Azodicarboxylate-free esterification with triphenylphosphine mediated by flavin and visible light: method development and stereoselectivity control†

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Triphenylphosphine (Ph₃P) activated by various electrophiles (e.g., alkyl diazocarboxylates) represents an effective mediator of esterification and other nucleophilic substitution reactions. We report herein an azareagent-free procedure using flavin catalyst (3-methyl riboflavin tetraacetate), triphenylphosphine, and visible light (448 nm), which allows effective esterification of aromatic and aliphatic carboxylic acids with alcohols. Mechanistic study confirmed that photoinduced electron transfer from triphenylphosphine to excited flavin with the formation of Ph₃P⁺ is a crucial step in the catalytic cycle. This allows reactive alkoxyphosphonium species to be generated by reaction of an alcohol with Ph₃P⁺ followed by single-electron oxidation. Unexpected stereoselectivity control by the solvent was observed, allowing switching from inversion to retention of configuration during esterification of (S)- or (R)-1-phenylethanol, for example with phenylacetic acid, the ratio shifting from 10 : 90 (retention : inversion) in trichloromethane to 99.9 : 0.1 in acetonitrile. Our method uses nitrobenzene to regenerate the flavin photocatalyst. This new approach to flavin re-oxidation has also been successfully proved in benzyl alcohol oxidation, which is a "standard" process among flavin-mediated photooxidations.

Introduction

Nucleophilic substitution of a hydroxy function mediated by triphenylphosphine (Ph₃P) is among the most powerful tools in organic synthesis.1 Such substitution is allowed as an alcohol molecule is transformed into an alkoxytriphenylphosphonium intermediate, which reacts smoothly with nucleophiles by virtue of the energetically favourable formation of phosphate oxide with a strong P=O bond (540 kJ mol⁻¹). Alcohols do not react with triphenylphosphine directly. For the formation of alkoxyphosphonium species, triphenylphosphine must be activated with an electrophile/oxidant, for example with a tetrahalomethane in the Appel reaction2 or with a dialkyl azodicarboxylate in Mitsunobu esterification1c,3 (see Scheme 1A). Under certain conditions, the carboxylic function can be activated analogously, resulting in the formation of acyloxyporphosphonium species capable of undergoing acyl substitution reaction.3,4 Whether the hydroxy or the carboxy group is activated significantly influences the stereoselectivity of the Mitsunobu esterification. Usually, an alkoxyphosphonium species is employed, which results in inversion of configuration of the chiral alcohol. In some cases, the acyloxyporphosphonium species prevails, which leads to retention of configuration.5,6

One-electron oxidation to Ph₃P⁺ could be a novel straightforward way to activate Ph₃P for substitution reactions. Such an approach would not require a dialkyl azodicarboxylate (or a tetrahalomethane), thus avoiding safety and stability problems and making the triphenylphosphine-mediated procedure more sustainable.4,2a,7

There are several indications that Ph₃P⁺ has the required properties to mediate substitutions of the OH group.

† It should be noted that Mitsunobu reactions catalytic in the dialkyl azodicarboxylate represents an alternative way how to reduce its amount.7
Electrochemically generated \( \text{Ph}_3\text{P}^{+} \) has been shown to react with alcohols to form alkoxypyrophosphonium species.\(^8\) \( \text{Ph}_3\text{P}^{+} \) generated from \( \text{Ph}_3\text{P} \) by photoinduced electron transfer to an excited acridinium salt, dicyanoanthracene, pyrylium salts, or Eosin Y has been proved to form triphenylphosphine oxide by reaction with oxygen or water.\(^9\) Despite these promising observations, to the best of our knowledge neither electrochemically nor photochemically generated \( \text{Ph}_3\text{P}^{+} \) has hitherto been utilized in organic synthesis. The only exception is a “dark” aerobic esterification reaction mediated by an iron phthalocyanine catalyst and 4-methoxy-pyridine \( \text{N} \)-oxide (MPO) as co-catalyst, as reported by Taniguchi (Scheme 1B),\(^10\) in which the carboxylic function is activated by \( \text{Ph}_3\text{P}^{+} \), thus affording an ester with retention of configuration.

Herein, we report the first azodicarboxylate-free esterification procedure based on photocatalytic activation of \( \text{Ph}_3\text{P} \). We use 3-methyl riboflavin tetraacetate (1) as a photoredox catalyst and visible light (Scheme 1c; Fig. 1). It is shown that this esterification allows switching from retention to inversion of configuration of chiral alcohols, depending on the structure and acidity of the acid and alcohol and on the solvent used.

