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Chemoselective generation of acyl phosphates, acylium ion equivalents, from carboxylic acids and an organophosphate ester in the presence of a Brønsted acid†

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We describe the chemoselective conversion of carboxylic acids to functional aromatic ketones promoted by a tailored organophosphate ester in the presence of a Brønsted acid. The protonated phosphate ester reacts with the carboxylic acid to form acyl phosphate, which reacts with benzenes to give aromatic ketones, probably through the acylium ion or its equivalent. The reaction time is short even at room temperature, and the reaction is compatible with various other functional groups, including amines, olefins, esters, amides and nitriles.

Organophosphate esters have various important functions in biological systems.[1] One of these is driving unfavorable reactions by lowering the activation energy of the rate-determining step, or by enabling a different reaction pathway, usually through multiple steps (*i.e.*, phosphate-coupled reaction).[1b] In general, coupled reactions allow conversion of one functional group to another *via* a reactive intermediate. For example, direct formation of an amide (**3**) from a carboxylic acid (**1**) and an amine in the biosynthesis of the amide side chains of asparagine (Asn) and glutamine (Gln) is an unfavorable reaction in terms of leaving-group ability. However, in the glutamine synthetase-catalyzed reaction, ATP phosphorylates the carboxylic acid first to form an acyl phosphate,[2,3] followed by attack of ammonia on the acyl phosphate (**2**) to generate the amide (**3**) in the side chains of Asn and Gln.[4] Thus, the intervention of ATP makes the overall reaction thermodynamically feasible because of the high reactivity of the acyl phosphate (Fig. 1a).

Importantly, production of acyl phosphate requires a Lewis acid such as Mg^{2+}, Mn^{2+}, or Zn^{2+} to activate ATP, though some other enzyme reactions utilize general acid catalysis from amino acid residues to the phosphate group.[5] By these means, the negative charge of the phosphate is overcome. Thus, additional coordination to the phosphate may afford a superior leaving group, facilitating cleavage of the P–O bond of the ATP moiety to produce acyl phosphates. While acyl phosphates are potentially highly reactive reagents toward various nucleophilic species, their applicability for functionalization of aromatic compounds is limited. For instance, classical phosphate reagents such as polyphosphoric acid (PPA),[6] or Eaton's reagent (phosphorus pentoxide in methanesulfonic acid)[7] have very poor substrate generality for intermolecular introduction of acyl groups onto aromatics.[8] Also, modern phosphate reagents such as diphenyl phosphorazidate[9a] and BOP reagents[9b] cannot mediate the reaction of carboxylic acids with very weak nucleophiles such as benzene, because of interference by nucleophilic azide anions and benzotriazole anions.[10]

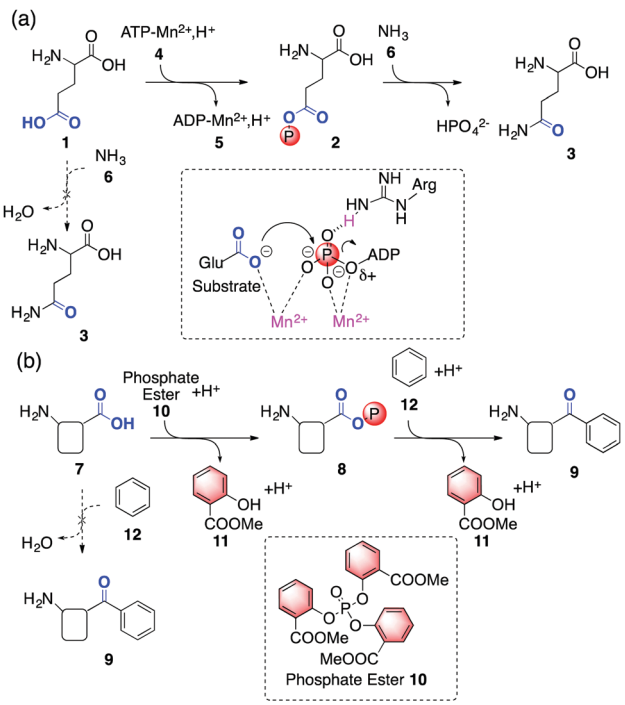

Fig. 1 (a) Mechanism of ATP-mediated glutamine synthetase reaction. (b) Phosphate-coupled aromatic acylation reaction inspired by the biological catalyst.

