Chemical Science

ROYAL SOCIETY OF CHEMISTRY

EDGE ARTICLE

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Cite this: *Chem. Sci.*, 2023, **14**, 5519

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Metal-free highly chemo-selective bisphosphorylation and deoxyphosphorylation of carboxylic acids†

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Received 2nd March 2023
Accepted 23rd April 2023

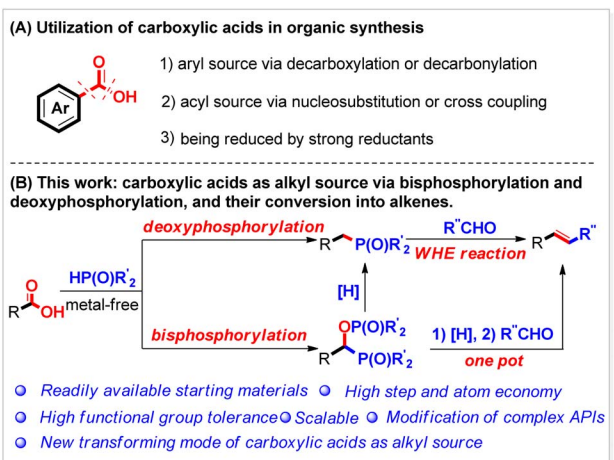
DOI: 10.1039/d3sc01148h

rsc.li/chemical-science

Carboxylic acids are readily available in both the natural and synthetic world. Their direct utilization for preparing organophosphorus compounds would greatly benefit the development of organophosphorus chemistry. In this manuscript, we describe a novel and practical phosphorylating reaction under transition metal-free reaction conditions that can selectively convert carboxylic acids into the P–C–O–P motif-containing compounds through bisphosphorylation, and the benzyl phosphorus compounds through deoxyphosphorylation. This strategy provides a new route for carboxylic acid conversion as the alkyl source, enabling highly efficient and practical synthesis of the corresponding value-added organophosphorus compounds with high chemo-selectivity and wide substrate scope, including the late modification of complex APIs (active pharmaceutical ingredients). Moreover, this reaction also indicates a new strategy for converting carboxylic acids into alkenes by coupling this work and the subsequent WHE reaction with ketones and aldehydes. We anticipate that this new mode of transforming carboxylic acids will find wide application in chemical synthesis.

Introduction

Carboxylic acids are one of the most ubiquitous functional chemicals found in chemistry, chemical engineering, and related industries.[1] Due to their abundance and availability, carboxylic acids are considered the ideal starting substrates in organic synthesis and attract tremendous attention from both academic and industrial researchers. Usually, carboxylic acids are extensively used as the building blocks through a decarboxylative[2] or decarbonylative[3] process (Scheme 1A(1)). They can also serve well as the acyl source for preparing target functional molecules[4] (Scheme 1A(2)) or be reduced by strong reductants[5] (Scheme 1A(3)). Herein, we report a new manifold for their conversion under metal-free reaction conditions as the alkyl source (Scheme 1B). It is found that after being activated *in situ* by Boc_2O, both aliphatic and aromatic carboxylic acids, including those bearing functional groups, can be bisphosphorylated by P(O)–H compounds to produce the corresponding phosphorus compounds bearing a P–C–O–P motif. By tuning the reaction conditions, various benzoic acids can also be selectively deoxyphosphorylated by P(O)–H compounds to give the corresponding benzylphosphorus compounds.



Scheme 1 Utilization of carboxylic acids in synthetic chemistry.

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† Electronic supplementary information (ESI) available: General information, experimental procedures, copies of ^1H, ^{13}C and ^{31}P NMR spectra for products. See DOI: https://doi.org/10.1039/d3sc01148H

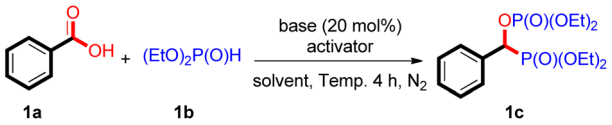
Organophosphorus compounds have wide applications in chemical science, medicinal science and materials science.[6] However, the methods for their synthesis are limited and highly depend on the transformation of (pseudo)halides.[7] The synthesis of organophosphorus compounds, starting from the readily available carboxylic acids, would greatly advance phosphorus chemistry forward. Functional molecules with a P–C–O–P skeleton can be used as ligands or building blocks.[8] They can also be used as a dental material and flame retardant material.[9] Moreover, some of these compounds have bioactivity exemplified by the PPARg-specific antagonist mifobate (SR-202), which can suppress the differentiation of adipocytes induced by hormones and affect the consumption of glucose in cells and sensitivity to insulin *in vivo*.[10]