**Results and discussion**

**Catalytic system design**

The design of the photocatalytic system for photoesterification reaction was inspired by our preliminary observations during development of the photocatalytic Mitsunobu reaction.\(^11\) In that case, a dialkyl azodicarboxylate was used in a catalytic amount and regenerated by aerial oxidation mediated by flavin photocatalyst 1 and visible light (448 nm) in the presence of molecular sieves 4A (MS 4A).§ Surprisingly, we also observed remarkable ester formation when a mixture of carboxylic acid, alcohol, triphenylphosphine, and a catalytic amount of flavin 1 was irradiated under oxygen in the absence of a dialkyl azodicarboxylate or its precursor, dialkyl hydrazine-1,2-dicarboxylate. This led us to investigate the azodicarboxylate-free system in more detail (Table 1).

We started with simple model substrates, 3-nitrobenzoic acid and benzyl alcohol, using 2 equivalents of triphenylphosphine and 10 mol% of 1 (entry 1). An interesting result was that almost the same ester conversion was obtained under argon atmosphere as under oxygen, showing that the flavin catalyst must have been regenerated in another way (cf. entries 1 and 2). The aromatic nitro group seemed to be responsible for this process, which was confirmed by the following results: (i) significantly more than 10% of the ester (expected amount when 10 mol% of flavin is used and it is not regenerated) was formed when the nitro group was part of a benzyl alcohol, benzoic acid or externally added in the form of nitrobenzene (entries 2, 3, and 6); (ii) reduction products of nitro compounds were observed in the reaction mixtures: \( N \)-3-carboxyphenyl 3-nitrobenezamide – condensation product of the reduced 3-aminobenzoic acid (entry 2) and \( N \)-[4-(hydroxymethyl)phenyl] benzamide – condensation product of the reduced 4-nitrobenzyl alcohol (entry 3); (iii) less than 10 mol% of ester was formed in the absence of an aromatic nitro group (entries 4 and 5). Thus, nitrobenzene was used as a sacrificial oxidant in the next experiments.

Optimizing the solvent and temperature (see entries 7–11 and the ESI† for details), we found trifluoromethylbenzene (BTF) and elevated temperature (40 °C) to be the best reaction conditions, giving almost quantitative conversion when

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\( \text{Ph}_3\text{P} \) **and** \( \text{Ph}_3\text{P}^{+} \)

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§ Molecular sieves were needed to decompose hydrogen peroxide (a possible substrate for Mitsunobu reaction) formed during aerial flavin re-oxidation and, consequently, to remove water generated by \( \text{H}_2\text{O}_2 \) decomposition.
3-trifluoromethylbenzoic acid was used as a redox-inactive alternative to electron-poor 3-nitrobenzoic acid (cf. entries 1 vs. 13 and 14). Modification of nitrobenzene (stoichiometric oxidant) by substitution had only a small effect on the ester conversion (see the ESI†). Blank experiments (performed with all substrates in Table 1) showed that esterification did not proceed in the absence of either 1, Ph3P, or light. In the absence of molecular sieves (MS), ester 2 was formed with only 10% conversion (entry 12), probably because of the negative effect of water formed during flavin re-oxidation with nitrobenzene.

### Substrate scope and stereoselectivity

Having established the optimized conditions, the scope of the reaction with respect to the structures of the alcohol and acid was investigated through preparative experiments (Table 2).

We found that benzyl alcohols react with 3-trifluoromethylbenzoic acid to provide esters 3–9 in moderate to good yields regardless of the nature and position of the substituent. Aliphatic alcohols react smoothly under our conditions (see entries for esters 10 and 11). Besides aromatic acids (see entries for esters 2, 12, and 13), aliphatic acids were also proved to react with 4-chlorobenzyl alcohol (see entries for esters 14–16). The formation of ester 16 is especially noteworthy as it was achieved with significantly higher conversion (62%) compared to the previously described11 aerial photocatalytic Mitsunobu reaction (16%).

Special attention was paid to the stereoselectivity of the new esterification with chiral secondary alcohols, (R)- and (S)-1-phenylethanol-1-ol and (R)- and (S)-ethyl lactate (Table 3, method A, first column). Interestingly, the stereoselective course varied significantly depending on the acidity and steric hindrance of the acid, shifting from dominant retention for ester 21 (90 : 10, entry 5) to highly selective inversion for 17 (0.1 : 99.1, entry 1). It was found that higher acidity of the carboxylic acid favoured production of the ester with retention of configuration (cf. entries 2–4), whereas sterically demanding acids favoured inversion of configuration (entry 1). These results can be explained in terms of two mechanistic pathways involving either alkoxyphosphonium or acyloxyphosphonium intermediates, which have been proved to be in equilibrium by several studies.16,4,5,6 Most probably, for more acidic acids, acyloxyphosphonium prevails, thus favouring acyl substitution, which results in the product with retention of configuration (see entries 2–4). Formation of the acyloxyphosphonium species and thus higher selectivity for retention of configuration seems to be supported when the nucleophilicity of the hydroxy function is decreased by the electron-withdrawing ethoxycarbonyl group (entry 5). With less acidic and/or sterically hindered acids, the alkoxyphosphonium species is preferred, which results in inversion of configuration with very good to excellent stereoselectivities (entries 1 and 2). The esterification of non-chiral benzyl alcohol and benzoic acid was inspected by an experiment with 18O-labelled acid, which showed the ester to be formed by acyl vs. alcohol activation in a ratio varying from 25 : 75 in BTF to 66 : 34 in acetonitrile (see the ESI†).

