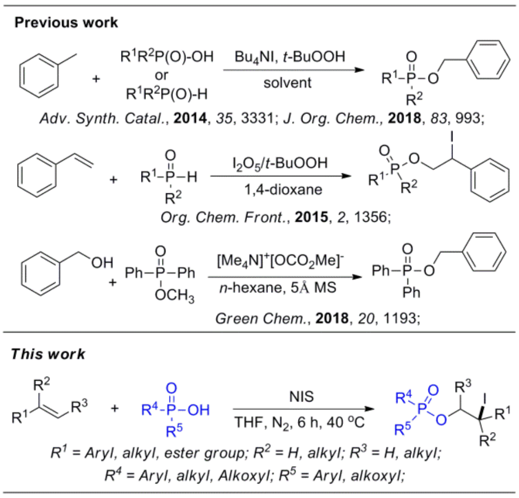
Abstract: A simple and efficient method for the regioselective iodophosphoryloxylation of alkenes with P(O)-OH bonds has been established by using NIS (N-iodosuccinimide) as the iodination reagent under transition-metal-free conditions. The present protocol is compatible with different functional groups, and suitable for various alkenes and P(O)-OH compounds. A variety of functionalized β-iodo-1-ethyl phosphinic/phosphoric acid esters are obtained in good to excellent yields, which could be further transformed to diversified building blocks for the synthesis of bioactive compounds, pharmaceuticals and functional materials.

Introduction

Organophosphorus compounds have been recognized as the important intermediates in biological chemistry, asymmetric catalysis, and preparation of functional materials for a half century, due to their unique structural features and potential pharmacological activities.[1,2] In particular, some β-iodo-α-alkyl phosphinic/phosphoric acid esters are significant building blocks present in a variety of biologically interesting natural products, pharmaceuticals, and synthetic intermediates of broad utility. Generally, these β-iodofunctionalized phosphinic/phosphoric acid esters are prepared either by the substitution of phosphoryl chlorides with β-iodo-α-ethanol compounds/direct iodination for the methyl group of 1-phenylethyl phosphinic or phosphoric acid esters or the direct cross coupling of (1-halo-2-iodo-alkyl) compounds with phosphinic/phosphoric acids and transition-metal-catalyzed [e.g., Fe, Cu, Pd] dehydrogenative coupling of β-iodo-α-ethanol derivatives with P(O)-H/P(O)-Cl bonds.[3] However, these protocols suffer from certain disadvantages such as the use of a large excess of P(O)-H motifs and co-oxidants, poor regioselectivity, and low yields.

The direct dehydrogenative coupling of P(O)-H or P(O)-OH bonds with C(sp^3)−H bonds of the methyl group in arenes has been achieved by Zhao and Xiong.[5a-b] In 2015, Wei and Wang et al. established a novel and efficient procedure for the direct difunctionalization of alkenes with I_2O_5 and P(O)–H compounds.[5c] Recently, Ishihara discovered a metal-free transesterification of phosphinates with alcohols via the catalysis of tetramethylammonium methyl carbonate.[5d] Jacobsen et al. reported the intramolecular reaction of carboxylic acids with pendant olefins in the presence of a source of I^+ for the enantioselective generation of five- and six-membered lactones.[4a] Since then, Fujioka et al. and Yeung et al. further demonstrated the enantioselective bromolactonization of 5-substituted 5-hexenoic acids catalyzed by the tris(imidazoline) and L-proline-derived S-alkyl thiocarbamate, respectively.[4b,4c] Feng et al. found a highly efficient catalytic chloroamination reaction of α,β-unsaturated γ-keto esters and chalcones via a chloronium-based mechanism to deliver anti-regioselective vicinal chloroamines instead of the aziridinium intermediates delivered aminochlorides.[4d] In 2012, Toste et al. invented a chiral anion phase-transfer system for enantioselective 6-exo-trig bromocyclization of styrenyl amides.[4e] Later, Mukherjee et al. discovered the catalytic asymmetric iodoetherification of oximes with the help of a bifunctional thiourea catalyst.[4f] In addition, Denmark and Burk have systematically studied the Lewis base catalyzed bromo- and iodolactonization reactions and also explored the effects of catalyst structure on the rate and cyclization selectivity.[4g] Although some elegant studies on the selective difunctionalization of carbon-carbon double bonds were achieved by these scientists,[5] the use of P(O)-OH compounds as starting materials has not been reported. Herein, we demonstrate an efficient regioselective iodophosphoryloxylation of alkenes with P(O)-OH bonds by using NIS (N-iodosuccinimide) as the iodination reagent under transition-metal-free conditions (Scheme 1).[6]



Scheme 1. Synthesis of phosphonate/phosphate esters or β-iodophosphate.