However, they can only be synthesized through the nucleophilic substitution of alpha-hydroxyl phosphorus compounds with P(O)–X compounds[11] or the phosphorylation of acyl derivatives such as acyl phosphorus compounds,[12] acyl thioesters,[13] acyl chlorides,[14] *etc.*[15] with P(O)–H compounds. Meanwhile, the benzyl phosphorus compounds are also important phosphorus reagents that can be used as synthetic intermediates, ligands, and bioactive and material functional molecules. For example, they are widely used in Wittig–Horner–Emmons (WHE) reactions and can react with ketones or aldehydes to produce alkenes.[16] Benzyl phosphorus compounds can be synthesized through nucleophilic substitution of benzyl metals (Li or Mg) with P(O)–X or the Arbuzov reaction of benzyl halides with phosphites at a high reaction temperature[17] (usually >140 °C). They can also be generated *via* coupling of benzyl halides, aromatic esters, and thiol esters with P(O)–H compounds.[18] The reactions described above can produce P–C–O–P skeleton-containing and benzyl phosphorus compounds; however, they obviously suffer from low step economic efficiency since the required intermediates, such as hydroxyl phosphorus compounds, acyl derivatives, and benzyl halides, must be pre-synthesized from the corresponding carboxylic acids.[19] Moreover, the conditions of some reactions are very hazardous, limiting their application in organic synthesis. Thus, new facile and efficient methods for their synthesis are still highly desired in the synthetic community.

Results and discussion

Decarbonylative coupling of benzoic acids emerged as a powerful method in organic synthesis.[20] Our group also made a contribution to this research field.[21] During the study on the mechanism of decarbonylative phosphorylation of carboxylic acids, a trace amount of bisphosphorus compound **1c** was detected by GC-MS. Regarding the importance of such compounds and their synthetic difficulty, we think this scientific finding deserves further investigation. We started this work by investigating the reactivity of benzoic acid (**1a**) with diethyl phosphite (**2a**), and the obtained results are compiled in Table 1. By heating a mixture of benzoic acid **1a** (0.2 mmol), $(EtO)_2P(O)H$ (**1b**, 2 equiv.), Boc_2O (2 equiv.) and Na_2CO_3 (20 mol%) in toluene at 80 °C for 4 h, the corresponding bisphosphorylating product **1c** was produced in 97% yield (Table 1, entry 1). The base is important for this reaction. In its absence, no **1c** was detected (Table 1, entry 2).

Table 1 Optimization of reaction conditions[a]