The stereic effect of the alcohol and/or acid structure on the stereoselectivity of Mitsunobu esterification has previously been observed in a few studies.16,5,6 Nevertheless, the results obtained by this new azocarboxylate-free photoesterification (Table 3, method A) are surprising compared to those from flavin-based photocatalytic esterification under Mitsunobu

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**Table 1** Preliminary results and selected optimization studies for photocatalytic esterification†

| Entry | R<sup>1</sup> | R<sup>2</sup> | Atmosphere (temperature) | Additive | Solvent | Conversion [%] |
|-------|--------------|--------------|--------------------------|----------|---------|--------------|
| 1     | NO<sub>2</sub> | Cl           | O<sub>2</sub> (25 °C)    | —        | CH<sub>3</sub>CN | 90†         |
| 2     | NO<sub>2</sub> | Cl           | Ar (25 °C)               | —        | CH<sub>3</sub>CN | 80†         |
| 3     | H            | NO<sub>2</sub> | Ar (25 °C)               | —        | CH<sub>3</sub>CN | 33†         |
| 4     | H            | Cl           | Ar (25 °C)               | —        | CH<sub>3</sub>CN | 5           |
| 5     | H            | H            | Ar (25 °C)               | —        | CH<sub>3</sub>CN | 3           |
| 6     | H            | H            | Ar (25 °C)               | PhNO<sub>2</sub> | CH<sub>3</sub>CN | 32          |
| 7     | H            | H            | Ar (25 °C)               | PhNO<sub>2</sub> | CH<sub>3</sub>C<sub>2</sub> | 32        |
| 8     | H            | H            | Ar (25 °C)               | PhNO<sub>2</sub> | Toluene  | 38          |
| 9     | H            | H            | Ar (25 °C)               | PhNO<sub>2</sub> | THF     | 15          |
| 10    | H            | H            | Ar (25 °C)               | PhNO<sub>2</sub> | BTF     | 47          |
| 11    | H            | H            | Ar (40 °C)               | PhNO<sub>2</sub> | BTF     | 66          |
| 12    | CF<sub>3</sub>| H            | Ar (40 °C)               | PhNO<sub>2</sub> | BTF     | 10          |
| 13    | CF<sub>3</sub>| Cl           | Ar (40 °C)               | PhNO<sub>2</sub> | BTF     | 84          |
| 14    | CF<sub>3</sub>| Cl           | Ar (40 °C)               | PhNO<sub>2</sub> | BTF     | 95          |

*Conditions: n(alcohol) = 0.15 mmol, n(acid) = 0.18 mmol, n(1) = 0.015 mmol, n(PhNO<sub>2</sub>) = 0.15 mmol, n(Ph<sub>3</sub>P) = 0.3 mmol, MS 4 Å (150 mg), 2 mL solvent, 448 nm, 24 h; conversion was determined by <sup>1</sup>H NMR. † In the absence of MS. †† 4-Chlorobenzyl 3-nitrobenzoate was observed as a sole product. †‡ Beside 4-chlorobenzyl 3-nitrobenzoate (main product) formation of N-(3-carboxyphenyl) 3-nitrobenzamide was also observed. †§ Beside 4-nitrobenzyl benzoate (main product) formation of N-[4-(hydroxymethyl)phenyl] benzamide was observed.
Table 2  Substrate scope for photocatalytic esterification mediated by 1 and Ph$_3$P$^a$

| A/ Alcohol scope | B/ Acid scope |
|------------------|---------------|
| ![Substrate A](image) | ![Substrate B](image) |
| ![Substrate C](image) | ![Substrate D](image) |
| ![Substrate E](image) | ![Substrate F](image) |
| ![Substrate G](image) | ![Substrate H](image) |
| ![Substrate I](image) | ![Substrate J](image) |
| ![Substrate K](image) | ![Substrate L](image) |
| ![Substrate M](image) | ![Substrate N](image) |
| ![Substrate O](image) | ![Substrate P](image) |
| ![Substrate Q](image) | ![Substrate R](image) |
| ![Substrate S](image) | ![Substrate T](image) |
| ![Substrate U](image) | ![Substrate V](image) |

$^a$ Conditions: $n$(alcohol) = 0.15 mmol, $n$(acid) = 0.18 mmol, $n$(1) = 0.015 mmol, $n$(PhNO$_2$) = 0.15 mmol, $n$(Ph$_3$P) = 0.3 mmol, MS 4 Å (150 mg), 2 ml BTF, 40 °C, 448 nm, 24 h; conversion was determined by $^1$H NMR. $^b$ Aldehyde conv. 51%.