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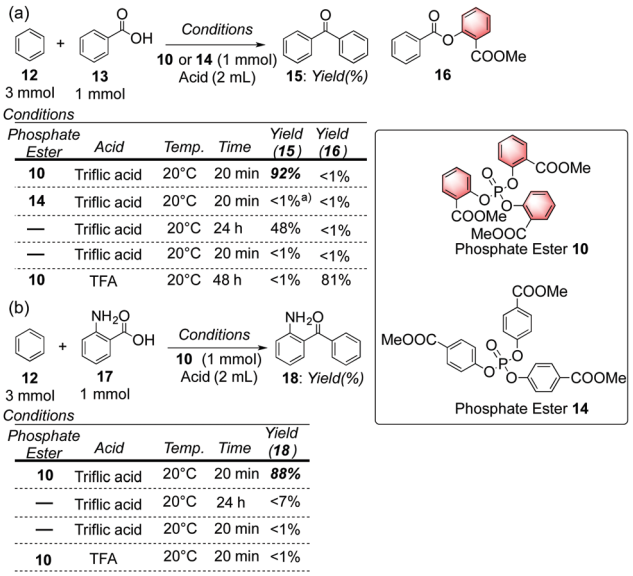
Amino acid compounds (7, Fig. 1b), which contain both carboxylic acid and amino functionalities in the same molecule, are attractive target molecules because reactions of the corresponding acylium ions with aromatics would produce aromatic ketones containing an amino group on the same aromatic moiety. Such compounds are important in medicinal chemistry, as exemplified by benzodiazepine structures.[11] The reaction of amino acids with aromatic rings to produce aromatic ketones is a challenging reaction even when strong Lewis acids[12] or transition metals are employed,[13] because selective activation of carboxylic acids is problematic.[14] Amino acid compounds hardly produce the corresponding acylium ion or its equivalent because of charge–charge repulsion between two cationic sites (NH_3^+ and $^+C{=}O$);[15] moreover, the nucleophilic amino group may react with activated carboxylic functional groups.

However, because the phosphorus atom possesses high oxygen affinity, chemoselective activation of a carboxylic functional group can be achieved *via* interaction with tailored organophosphate reagents. Organophosphate esters possess three kinds of ester linkages, and this offers opportunities to tune the reactivity. To make phosphate esters sufficiently electrophilic to react with carboxylic acid oxygen atoms, we focused on the putative cationic phosphorus species generated by P–O bond cleavage.[16] Inspired by biological phosphate ester-coupled reactions, we set out to design a suitable phosphate ester//Brønsted acid combination (instead of ATP//metal cation/hydrogen bonding) to activate the carboxylic acid functionality chemoselectively (Fig. 1b). We hypothesized that salicylic acid or methyl salicylate would be a good leaving group to the phenolic oxygen atom from the protonated carbonyl group of an acid or ester functionality due to intramolecular hydrogen-bond formation.[17,18] Finally, we found that phosphate ester (**10**) efficiently promoted the reaction of carboxylic acids with aromatics in the presence of the acid (Table 1). One of the three methyl salicylates incorporated into phosphate ester (**10**) serves as a good leaving group, enabling cleavage of the P–O bond upon protonation and promoting the electrophilic coupled reaction of carboxylic acids with aromatics to give aromatic ketones.

Usually acid-catalyzed reaction of carboxylic acids with benzene takes a long time at room temperature, even under strongly acidic conditions. For example, the reaction of benzoic acid (**13**) with benzene (**12**) under strongly acidic conditions at 20 °C gave the desired benzophenone (**15**) in 48% yield after 24 h (Table 1). When the reaction was quenched after 20 min, essentially none of the desired benzophenone (**15**) was obtained. On the other hand, when one equivalent of phosphate ester (**10**) was added to the reaction system, the desired benzophenone (**15**) was obtained in 92% yield in 20 min at room temperature. When the acidity of the reaction system was lower (*e.g.*, in the case of TFA), the phosphate ester (**10**) did not promote the acylation reaction; thus strongly acidic conditions were needed to enhance the reactivity of the phosphate ester **10**.[19] From this result, activation of phosphate ester (**10**) required strongly acidic conditions, probably because two kinds of protonation at the oxygen atom of P═O and the oxygen atom of the methyl ester of methyl salicylate are needed. Importantly, when we used the regioisomeric phosphate ester (**14**), in which three