1a 1b 1c

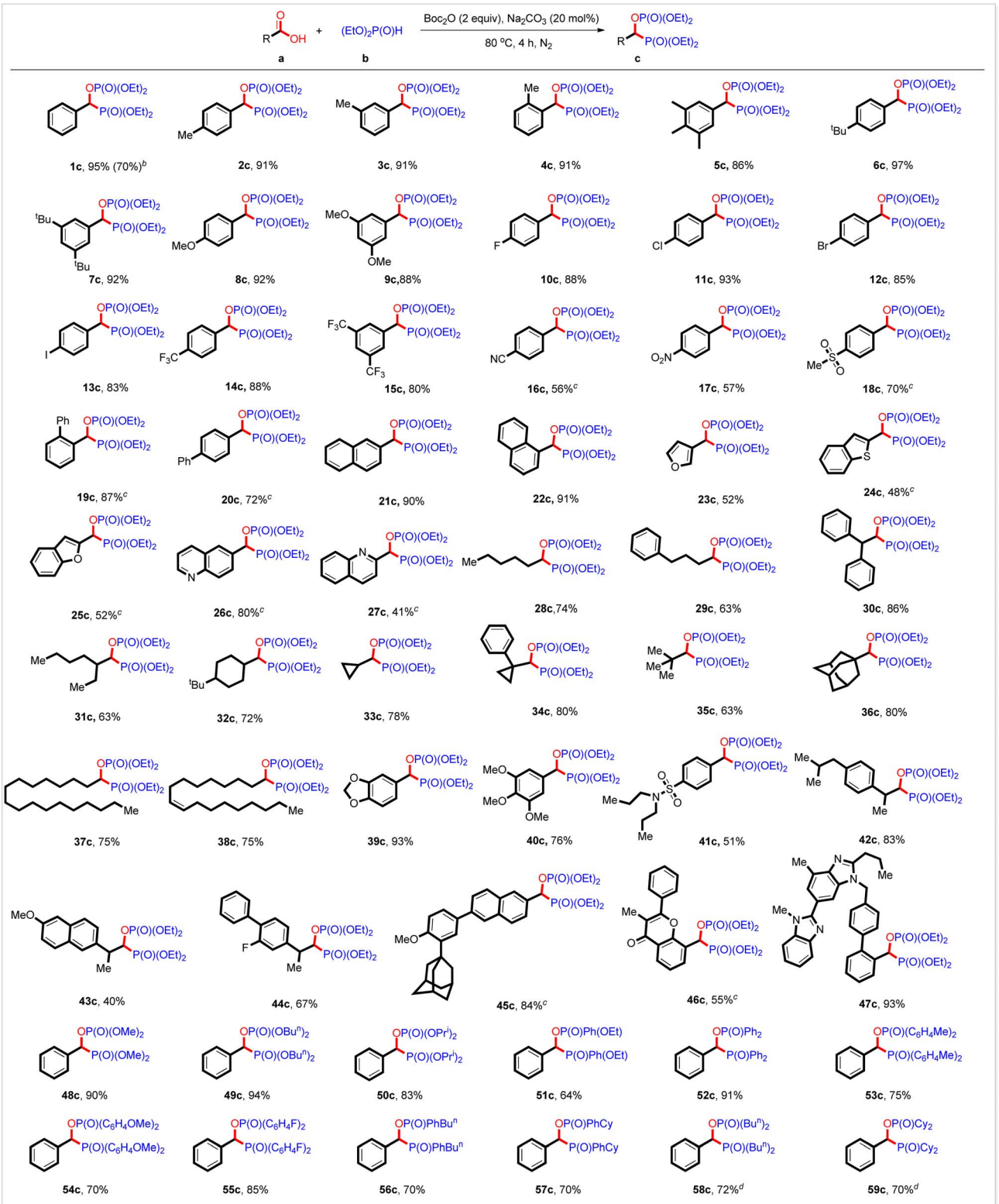
Entry	Base	Activator	Solvent	Temp. (°C)	Yield[b]/%
1	Na_2CO_3	Boc_2O	Toluene	80	97
2	—	Boc_2O	Toluene	80	None
3	$NaHCO_3$	Boc_2O	Toluene	80	95
4	NaOAc	Boc_2O	Toluene	80	Trace
5	Et_3N	Boc_2O	Toluene	80	49
6[c]	Et_3N	Boc_2O	Toluene	80	95
7	Na_2CO_3	Boc_2O	Toluene	80	93
8	Na_2CO_3	—	Toluene	80	None
9	Na_2CO_3	Ac_20	Toluene	80	None
10	Na_2CO_3	Piv_2O	Toluene	80	None
11	Na_2CO_3	TFAA	Toluene	80	Trace
12	Na_2CO_3	Boc_2O	Cyclohexane	80	98
13	Na_2CO_3	Boc_2O	THE	80	95
14	Na_2CO_3	Boc_2O	Dioxane	80	98
15	Na_2CO_3	Boc_2O	CH_3CN	80	30
16	Na_2CO_3	Boc_2O	NMP	80	49
17	Na_2CO_3	Boc_2O		80	98 (95[d])
18	Na_2CO_3	Boc_2O		60	25
19[e]	Na_2CO_3	Boc_2O		80	53

[a] Reaction conditions: **1a** (0.2 mmol), **1b** (0.4 mmol), base (20 mol%), activator (0.4 mmol), solvent (1 mL), 4 h, N_2. [b] GC yield using dodecane as an internal standard. [c] Base (1 equiv.). [d] Isolated yield. [e] 2 h.