Table 3  Stereoselectivity of ester formation with chiral non-racemic alcohols

| Entry | Product  | Method A$^a$ (from this work) | Method B$^b$ (according to ref. 11) | Method C$^c$ (non-catalytic M.R.) |
|-------|----------|------------------------------|-----------------------------------|----------------------------------|
|       |          | Yield$^d$ [%] | er$^e$ | Yield$^d$ [%] | er$^e$ | Yield$^d$ [%] | er$^e$ |
| 1     | ![](image) | 33 | 0.1 : 99.9 | 0 | — | 38 | 10 : 90 |
| 2     | ![](image) | 19 | 10 : 90 | 23 | 99.9 : 0.1 | 1 | 10 : 90 |
| 3     | ![](image) | 52 | 40 : 60 | 28 | 99.9 : 0.1 | 65 | 13 : 87 |
| 4     | ![](image) | 42 | 68 : 32 | 50 | 99 : 1 | 63 | 9 : 91 |
| 5     | ![](image) | 24 | 90 : 10 | 19 | 99.1 : 0.1 | 43 | 0.1 : 99.9 |

$^a$ For conditions, see Table 2. $^b$ $n$(alcohol) = 0.15 mmol, $n$(acid) = 0.18 mmol, $n$(1) = 0.015 mmol, $n$(DIAD$_2$) = 0.015 mmol, $n$(Ph$_3$P) = 0.3 mmol, MS 4 Å (150 mg), 2 mL CH$_3$CN, 50 °C, 448 nm, 72 h. $^c$ Condition of non-catalytic reaction: $n$(alcohol) = 0.15 mmol, $n$(acid) = 0.18 mmol, $n$(DIAD) = 0.2 mmol, $n$(Ph$_3$P) = 0.3 mmol, 2 mL CH$_3$CN, 25 °C, 24 h. $^d$ Preparative yields. $^e$ Retention: inversion from HPLC, average value from experiments with (S)- and (R)- alcohol, see ESI.
conditions with a catalytic amount of dialkyl azodicarboxylate (method B) and those from “dark” stoichiometric Mitsunobu reaction (method C), which clearly showed either retention or inversion of configuration, respectively, with all investigated substrates. The question then arose as to the origin of this difference. Although solvent has never been observed as the dominant factor in determining the stereochemistry of Mitsunobu esterification, we firstly examined whether substitution of acetonitrile (used in method B) by BTF (used in method A) could play a role in defining the stereochemistry. Results with trifluorobenzoic acid and (S)-1-phenylethan-1-ol generating ester 19 (Table 4, first column) confirmed this premise, showing the stereosechemistry of the new esterification (method A) to significantly vary with the solvent. In polar solvents such as acetonitrile or acetone, the reaction predominantly proceeded with retention of configuration, whereas in non-polar solvents, inversion of configuration prevailed. An even more significant effect of the solvent was observed with phenylacetic acid in forming ester 18, for which the stereoselectivity shifted from 99.9 : 0.1 in acetonitrile to 10 : 90 in BTF. On the contrary, the stereoselectivity of the “dark” Mitsunobu reaction leading to ester 19 was found to be unaffected by solvent (er 13 : 87 and 7 : 93 in acetonitrile and BTF, respectively) and thus our photocatalytic process remains unique in this respect.

Mechanistic investigation

The key step of the photoesterification is oxidation of Ph₃P to Ph₃P⁺⁺ by single-electron transfer to the excited flavin 1 (Fl*; see Scheme 2 for the proposed mechanism). Flavin 1 in the singlet excited state (1Fl*) is strong enough (Eₑ⁺ (S) = 1.76 V vs. SCE) to induce the oxidation of Ph₃P (Eₒ = 1.0 V vs. SCE, ref. 9c). This process was confirmed by the observation of efficient quenching of the steady-state fluorescence emission of 1 upon addition of Ph₃P. The value of the quenching constant (kₒ = 6 × 10⁹ M⁻¹ s⁻¹) was obtained both from fluorescence intensity as well as lifetime measurements in the presence of various amounts of Ph₃P (for the Stern–Volmer plots, see ESI†).