Results and Discussion

To test our initial hypothesis, the reaction of styrene (**1a**) and diphenylphosphinic acid (**2a**) was investigated to delineate the reaction parameters.[7] The reaction of **1a** with **2a** was carried out at room temperature in toluene under a N_2 atmosphere with the addition of iodine reagent NIS, and the corresponding addition product of 2-iodo-1-phenylethyl diphenylphosphinate (**3a**) was generated in 7% yield. Besides toluene, other solvents, such as THF, DMF, CH_3CN, 1,4-dioxane and CH_2Cl_2 were further tested (Table 1, entries 2-6), and THF gave the product in a preferable

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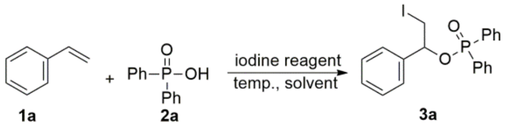
Supporting information for this article is given via a link at the end of the document yield of 78%. We then chose THF as the solvent for further optimization. When the reaction was operated under an air atmosphere, the expected product could only be produced in 66% yield (Table 1, entry 7). This phenomenon may be ascribed to the influence of water in air, which interrupted the phosphoryloxylation path of the reaction. Besides NIS, other iodine sources such as I_2, KI, NaI and tetrabutylammonium iodide (TBAI) showed negative results toward the reaction (Table 1, entries 8-11). The increase of reaction temperature within the 25-40 °C range is beneficial, but a further increase from 40 to 80 °C results in a little decrease of the product yield (Table 1, entries 12-14). Additionally, it is worth noting that the reaction would not produce any products in the absence of NIS (Table 1, entry 15). We further optimized the amount of NIS used, and the optimal condition was obtained at a "diphenyl phosphinic acid/styrene/NIS molar ratio" of 1:1:1.2 (Table 1, entries 16-18). Some other iodination systems were further screened for the reaction, and I_2 still showed negative results for the reaction even with the addition of an oxidant (H_2O_2, TBHP, DTBP, $K_2S_2O_8$). According to M. C. Mattos's method, TICA (triiodoisocyanuric acid) was synthesized in 86% yield, [7e] which could promote the reaction with the generation of the desired product in 82% yield.