$NaHCO_3$ could also mediate this reaction (Table 1, entry 3), while the weaker base NaOAc showed no reactivity (Table 1, entry 4). The organic base Et_3N could also mediate this reaction, but with a relatively low yield (Table 1, entry 5). By increasing the loading to 1 equiv, 95% yield of **1c** was obtained (Table 1, entry 6). A similar yield was obtained with 1 equiv. Na_2CO_3 (Table 1, entry 7). The activator anhydride of a carboxylic acid is also essential to this reaction. Without the addition of anhydride, the reaction did not progress (Table 1, entry 8). Other selected anhydrides, such as Ac_2O, Piv_2O, and TFAA, did not work either (Table 1, entries 9–11). This reaction could also take place in cyclohexane, THF, and dioxane, but poorly in polar CH_3CN and NMP (Table 1, entries 12–16). To our delight, when the reaction was conducted under solvent-free conditions, a high yield was obtained (Table 1, entry 17). Lowering the reaction temperature decreased the yield of **1c** (Table 1, entry 18). Shortening the reaction time to 2 h also decreases the yield (Table 1, entry 19). Obviously, the reaction conditions are rather facile and mild. In addition, the atom utilization efficiency of the starting material carboxylic acid and $(EtO)_2P(O)H$ is over 90%. This reaction would undoubtedly be a simple and efficient method for preparing bisphosphorus compound **1c**.

We subsequently investigated the substrate scope with the optimized reaction conditions. As shown in Table 2, the substrate scope is rather general. Electron-rich and electron-deficient aromatic carboxylic acids and aliphatic ones served well. All the three kinds of hydrogen phosphoryl compounds, H-

Table 2 Substrate scope of carboxylic acids and hydrogen phosphoryl compounds[a]

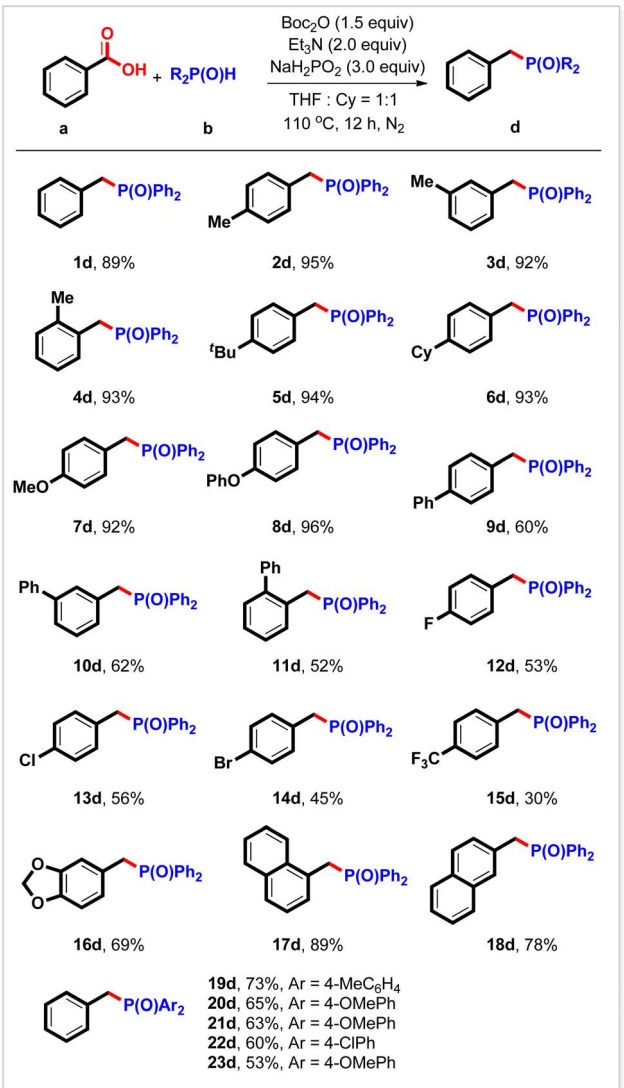


[a] Reaction conditions: carboxylic acid **a** (0.2 mmol), hydrogen phosphoryl compound **b** (0.2 mmol), Na_2CO_3 (20 mol%), Boc_2O (0.4 mmol), 80 °C, 4 h. Isolated yields. [b] 5 mmol scale and 20 h. [c] Et_3N (1 equiv.) was used instead of Na_2CO_3. [d] 100 °C.