Table 1 Examination of various combinations of phosphate esters and Brønsted acids



Conditions

Phosphate Ester	Acid	Temp.	Time	Yield (15)	Yield (16)
10	Triflic acid	20°C	20 min	**92%**	<1%
14	Triflic acid	20°C	20 min	<1%[a)]	<1%
—	Triflic acid	20°C	24 h	48%	<1%
—	Triflic acid	20°C	20 min	<1%	<1%
10	TFA	20°C	48 h	<1%	81%

Conditions

Phosphate Ester	Acid	Temp.	Time	Yield (18)
10	Triflic acid	20°C	20 min	**88%**
—	Triflic acid	20°C	24 h	<7%
—	Triflic acid	20°C	20 min	<1%
10	TFA	20°C	20 min	<1%

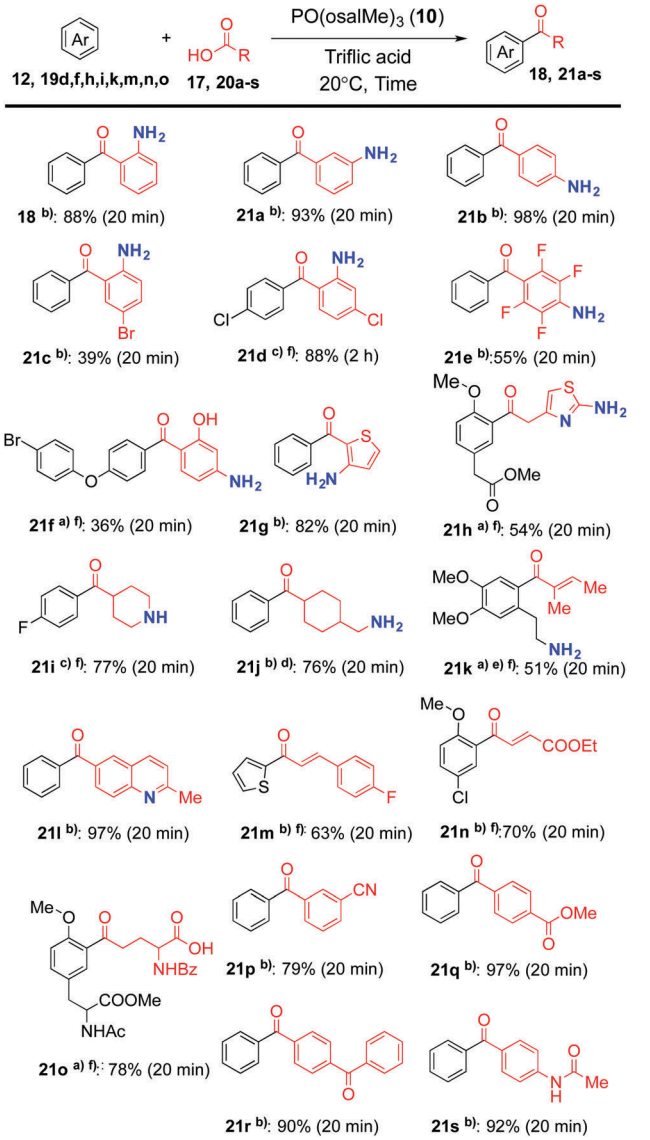
[a] 98% recovery of (**14**) was obtained. General procedure: to a mixture of benzene (**12**) (3.0 mmol), benzoic acid (**13**/**17**) (1.0 mmol) and phosphate (**10**/**14**) (1.0 mmol), acid (triflic acid/TFA) (2.0 mL) was added at 20 °C. Then the whole reaction mixture was stirred at 20 °C for a specified time. After the reaction was completed, the reaction was quenched with ice-water.

methyl 4-hydroxybenzoate moieties are attached to the phosphorus atom, the reaction of the carboxylic acid with benzene was not promoted; moreover, the phosphate ester was recovered almost intact (98% yield) after 20 min (Table 1(a)). Interestingly, phosphate ester (**10**) could also ionize 2-aminobenzoic acid (**17**) to the corresponding acylium ion, and reaction with benzene gave 2-aminobenzophenone (**18**) in 88% yield within 20 min (Table 1(b)).