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

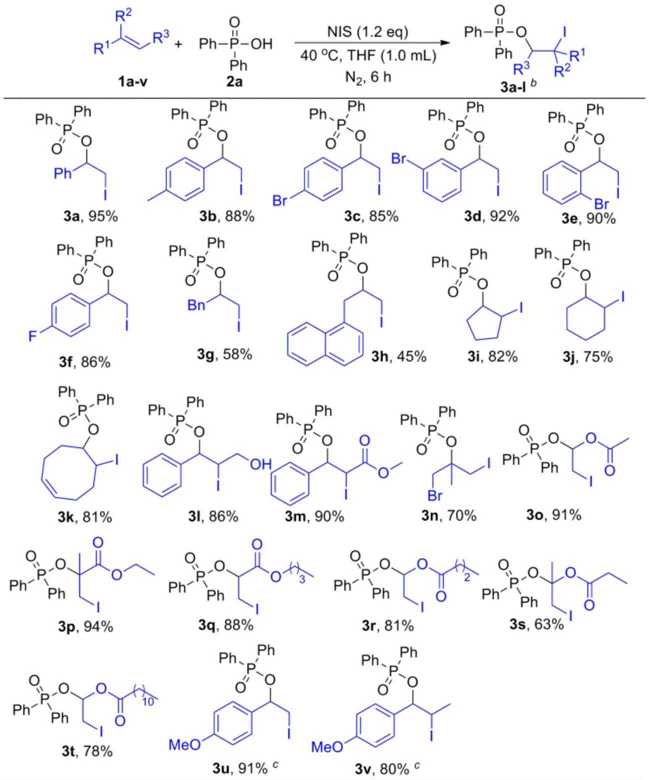


Entry	Solvent	Iodine reagent	Temp.	Yield of **3a** [b]
1	toluene	NIS	r.t.	7%
2	THF	NIS	r.t.	78%
3	DMF	NIS	r.t.	49%
4	CH_3CN	NIS	r.t.	58%
5	1,4-dioxane	NIS	r.t.	23%
6	CH_2Cl_2	NIS	r.t.	65%
7	THF	NIS	r.t.	66% [c]
8	THF	I_2	r.t.	N.D.
9	THF	KI	r.t.	N.D.
10	THF	NaI	r.t.	N.D.
11	THF	TBAI	r.t.	N.D.
12	THF	NIS	40 ºC	95%
13	THF	NIS	60 ºC	93%
14	THF	NIS	80 ºC	92%
15	THF	-	40 ºC	N.D.
16	THF	NIS	40 ºC	22% [d]
17	THF	NIS	40 ºC	46% [e]
18	**THF**	**NIS**	**40 ºC**	**96%** [f]
19	THF	I_2/H_2O_2	40 ºC	N.D. [g]
20	THF	I_2/TBHP	40 ºC	N.D. [h]
21	THF	I_2/DTBP	40 ºC	N.D. [i]
22	THF	$I_2/K_2S_2O_8$	40 ºC	N.D. [j]
23	THF	TICA	40 ºC	82% [k]

[a] Reagents and conditions: styrene (**1a**, 0.5 mmol), diphenylphosphinic acid (**2a**, 0.5 mmol) and iodine reagent (1.0 eq) in solvent (1.0 mL), N_2 atmosphere, temp., 6 h. [b] ^{31}P NMR yields. [c] Air conditions. [d] NIS (0.125 mmol, 25 mol%). [e] NIS (0.25 mmol, 50 mol%). [f] NIS (0.6 mmol, 120 mol%). [g] H_2O_2 (0.6 mmol, 25% solution in water). [h] TBHP (0.6 mmol, 70% solution in water). [i] DTBP (di-*t*-butyl peroxide, 0.6 mmol). [j] $K_2S_2O_8$ (0.6 mmol). [k] TICA (triiodoisocyanuric acid, 0.6 mmol).

As shown in **Table 2**, the regioselective iodophosphoryloxylation of alkenes with NIS and P(O)-OH bonds leading to β-iodophosphates can be applied to different kinds of alkenes. It is clear that styrene (**1a**), 1-methyl-4-vinylbenzene (**1b**), 1-bromo-4-vinylbenzene (**1c**), 1-bromo-3-vinylbenzene (**1d**), 1-bromo-2-vinylbenzene (**1e**) and 1-fluoro-4-vinylbenzene (**1f**) can react efficiently with diphenylphosphinic acid (**2a**) under the optimized reaction conditions, affording the corresponding iodophosphorylaxylation products of **3a**-**3f** in 85-95% isolated yields. For most cases, electron-donating or electron-withdrawing groups which are located on the aryl ring of styrenes do not change the yields of the products significantly. In addition, special alkenes such as allylbenzene (**2g**) and 1-allylnaphthalene (**2h**) could also afford the desired products of **3g** and **3h** in 58% and 45% yields, respectively. To our delight, when cyclic alkenes (**2i**-**2k**) were employed as the starting materials, **3i**-**3k** were synthesized in 75-82% yield. In addition, straight-chain alkenes such as cinnamyl alcohol (**1l**), and methyl cinnamate (**1m**) also showed positive results toward the reaction, and the expected products of **3l** and **3m** were generated in 86% and 90% yields, respectively. Furthermore, various kinds of alkenes containing ester group (**1o**-**1t**) also exhibited high reactivities for the present reaction, affording the corresponding addition products in 63-94% yields. While 1-methoxy-4-vinylbenzene (**1u**) and (*E*)-1-methoxy-4-(prop-1-en-1-yl)benzene (**1v**) were used for the reaction, the desired iodophosphoryloxylation products can be synthesized in 91% and 80% ^{31}P NMR yields, but unfortunately, these compounds could not be isolated from the reaction mixture via the short silica-column. It is deduced that these compounds might decompose during the purification process.

Table 2. Scope of alkenes. [a]