phosphonates, H-phosphinates, and secondary phosphine oxides, were suitable for this reaction. Thus, when the reaction of benzoic acid with diethyl phosphonate was conducted at a 5 mmol scale, **1c** was generated in 70% yield. In addition to benzoic acid, substrates bearing 4-methyl, 3-methyl, 2-methyl, 3,4,5-trimethyl, 4-*tert*-butyl, 3,5-di(*tert*-butyl), 4-methoxyl and 3,5-dimethoxyl groups at the benzene ring all coupled readily with diethyl phosphonate **1b** to produce the corresponding products in high yields (Table 2, **1c–9c**). Halo groups (F, Cl, Br, and I) survived well under the reaction conditions, greatly facilitating further derivation of those products (Table 2, **10c–13c**). Benzoic acids with electron-withdrawing groups such as 4-trifluoromethyl, 3,5-ditrifluoromethyl, 4-nitrile, 4-nitro, and 4-methylsulfonyl groups also worked well and were transformed into the expected bisphosphorus compounds in high yields (Table 2, **14c–18c**). The steric hindrance seemed not to affect the yield of this reaction. For example, 2-phenyl and 4-phenyl benzoic acid acted as the right substrate to give the desired products **19c** and **20c** in 87% and 74% yield, respectively. High yields were also obtained from the π-extended and heterocyclic derivatives (Table 2, **21c–27c**). By using this strategy, aliphatic carboxylic acids were also smoothly bisphosphorylated. It should be noted that primary, secondary, and tertiary carboxylic acids all were workable under the reaction conditions, furnishing the expected products in high yields (Table 2, **28c–35c**). Notably, this bisphosphorylation strategy enables the late modification of bioactive carboxylic acids, including some drugs used in the clinic, showing the potential application of this new reaction in the design and development of drugs. For instance, bioactive adamantanyl carboxylic acid, stearic acid, oleic acid, piperic acid, and eudesmic acid all reacted with diethyl phosphonate to produce the expected bisphosphorus compounds in high yields (Table 2, **36c–40c**). Probenecid, ibuprofen, naproxen, flurbiprofen, adapalene, 3-methylflavone-8-carboxylic acid and telmisartan are widely used in clinics. By using this strategy, they are also converted smoothly into the corresponding coupling products in high yields (Table 2, **41c–47c**). The substrate scope of hydrogen phosphoryl compounds is also investigated. In addition to diethyl phosphonate, other selected H-phosphonates such as dimethyl phosphonate, dibutyl phosphonate, and diisopropyl phosphonate also reacted readily with benzoic acid to produce the corresponding products in high yields (Table 2, **48c–50c**). H-phosphinates exemplified by ethyl phenylphosphinate also acted well (Table 2, **51c**). To our delight, both aromatic and aliphatic secondary phosphine oxides worked well under the present reaction conditions. Thus, various biaryl phosphine oxides are coupled with benzoic acids (Table 2, **52c–55c**). Phenyl butyl phosphine oxide and phenyl cyclohexyl phosphine oxide served as the right substrates (Table 2, **56c** and **57c**). Aliphatic dibutyl phosphine oxides and the sterically hindrant dicyclohexyl phosphine oxide also reacted with benzoic acid and were transformed smoothly into the expected products in high yields (Table 2, **58c** and **59c**). These results outlined in Table 2 demonstrated well that this reaction would be a facile, general, and efficient method for preparing bisphosphorus compound **c**.

During the reaction of diphenyl phosphine oxide with benzoic acid, it was found that when over-stoichiometric $Ph_2P(O)H$ was used, a new benzyl phosphorus compound **1d** *via* deoxyphosphorylation was detected by GC-MS. Boc_2O (1.5 equiv.), Et_3N (2 equiv.), and NaH_2PO_2 (3 equiv.)[20] in a mixed solvent (THF/cyclohexane) at 110 °C for 12 h produced the corresponding benzyl phosphorous compounds in 89% yield (Table 3, **1d**). This reaction was also suitable for other substituted benzoic acids. Thus, high yields were obtained from derivatives bearing 4-methyl, 3-methyl, 2-methyl, 4-*tert*-butyl, 4-cyclohexyl, 4-methoxyl, and 4-phenoxyl groups at the benzene ring (Table 3, **2d–8d**). All three kinds of phenyl group-substituted benzoic acids were readily deoxyphosphorylated, furnishing the expected products in moderate yields (Table 3, **9d–11d**). The halogen groups (F, Cl, and Br) survived under the reaction conditions (Table 3, **12d–14d**). The electron-deficient benzoic

Table 3 Deoxyphosphorylation of carboxylic acids forming benzyl phosphorus compounds[a]