The driving force for photoinduced electron transfer from Ph₃P to the flavin triplet state (3Fl*) estimated from corresponding redox potentials (ΔGₑ = Eₒ(Ph₃P) − Eₑ⁺(Fl) = 1.00 − 1.25 = −0.25 eV) shows that it is also an exergonic process and, indeed, laser-flash photolysis experiments gave direct evidence that flavin in its triplet excited state participates in electron transfer. Although the excited triplet state of flavin exists in dry acetonitrile for tens of microseconds, with an estimated lifetime of 68 µs (Fig. 2A), this is significantly shortened by the addition of Ph₃P (Fig. 2B). The quenching rate of the triplet excited state of flavin by Ph₃P was estimated to be 4.1 × 10⁹ m⁻¹ s⁻¹ from a Stern–Volmer plot (Fig. 2C). The reaction pathway of photoinduced ET from Ph₃P to 3Fl* can be expected to predominate under conditions of esterification because of the much longer intrinsic lifetime of 3Fl* (68 µs) compared to that of 3Fl* (5.7 ns). For instance, at the Ph₃P concentration of 10⁻² M, over 99% of 3Fl* undergoes quenching, while only approximately 20% in the case of 1Fl*. Electron transfer from Ph₃P to flavin 1 in an excited state leads to flavin radical anion Fl⁻, formation of which was detected by transient spectra (see ESI†). Unfortunately, Ph₃P⁺⁺ was not clearly observed in our transient spectroscopy experiments, most probably because of its very low molar absorption coefficient (see ref. 9c) and overlap with the signals of flavin anion species (see ESI†).

Additionally, we observed Ph₃P to react with water under argon atmosphere or with oxygen under air in dry solvent to form triphenylphosphine oxide in acetonitrile or BTF in the presence of 10 mol% of flavin 1 when the solution was irradiated (see Scheme 3). Under argon atmosphere in the absence of water (in dry solvent) or in the dark, oxidation reaction was not observed. These results provide further evidence that excited flavin is able to generate Ph₃P⁺⁺, which can then react with an oxygen source or a nucleophile. It should be noted that the formation of triphenylphosphine oxide from Ph₃P has been proved several times to occur through Ph₃P⁺⁺, which is believed to react smoothly with water or oxygen.⁹

| Table 4 | Effect of solvent on the stereoselectivity of ester formation using method A* |
| Solvent | Yield⁻ (%) | cr⁻ | Yield⁺ (%) | cr⁺ |
| CH, CN | 35 | 93 : 7 | 40 | 99.9 : 0.1 |
| Acetone | 20 | 90 : 10 | — | — |
| THF | 18 | 55 : 45 | — | — |
| PhCl | 36 | 38 : 62 | — | — |
| Toluene | 33 | 40 : 60 | — | — |
| BTF | 53 | 40 : 60 | 19 | 10 : 90 |

* For conditions, see Table 2.
⁻ Retention : inversion from HPLC, see ESI.
It is reasonable to assume that flavin radical anion F$^-$
($pK_a$ of conjugated acid is 8.4, ref. 14) will be immediately pro-
tonated by a carboxylic acid to form radical FH$^-$ (Scheme 2). Subsequently, Ph$_3$P$^+$ can react with an alcohol (analogously to the abovementioned reaction with water) or carboxylate to form a phosphoranyl radical Ph$_3$P-X, which is likely to be rapidly oxidized to corresponding alkoxy- or acyloxyphosphonium species. The redox potential of the Ph$_3$P$^-$/Ph$_3$P-X redox couple can be estimated based on reduction half-wave potentials of related compounds, tetraphenylphosphonium ($E^° = -2.16$ V vs. SCE) or methyltriphenylphosphonium ($E^° = -2.22$ V vs. SCE). Several agents in the reaction mixture are sufficiently oxidizing to induce this oxidation, e.g. nitro-
benzene ($E(\text{PhNO}_2/\text{PhNO}_2^-) = -1.22$ V vs. SCE, ref. 16) or flavin 1, even in its ground state ($E(1/1^-) = -0.82$ V vs. SCE).

In a separate experiment, we confirmed that an alkoxyphos-
phonium species is formed from Ph$_3$P in the presence of an alcohol and flavin, as evidenced by the $^{31}$P NMR spectrum of the mixture following irradiation with visible light. Only a low concentration of alkoxyphosphonium species was observed under conditions of photoesterification, showing that this reactive species reacts smoothly with a nucleophile. In an excess of alcohol (experiment performed in methanol), a signif-
ificant amount of alkoxyphosphonium salt was detected together with methyltriphenylphosphonium, the product of alkylation of Ph$_3$P with methoxytriphenylphosphonium (see Fig. 3).

A final question remained unanswered about functioning of nitrobenzene in the photocatalytic esterification. In studying the reaction of 3-trifluoromethylbenzoic acid with benzyl alcohol in the absence of nitrobenzene using various amounts of flavins (0–20 mol% with respect to the substrate), we observed ester formation in slightly lower amounts (possibly as a result of flavin bleaching) than might have been expected by taking into account the amount of flavin that was not regen-

Fig. 2 Transient absorption spectra of 1 ($c = 5.8 \times 10^{-5}$ mol L$^{-1}$) in the absence (A) and in the presence (B) of Ph$_3$P ($c = 7 \times 10^{-4}$ mol L$^{-1}$) in various times after laser pulse excitation ($\lambda = 355$ nm, 1 mJ) and reciprocal of the triplet excited state lifetime in function of Ph$_3$P concentration (C). Dry acetonitrile has been used as a solvent.