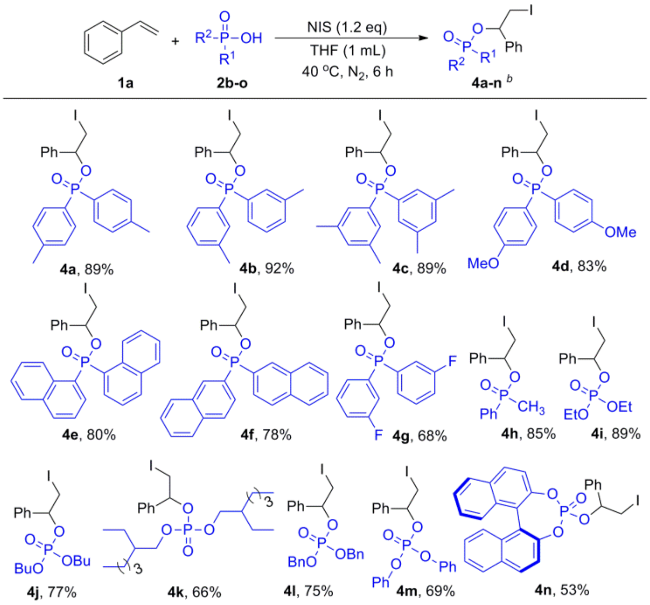


[a] Reagents and conditions: alkene (**1a**, 0.5 mmol), diphenylphosphinic acid (**2a**, 0.5 mmol) and NIS (0.6 mmol) in THF (1.0 mL), at 40 ºC under a N_2 atmosphere stirred for 6 h. [b] Isolated yields. [c] ^{31}P NMR yield, light sensitive, cannot be separated and decomposed during passing through the silica gel column.

As depicted in **Table 3**, a range of substituted P(O)-OH compounds (**2b**-**2o**) were screened under the optimized reaction conditions with styrene. It is clear that symmetrically substituted diarylphosphinic acid with electron-donating groups such as di-*p*-tolylphosphinic acid (**2b**), di-*m*-tolylphosphinic acid (**2c**), bis(3,5-dimethylphenyl)phosphinic acid (**2d**) and bis(4-methoxyphenyl)phosphinic acid (**2e**), exhibit high reactivity toward styrene, giving the corresponding products of **4a-4d** in 83-92% yields. For large functional groups in substituted diarylphosphinic acids, such as di(naphthalen-1-yl)phosphinic acid (**2f**) and di(naphthalen-2-yl)phosphinic acid (**2g**), they also showed positive results, affording the corresponding products in 80% and 78% yields.

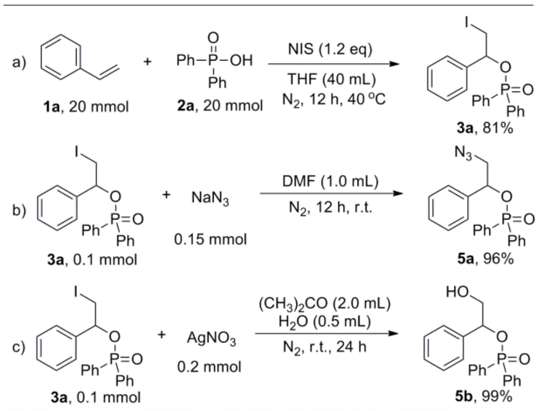
When bis(3-fluorophenyl)phosphinic acid (**2h**) was used, the corresponding iodophosphoryloxylation product of 2-iodo-1-phenylethyl bis(3-fluorophenyl)phosphinate (**4g**) could be produced in 68% yield. Moreover, asymmetric phosphonic acid, such as methyl(phenyl)phosphinic acid (**2i**), is also suitable for the reaction and yielded the product of **4h** in 85% yield. Notably, different kinds of hydrogen phosphates such as diethyl hydrogen phosphate (**2j**), dibutyl hydrogen phosphate (**2k**), 2-ethylhexyl (2-ethylpentyl) hydrogen phosphate (**2l**), dibenzyl hydrogen phosphate (**2m**) and diphenyl hydrogen phosphate (**2n**) were also appropriate for this protocol to generate the corresponding products (**4i**–**4m**) in moderate to good yields. When (S)-(+)-1,1'-binaphthyl-2,2'-diyl hydrogenphosphate (**2o**) was used for the reaction, despite its low solubility and reactivity as a nucleophile, in this case it was quite effective with 53% yield for the synthesis of (11bS)-4-(2-iodo-1-phenylethoxy)dinaphtho[2,1-d:1',2'-f][1,3,2] dioxaphosphepine 4-oxide (**4n**) as the desired product.

Table 3. Scope of the P(O)-OH compounds.[a]

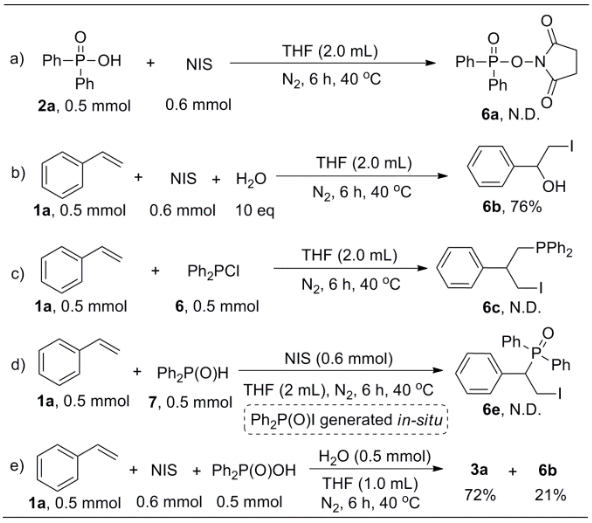


[a] Reagents and conditions: styrene (**1,** 0.5 mmol), P(O)-OH compounds (0.5 mmol), NIS (0.6 mmol), THF (1.0 mL), under N_2 atmosphere, 40 °C , 6 h. [b] Isolated yields.