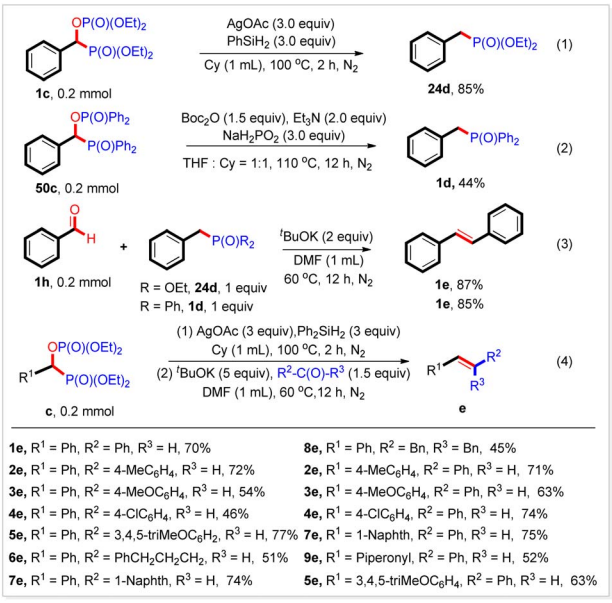
[a] Reaction conditions: carboxylic acid (0.2 mmol), $R_2P(O)H$ (0.4 mmol), Boc_2O (0.3 mmol), NaH_2PO_2 (0.6 mmol), mixed solvent ($V_{THF}/V_{cyclohexane}$ = 1 : 1, 0.5 mL), 110 °C, 12 h, N_2. Isolated yield.

acid exemplified by 4-trifluoromethyl benzoic acid showed relatively low reactivity, giving the desired product **15d** in 30% yield. By using this strategy, heterocyclic and π-extensive substrates were also transformed readily into the corresponding benzyl phosphorus compounds in good yields (Table 3, **16d**, **17d**, and **18d**). Other selected secondary phosphine oxides can also be transformed into the expected benzyl phosphorus compounds in good yields under the current reaction conditions through deoxyphosphorylation (Table 3, **19d–23d**).

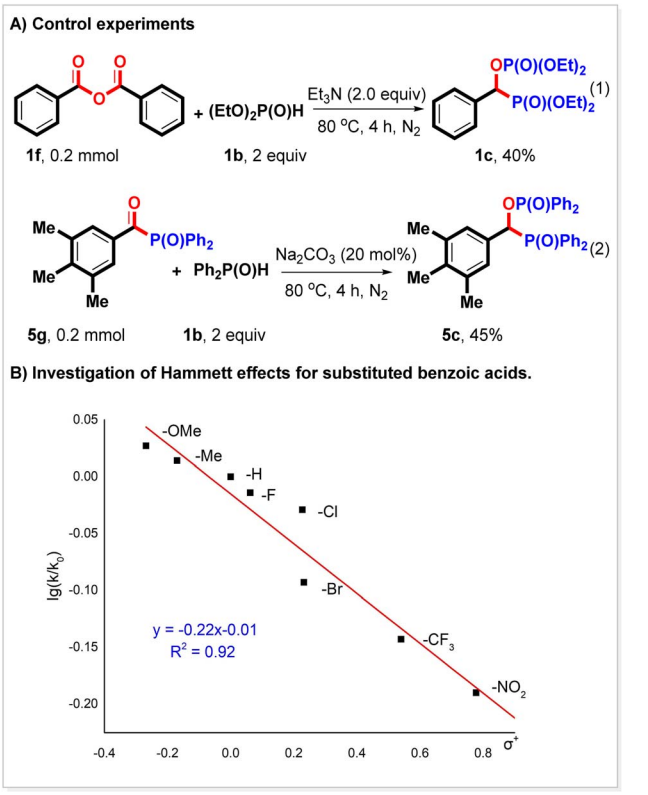
It should be noted that when diethyl phosphonate was used, only a trace amount of the desired product (**24d**) was produced. To our delight, **24d** could be obtained in 85% yield after treatment of the isolated bisphosphorus compound **1c** in the presence of AgOAc and Ph_2SiH_2 in cyclohexane at 100 °C for 2 h (Scheme 2, eqn (1)). Meanwhile, **52c** could be converted into **1d** in 44% yield under the conditions of a deoxyphosphorylation reaction (Scheme 2, eqn (2)). These results would be a good complement to the deoxyphosphorylation reaction described above. Worth noting is that benzyl phosphorus compounds are widely used in Wittig–Horner–Emmons (WHE) reactions. Indeed, both **1d** and **24d** could react with benzaldehyde to produce the corresponding alkene **1e** in 85% and 87% yield, respectively (Scheme 2, eqn (3)). In particular, we found that the alkene **1e** could also be obtained in 70% yield by adding benzaldehyde and a base to the reaction mixture after completing eqn (1) and stirring at 60 °C for 12 h (Scheme 2, eqn (4)). By using this strategy, a variety of alkenes were synthesized in good to high yields (Scheme 2, eqn (4)). These results indicated that carboxylic acids could be easily transformed into alkenes by coupling the current reaction and subsequent WHE reaction, and would find wide applications in organic synthesis.