Scheme 3 Flavin-mediated photocatalytic oxidations of triphenyl-
phosphine in the presence of oxygen or water.
erated; e.g. 5% or 7% ester employing 10% and 20% of 1, respectively (see the ES†). Thus, nitrobenzene seems to be crucial for flavin re-oxidation, allowing 84% of the ester to be formed under the same conditions. On the other hand, the fact that some ester is also formed in the absence of nitrobenzene shows that its side-role, if indeed there is one, is rather minor; e.g. nitrobenzene could participate in the oxidation of Ph₃P-X to Ph₃P-X.

In looking for products of nitrobenzene reduction during esterification under common conditions, we invariably detected only a small amount of the amide of the corresponding acid (1–5% with respect to the amount expected) and unreacted nitrobenzene (up to 15%) as the only compounds containing nitrogen. Interestingly, a significant amount (48%) of amide was found in the reaction mixture when an excess (2 equiv.) of carboxylic acid was added. Most probably, aniline formed as a final product of nitrobenzene reduction was trapped by acyloxyphosphonium to form an amide. If there is unreacted nitrobenzene (up to 15%) as the only compounds we always observed nitrobenzene (up to 15%) remaining in the reaction mixture after photoesterification. Moreover, nitrobenzene and nitrosobenzene are reported to be deoxygenated with Ph₃P with the formation of Ph₃P=O. This undesired process also occurs under our conditions, as evidenced by a blank experiment conducted in the absence of alcohol and carboxylic acid (see the ES†). Deoxygenation of nitrobenzene and nitrosobenzene explains why an excess of nitrobenzene is necessary in our photocatalytic system and also the fact that 48% of aniline (see above) was captured in the form of amide in esterification with an excess of carboxylic acid which is remarkably more than expected amount 33% (relative to amount ester formed). Theoretically, only one-third of an equivalent of nitrobenzene could be enough, considering that all reduction intermediates, nitrobenzene (E(PhNO/PhNO") = -1.07 V vs. SCE, ref. 16), azoxybenzene (E(PhN==N(O)Ph/PhN==N(O)Ph") = -1.44 V vs. SCE, ref. 16), and azobenzene (E(PhN==NPh/PhN==NPh") = -1.42 V vs. SCE, ref. 16), could participate in flavin re-oxidation, based on their reduction potentials. Indeed, the high conversion to ester of 3 corroborated flavin catalyst recycling by these agents (Scheme 5). It should be noted that by using 1 equivalent of nitrobenzene relative to alcohol (triple excess relative to theoretical amount) we always observed nitrobenzene (up to 15%) remaining in the reaction mixture after photoesterification. However any attempt to reduce nitrobenzene loading led to lower ester yields (see the ES†).

The use of a nitro compound as a sacrificial oxidizing agent in flavin catalysis is still unknown in artificial systems. To gain insight into this process, we investigated it in flavin-mediated 4-methoxybenzyl alcohol oxidation, which is a “standard” oxidation process studied by many authors. Whereas in the absence of a sacrificial oxidant, a small amount of aldehyde was formed in an irradiated mixture containing a catalytic amount of flavin 1 (Table 5, entry 1), nitrobenzene substantially increased the amount of aldehyde formed (entries 2 and 3). With an excess of nitrobenzene, quantitative chemoselective formation of aldehyde (no overoxidation) was observed (entry 4). In this case, approximately 20% of benzaldehyde was transformed to an imine by aniline formed from nitrobenzene. Importantly, similar results were obtained when nitrosobenzene, azoxide, and azobenzene (entries 5–7) were used instead, thus confirming their possible participation in the flavin regeneration process.

Finally, to gain direct evidence concerning flavin re-oxidation with nitrobenzene, we generated the reduced flavin 1 by catalytic hydrogenation (see the ES†). After filtering off palladium and addition of 1 equivalent of nitrobenzene (all oper-

Scheme 4 Competitive reaction of benzoic acid with benzyl alcohol and aniline (A) and controlled amide formation by flavin-Ph₃P-mediated photocatalytic process (B).