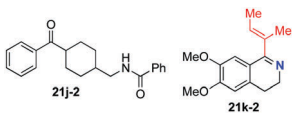
We investigated the substrate generality of the reaction under optimized conditions (Table S1, ESI† and Table 2). *o*-, *m*-, *p*-Aminobenzoic acids (**17**, **20a**, and **20b**) reacted with benzene (**12**) in the presence of phosphate ester (**10**) to give aromatic ketones bearing an amino group (**18**, **21a**, and **21b**, respectively) in excellent yields. When halogen was substituted at the *meta* position with respect to the carboxylic acid group of *o*-aminobenzoic acid (**20c**), the yield was low. On the other hand, when the halogen was substituted at the *para* position (**20d**), the yield was high if the reaction time was extended. The low yield of **21c** may be due to insufficient electron density at the carboxylic acid functional group, resulting in low reactivity toward phosphate ester (**10**).

Other kinds of aromatic or aliphatic amines were also available and the desired aromatic ketones were obtained in moderate to high yield (**21f**, **21g**, **21h**, **21i**, **21j**, and **21k**). However, the yield became lower in the case of phenol (**21f**), probably because the phenol oxygen atom also reacted with the phosphate ester (**10**), reducing the product yield. Because heating was not needed and the reaction time was short in this system, some heterocycles, such as thiophenes (**21g** and **21m**), quinoline (**21l**) and thiazole (**21h**), were tolerated.

Table 2 Substrate generality



Yields are isolation yields. [a] With 1 equivalent of the aromatic ring. [b] With 3 equivalents of the aromatic ring. [c] With 5 equivalents of the aromatic ring. [d] Isolated as the *N*-acylated compound (**21j-2**). [e] After work-up, cyclized compound (**21k-2**) was obtained. [f] No other regioisomers were detected.



This also made it possible to activate only the carboxylic acid group even in the presence of the ester group (**21n, 21o,** and **21q**),[14] or to produce conjugated aromatic ketones (**21m** and **21n**).[20] Connection of the aromatic ring of the tyrosine derivative (**19o**) with the glutamine acid derivative (**20o**) at the γ-position also proceeded (**21o**) with **10**.

Intriguingly, the ketones (**21d**, **21f**, **21h**, **21i**, **21k**, **21m**, **21n** and **21o**) were generated regioselectively even in the reaction of a substituted benzene (**19d**, **19f**, **19h**, **19i**, **19k**, **19m**, **19n** and **19o**).

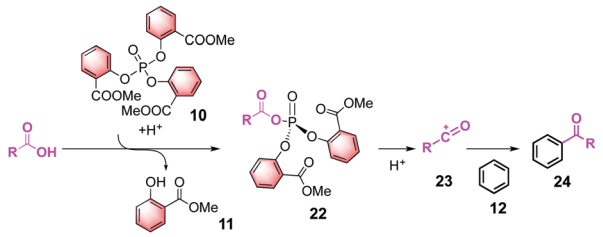


Fig. 2 Possible reaction pathways.

Possible reaction pathways are illustrated in Fig. 2. The presented results suggest that the position of the protonated (or protosolvated) methyl ester is important to enhance the reaction rate of phosphate ester (**10**) and carboxylic acid. Elimination of **11** was probably enhanced by formation of an intramolecular hydrogen bond between phenolic oxygen and protonated methyl ester, so that phosphate ester (**10**) could rapidly release the leaving group (**11**). On the other hand, in the case of phosphate ester (**14**) (Table 1), the intramolecular hydrogen bond could not be formed. Thus the phosphate ester (**14**) could not release the leaving group.