To probe the mechanism of the reaction, more control experiments were performed. It is known that Boc_2O can activate carboxylic acids to form a mixed anhydride. We think anhydride might be the key intermediate in this reaction.[21,22] We found that benzoic anhydride could react with diethyl phosphonate to produce **1c** in 40% yield (Scheme 3A, eqn (1)). It is deduced that anhydride can react with the P(O)–H compound to give an acyl phosphorus compound, which might also be an intermediate in this reaction. We synthesized acyl phosphorus compound **5g** and found that it indeed could couple with diphenyl phosphine oxide to generate **5c** in 45% yield (Scheme 3A, eqn (2)). A Hammett analysis was subsequently performed (Scheme 3B). Under the conditions of a bisphosphorylation reaction, a negative slope ($\rho = -0.22$) was observed for the reaction of substituted aromatic carboxylic acids with diethyl phosphonate. This result indicated that the release of the Boc fragment might be the rate-determining step in the bisphosphorylation reaction.

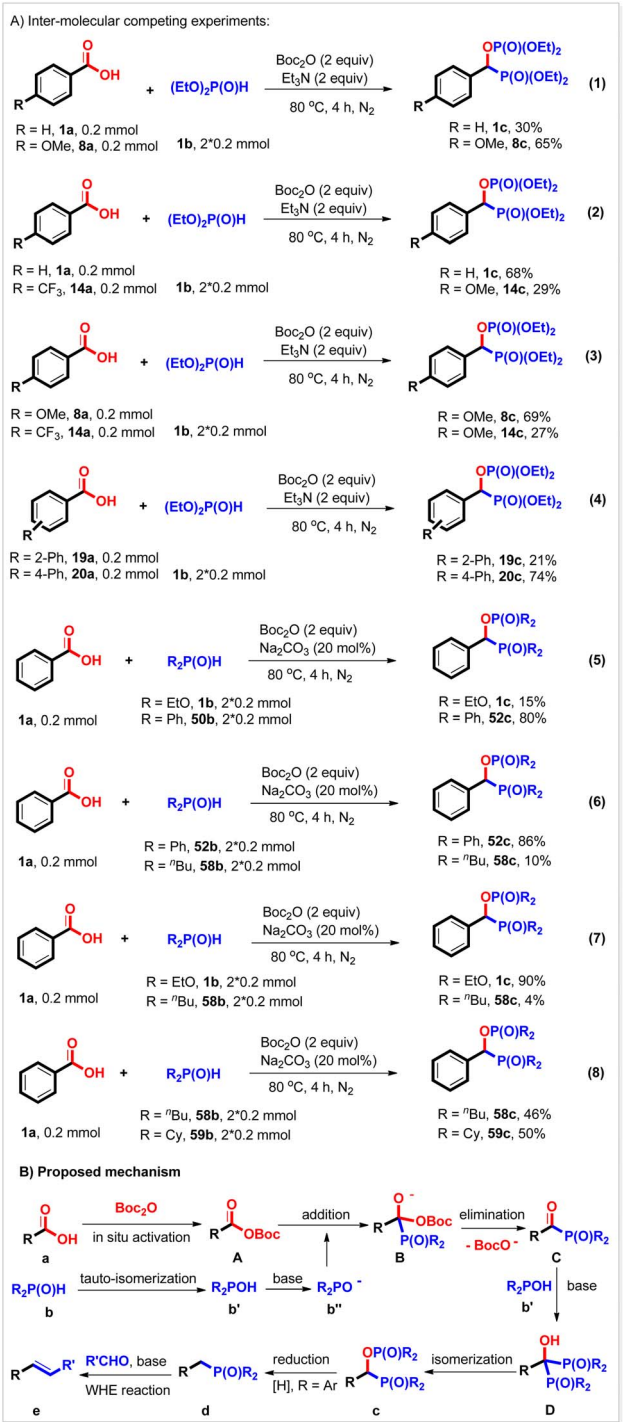
Several inter-molecular competing experiments were conducted to investigate the chemo-selectivity of the bisphosphorylation reaction (Scheme 4A). When benzoic acid **1a** was allowed to compete with electron-rich 4-methoxyl benzoic acid **8a** to react with diethyl phosphonate **1b** under the conditions of the bisphosphorylation reaction, the expected products **1c** and **8c** were produced in 37% and 65% yield, respectively (Scheme 4A, eqn (1)). Similar results were also observed with the competing reactions between benzoic acid **1a** and 4-trifluoromethyl benzoic acid **14a** and 4-methoxyl benzoic acid **8a** and 4-trifluoromethyl benzoic acid **14a** (Scheme 4A, eqn (2) and (3)), indicating that this reaction favored electron-richer carboxylic acids. It seems that the steric hindrance of the