Scheme 5 Photocatalytic esterification using various oxidizing agents.
Conclusions

We have proved that the triphenylphosphine radical cation Ph3P+, generated by photoinduced electron transfer to flavin 1, can be utilized for the activation of alcohols or acids to promote ester formation by nucleophilic substitution reaction (both S_N or S_NAc). It should be noted that photooxidation to phosphine oxides has hitherto been the sole reported photo-redox procedure with triphenylphosphine. Thus, our finding could provide impetus for the design of other methods utilizing photoactivated phosphine in various organic transformations. It could be expected that not only flavins, but also other dyes, might be suitable for this purpose. In the present case, application of this new approach has led to the development of an effective esterification method based on flavin photocatalyst, triphenylphosphine, and visible light, which has proved applicable to a broad range of substrates, including less reactive aliphatic acids and alcohols. Regarding stereo-selectivity, we observed an unusual switch from preferential inversion to retention of configuration in the esterification of chiral alcohols which was caused merely by changing the solvent. Previously, such a change has been mainly associated with a change of alcohol or acid structure. It should be noted that also such a preferential inversion of configuration inaza-reagent-free esterification is unique. The presented method uses nitrobenzene as a novel sacrificial oxidant to regenerate the flavin catalyst. It could also be helpful in other flavin-based oxidative procedures, especially with substrates sensitive to oxygen, which has hitherto been the sole stoichiometric oxidant used in flavin photocatalysis. This would seem to be of great value, in view of the recent growing interest in flavin photocatalysis.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

1 (a) K. C. K. Swamy, N. N. B. Kumar, E. Balaraman and K. V. P. Kumar, Chem. Rev., 2009, 109, 2551–2651; (b) L. F. Pedrosa, Synlett, 2008, 1581–1582; (c) J. An, R. M. Denton, T. H. Lambert and E. D. Nacsa, Org. Biomol. Chem., 2014, 12, 2993–3003.
2 (a) H. A. Van Kalkeren, F. L. Van Delft and F. P. J. T. Rutjes, Pure Appl. Chem., 2013, 85, 817–828; (b) R. Appel, Angew. Chem., Int. Ed. Engl., 1975, 14, 801–811.
3 (a) S. Fletcher, Org. Chem. Front., 2015, 2, 739–752; (b) A. J. Reynolds and M. Kassiou, Curr. Org. Chem., 2009, 13, 1610–1632; (c) T. Y. S. But and P. H. Toy, Chem. – Asian
J., 2007, 2, 1340–1355; (d) M. Oyo and Y. Masaaki, Bull. Chem. Soc. Jpn., 1967, 40, 2380–2382.

4 S. Schenk, J. Weston and E. Anders, J. Am. Chem. Soc., 2005, 127, 12566–12576.

5 (a) G. Wang, J.-R. Ella-Menye, M. St. Martin, H. Yang and K. Williams, Org. Lett., 2008, 10, 4203–4206; (b) A. B. Hughes and M. M. Sleeb, J. Org. Chem., 2005, 70, 3079–3088; (c) J. McNultey, A. Capretta, V. Laritchev, J. Dyck and A. J. Robertson, Angew. Chem., Int. Ed., 2003, 42, 4051–4054; (d) A. B. Smith, I. G. Safonov and R. M. Corbett, J. Am. Chem. Soc., 2002, 124, 11102–11113; (e) C. Ahn and P. DeShong, J. Org. Chem., 2002, 67, 1754–1759.

6 (a) J. Dyck, S. Zavorine, A. J. Robertson, A. Capretta, V. Laritchev, J. Britten and J. McNultey, J. Organomet. Chem., 2005, 690, 2548–2552; (b) J. McNultey, A. Capretta, V. Laritchev, J. Dyck and A. J. Robertson, J. Org. Chem., 2003, 68, 1597–1600.

7 (a) D. Hirose, M. Gazvoda, J. Košmrlj and T. Taniguchi, Chem. Sci., 2016, 7, 5148–5159; (b) D. Hirose, T. Taniguchi and H. Ishibashi, Angew. Chem., Int. Ed., 2013, 52, 4613–4617; (c) T. Y. S. But and P. H. Toy, J. Am. Chem. Soc., 2006, 128, 9636–9637.

8 (a) H. Maeda, T. Koide, T. Maki and H. Ohmori, Chem. Pharm. Bull., 1995, 43, 1076–1080; (b) H. Ohmori, H. Maeda, M. Kikuoka, T. Maki and M. Masui, Tetrahedron, 1991, 47, 767–776; (c) H. Ohmori, S. Nakai, M. Sekiguchi and M. Masui, Chem. Pharm. Bull., 1980, 28, 910–915.

9 (a) S. Yasui and M. Tsujimoto, J. Phys. Org. Chem., 2013, 26, 1090–1097; (b) O. Kei, N. Takashi and F. Shunichi, Bull. Chem. Soc. Jpn., 2006, 79, 1489–1500; (c) M. Nakamura, M. Miki and T. Majima, J. Chem. Soc., Perkin Trans. 2, 2000, 1447–1452; (d) S. Yasui, K. Shioji, A. Ohno and M. Yoshihara, J. Org. Chem., 1995, 60, 2099–2105; (e) Y. B. Zhang, C. Ye, S. J. Li, A. S. Ding, G. X. Gu and H. Guo, RSC Adv., 2017, 7, 13240–13243; (f) S. M. Bonesi, S. Protti and A. Albini, J. Org. Chem., 2016, 81, 11678–11685; (g) S. Yasui, S. Tojo and T. Majima, Org. Biomol. Chem., 2006, 4, 2969–2973.