The same reactive intermediate, acyl phosphate (**22**), is formed from **10** with release of methyl salicylate (**11**). The results shown in Fig. 3 support the involvement of the common acyl phosphate (**25**): after complete consumption of phosphate ester (**10**) by mixing carboxylic acid (**13**) in the presence of the acid, benzene (**12**) was added, and benzophenone (**15**) was obtained in 63% yield. Also, the ESI-MS positive peak of acyl phosphate (**25**) was detected in the reaction mixture of triflic acid, phosphate ester (**10**), and carboxylic acid (**13**) (Fig. S3, ESI†).

Moreover, ^{31}P NMR measurements indicated that the phosphate ester (**10**) (−78 ppm) was converted to another species (showing a signal at −5 ppm) (probably **25**) under strongly acidic conditions at low temperature (Fig. S2, ESI†). This newly appearing signal (−5 ppm) was consistent with the signals of previously reported or authentic acyl phosphates (**26**)–(**28**) (Fig. 4).[21] Moreover, DFT calculations[22] indicated that the ^{31}P NMR peak of acyl phosphate (**25**) was −5.80 ppm (calculation level: CPCM-PBEPBE/6-311++G(d,p)//CPCM-M06-2X/6-31+G(d) (solvent: triflic acid), GIAO method), and this value matched with the experimental value (^{31}P = −5.37 ppm) (see the ESI,† Section VII).

Thus, these NMR results indicate that acyl phosphate (**25**) is generated in the acid solution, which is in accordance with both the reaction products and the ESI-MS results (Fig. 3). Therefore, acyl phosphates serve as intermediates in the present reactions.

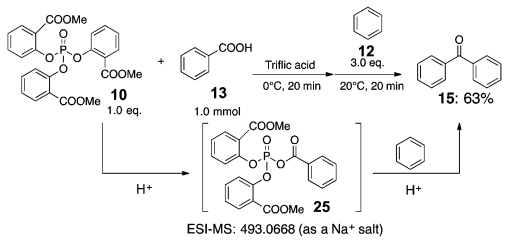


Fig. 3 Evidence supporting the intermediacy of acyl phosphate.

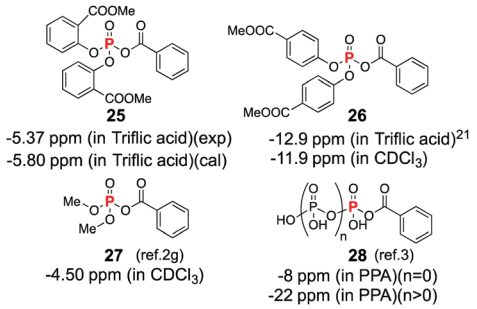


Fig. 4 ^{31}P NMR spectral evidence for the intermediacy of acyl phosphate.

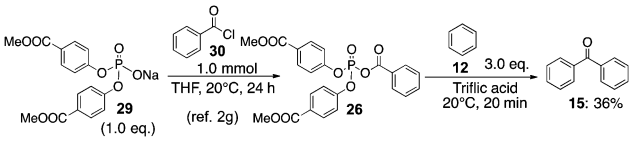


Fig. 5 Acylation reaction of acyl phosphate (**26**).

This acyl phosphate (**25**) can generate the putative acylium ion (**23**) or its equivalent, which reacts with aromatics (**12**) to give aromatic ketones (**15**). A similar acyl phosphate can be generated by a different method without using the acid: when the sodium salt of phosphate diester (**29**) is mixed with benzoyl chloride, acyl phosphate (**26**) is formed,[2g] as judged from ESI-TOF measurements (Fig. 5). This acyl phosphate (**26**) can react with benzene (**12**) in the presence of the acid (triflic acid) to afford benzophenone (**15**) in 36% yield. This result supports the idea that acyl phosphate is a good acylation agent for benzene, probably because O–C bond cleavage of acyl phosphate (**26**) (and plausibly also **25**) is energetically favored over P–O bond cleavage upon protonation under strongly acidic conditions, thus generating the acylium ion or its equivalent.

In summary, we present a chemoselective coupled reaction in which the carbonyl functionality of carboxylic acids is activated by a phosphate ester, followed by reaction of the resulting acyl phosphate with benzenes to afford aromatic ketones. The reaction conditions are compatible with various other functional groups, including amines and esters. The reaction mechanism of the phosphate ester and carboxylic acid appears to involve both unimolecular and bimolecular reaction pathways. A detailed study of the mechanism is in progress.

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