Scheme 2 Application of this new transformation.



Scheme 3 Control experiments and Hammett analysis.



Scheme 4 Inter-molecular competing experiments and the proposed mechanism.

carboxylic acid substrate did not affect the yield as described above, but it would reduce the reaction rate. For example, when 2-phenyl benzoic acid **19a** competed with 4-phenyl benzoic acid **20a**, **20c** was produced in 74% yield, while **19c** was only obtained in 21% yield (Scheme 4A, eqn (4)). The chemo-selectivity was also studied with a P(O)H substrate. It was found that diphenyl phosphine oxide reacted with benzoic acid more quickly than diethyl phosphonate under the reaction conditions (Scheme 4, eqn (5)). Its reaction rate was also faster than dibutyl phosphine oxide's (Scheme 4A, eqn (6)). However, when diethyl phosphonate competed with dibutyl phosphine oxide in one pot, the expected **1c** was generated in 90% yield, while **58c** was only given in 4% yield (Scheme 4A, eqn (7)). These results would be ascribed to the stability, and not the nucleophilicity of the conjugated base of P(O)H compounds. The more stable the conjugated base, the faster the rate of this reaction. The steric hindrance of the P(O)H substrate was also investigated and found not to affect the reaction. For instance, similar yields of the corresponding products were obtained with the competing experiment of dibutyl phosphine oxide and dicyclohexyl phosphine oxide (Scheme 4A, eqn (8)). It should be noted that these results herein were consistent with the Hammett analysis described above.

On the basis of the mechanistic studies described above and previous references, a probable mechanism was proposed for this reaction. As shown in Scheme 4B, carboxylic acid **a** was first activated by Boc_2O to generate a mixed anhydride **A**,[21,22] which then reacted with hydrogen phosphoryl compound **b** to give acyl phosphorus compound **C** and released a Boc fragment. The resulting acyl species **C** subsequently underwent addition with another hydrogen phosphoryl compound **b**, followed by [1, 2]-phospha-Brook isomerization[23] to produce the target bisphosphorus compound **c**. When diaryl phosphine oxides were used, product **c** could be further reduced by the external reductant NaH_2PO_2 to afford the corresponding benzyl phosphorus compound **d** and therefore, complete deoxyphosphorylation in one pot. By further addition of aldehydes (ketones) and base, this reaction could efficiently couple with the WHE reaction, thus converting carboxylic acids into value-added alkenes.

Conclusions

In summary, we have achieved both bisphosphorylation and deoxyphosphorylation of carboxylic acids under metal-free and mild reaction conditions, generating the corresponding P–C–O–P motif-containing compounds and benzyl phosphorus compounds selectively. Specifically, this reaction can efficiently couple with the WHE reaction and thus also provides an efficient method for converting carboxylic acids into valuable alkenes. Wide substrate scope for both carboxylic acids and P(O)H compounds was demonstrated with high functional group tolerance. The scale-up experiments and application to modification of complex APIs will also show this new reaction's practicality. This work extends the application of carboxylic acids and provides efficient methods for preparing related organophosphorus compounds and alkenes. We think these new reactions would find wide application in the synthetic community.

Author contributions

L. G., T. X., Q. T., M. C., L. W., J. Z. and K. L. did the experiments. L. L. and W. C. discussed the mechanism and revised the

manuscript. L. H., J. N. and T. C. designed the experiment project, discussed the mechanism and wrote the manuscript.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

T. C. thanks the National Nature and Science Foundation of China (Grant No. 22261015 and 21871070) and the Key R&D project of Hainan province (No. ZDYF2020168) for financial support. L. H. thanks Zhejiang Province (2022R01021) and Zhejiang Yangfan New Materials Co. Ltd for financial support.

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