10 T. Taniguchi, D. Hirose and H. Ishibashi, ACS Catal., 2011, 1, 1469–1474.

11 M. März, J. Chudoba, M. Kohout and R. Cibulka, Org. Biomol. Chem., 2017, 15, 1970–1975.

12 (a) Y. Arakawa, K. Yamanomoto, H. Kita, K. Minagawa, M. Tanaka, N. Haraguchi, S. Itsuno and Y. Imada, Chem. Sci., 2017, 8, 5468–5475; (b) H. Iida, Y. Imada and S. I. Murahashi, Org. Biomol. Chem., 2015, 13, 7599–7613; (c) R. Cibulka, Eur. J. Org. Chem., 2015, 915–932; (d) T. Ishikawa, M. Kimura, T. Kumoi and H. Iida, ACS Catal., 2017, 7, 4986–4989.

13 (a) G. Tang, Z. Gong, W. Han and X. Sun, Tetrahedron Lett., 2018, 59, 658–662; (b) V. Mojr, G. Pitrová, K. Straková, D. Pruška, S. Brazevic, E. Svobodová, I. Horskovcová, G. Burdišinský, T. Slanina, M. Sikorski and R. Cibulka, ChemCatChem, 2018, 10, 849–858; (c) B. Mühlendorf and R. Wolf, ChemCatChem, 2017, 9, 920–923; (d) J. B. Metternich, D. G. Artiukhin, M. C. Holland, M. von Bremen-Kühne, J. Neugebauer and R. Gilmour, J. Org. Chem., 2017, 82, 9953–9977; (e) R. Martinez-Haya, M. A. Miranda and M. L. Marin, Eur. J. Org. Chem., 2017, 2164–2169; (f) M. Jirásek, K. Straková, T. Neveselý, E. Svobodová, Z. Rottnerová and R. Cibulka, Eur. J. Org. Chem., 2017, 2139–2146; (g) T. Neveselý, E. Svobodová, J. Chudoba, M. Sikorski and R. Cibulka, Adv. Synth. Catal., 2016, 358, 1654–1663; (h) B. Mühlendorf and R. Wolf, Angew. Chem., Int. Ed., 2016, 55, 427–430; (i) J. B. Metternich and R. Gilmour, J. Am. Chem. Soc., 2016, 138, 1040–1045; (j) T. Morack, J. B. Metternich and R. Gilmour, Org. Lett., 2018, 20, 1316–1319; (k) M. Insińska-Rak, E. Sikorska, J. L. Bourdelande, I. V. Khmelinskii, W. Pruška, K. Dobek, J. Karolczak, I. F. Machado, L. F. V. Ferreira, E. Dulewicz, A. Komasa, D. R. Worrall, M. Kubicki and M. Sikorski, J. Photochem. Photobiol., A, 2007, 186, 14–23.

14 A. Ehrenberg, F. Müller and P. Hemmerich, Eur. J. Biochem., 1967, 2, 286–293.

15 L. Horner, F. Röttger and H. Fuchs, Chem. Ber., 1963, 96, 3141–3147.

16 H. Youjin and L. Jean, Electroanalysis, 2016, 28, 2716–2727.

17 W. F. Marqués, R. Roque-Malherbe, J. Ducongé and W. del Valle, Surf. Interface Anal., 2004, 36, 1060–1063.

18 (a) V. S. Khursan, V. A. Shamukaev, E. M. Chainikova, S. L. Khursan and R. L. Sfaullin, Russ. Chem. Bull., 2013, 62, 2477–2486; (b) J. I. G. Cadogan, Q. Rev., Chem. Soc., 1968, 22, 222–251.

19 Flavin-based nitro group reductions are known from biological systems, see: K. Durchschein, M. Hall and K. Faber, Green Chem., 2013, 15, 1764–1772.

20 (a) B. Mühlendorf and R. Wolf, Chem. Commun., 2015, 51, 8425–8428; (b) C. Feldmeier, H. Bartling, K. Mayerl and R. M. Gschwind, Angew. Chem., Int. Ed., 2015, 54, 1347–1351; (c) U. Megerle, M. Wenninger, R.-J. Kutta, R. Lechner, B. König, B. Dick and E. Riedle, Phys. Chem. Chem. Phys., 2011, 13, 8869–8880; (d) S. Fukuzumi, K. Yasui, T. Suenobu, K. Okhubo, M. Fujitsuka and O. Ito, J. Phys. Chem. A, 2001, 105, 10501–10510.

21 I. K. Sideri, E. Voutyritsa and C. G. Kokotos, Org. Biomol. Chem., 2018, 16, 4596–4614.