In order to demonstrate the practical application of this method, we further performed a large-scale reaction of styrene (**1a**, 20 mmol) with diphenyl phosphinic acid (**2a**, 20 mmol) in the presence of NIS which afforded **3a** in 81% yield (7.257 g) (**Scheme 2**). In the solvent of DMF, **3a** could react efficiently with sodium azide to afford 2-azido-1-phenylethyl diphenylphosphinate (**5a**) in 96% yield.[8] This compound provides great synthetic versatility to the phosphorus derivatives, allowing a variety of subsequent structural modification such as radical reaction for the synthesis of triazolyl-functionalized phosphinates with distinct biological activity. In addition, we further conducted the reaction of **3a** with water in the presence of silver nitrate (2.0 equiv.), and the corresponding hydroxylation product of 2-hydroxy-1-phenylethyl diphenylphosphinate (**5b**) was obtained in 99% yield.[8]

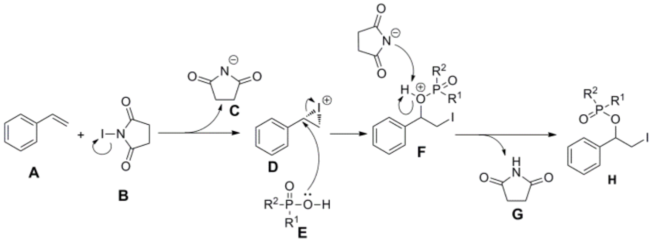


Scheme 2. Large-scale production and selective functionalization of **3a**.



Scheme 3. Control experiments.

Control experiments were conducted for the reaction in order to gain the insight of the reaction mechanism. As depicted in **Scheme 3**, while the reactions were only performed with diphenyl phosphinic acid (**2a**) and NIS under the optimized reaction conditions, the desired coupling product was not detected after the reaction. Meanwhile, while we employed H_2O instead of diphenyl phosphinic acid in the reaction, the corresponding product of 2-iodo-1-phenylethanol (**6b**) could be obtained in 76% yield.[9] Besides diphenyl phosphinic acid, diphenyl phosphine chloride and diphenylphosphinic iodide were also tested for the reaction, but unfortunately, the desired adducts were not formed during the reaction. A competitive reaction between diphenyl phosphinic acid (**2a**) and water was operated under the optimized reaction conditions, and 2-iodo-1-phenylethyl diphenylphosphinate (**3a**) and 2-iodo-1-phenylethanol (**6b**) were generated in 72% and 21% yields, respectively. It is deduced that diphenyl phosphinic acid (**2a**) has a higher reactivity than water as a nucleophile.



Scheme 4. Plausible mechanism.

A plausible mechanism for the present regioselective iodophosphoryloxylation reaction is proposed as illustrated in **Scheme 4**.[10] The *N*-iodosuccinimide (**B**) first undergoes the attack of styrene (**A**) leading to the formation of iodonium intermediate **D** with the release of pyrrolidine-2,5-dione anion (**C**). In the presence of P(O)-OH compound (**E**), which could easily operate the ring-opening reaction with **D** to form the unstable corresponding oxonium intermediate (**F**). In the presence of pyrrolidine-2,5-dione anion (**C**), **F** could undergo the deprotonation process to give the iodophosphoryloxylation product **H** with the release of one molecule of pyrrolidine-2,5-dione (**G**).

Conclusion

In summary, we have developed an efficient NIS-induced regioselective iodophosphoryloxylation of unactivated alkenes with P(O)-OH bonds under transition metal-free conditions. A wide range of P(O)-OH compounds and alkenes bearing diverse functional groups were applicable for this protocol, providing the related β-iodo-1-ethyl phosphinic/phosphoric acid esters with good to excellent yields. To the best of our knowledge, it appears that the regioselective iodophosphoryloxylation of alkenes with P(O)-OH bonds has not been exploited previously, and the salient features of the reaction include its broad substrate scope, high step economy, and good chemoselectivity. The synthetic method also exhibits high potential for the construction of biologically active molecules, and organophosphorus compounds

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Conflicts of interest

There are no conflicts to declare

Keywords: P(O)-OH bonds • Iodophosphoryloxylation • alkenes • transition metal-free

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