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Redox-neutral organocatalytic Mitsunobu reactions

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Nucleophilic substitution reactions of alcohols are among the most fundamental and strategically important transformations in organic chemistry. For over half a century, these reactions have been achieved by using stoichiometric, and often hazardous, reagents to activate the otherwise unreactive alcohols. Here, we demonstrate that a specially designed phosphine oxide promotes nucleophilic substitution reactions of primary and secondary alcohols in a redox-neutral catalysis manifold that produces water as the sole by-product. The scope of the catalytic coupling process encompasses a range of acidic pronucleophiles that allow stereospecific construction of carbon-oxygen and carbon-nitrogen bonds.

Alcohols are important feedstocks (*1*–*5*) for chemical synthesis because they are abundant and inexpensive and can be converted into a wide range of additional functional groups by using, among others, nucleophilic substitution reactions (*6*). The ideal (hypothetical) nucleophilic substitution would involve direct stereospecific displacement of the hydroxyl group with concomitant elimination of water (Fig. 1A) (*7*). In practice, kinetic and thermodynamic barriers prevent direct substitution, and therefore, additional chemical activating agents must be used. However, conventional methods, such as the Mitsunobu protocol (Fig. 1B) (*8*, *9*), involve hazardous stoichiometric reagents that are incongruous with the principle of atom economy (*10*). Nevertheless, this method is used very frequently and remains the state of the art in terms of stereospecific nucleophilic substitution (*11*). Therefore, it is clear that alternative catalytic substitution reactions would have a major impact on chemical synthesis and eventually replace the inherently inefficient current methods (*12*). To date, a variety of strategies have been devised to enable catalytic coupling of π-activated alcohols and nucleophiles, which include Brønsted or Lewis acid catalysis (*13*) and transition metal–catalyzed substitution (*14*). In many cases, these reactions occur through stabilized carbocation intermediates and, necessarily, generate racemic products. However, there are notable examples in which excellent stereoselectivity has been achieved (*15*). A conceptually different approach to catalytic nucleophilic substitution termed "borrowing hydrogen" (*16*–*18*) involves oxidation of the alcohol, condensation with a nucleophile, and then reduction to achieve the product of a direct substitution reaction. Despite these advances, the development of catalytic methods that enable stereospecific bimolecular substitution of nonactivated chiral alcohols remains a major challenge (*19*, *20*). Although some progress has been made by using cyclopropenone catalysis (*21*), most effort to date has been focused on modifying the original Mitsunobu protocol by redox recycling of the stoichiometric reagents. Although this approach is intuitive, implementation is challenging because recycling the phosphine reagent requires a stoichiometric reductant and recycling the azo oxidant requires a mutually compatible stoichiometric oxidant (Fig. 1C).

An early reaction of this type was reported in 2006 and involved the use of substoichiometric [10 mole % (mol %)] azodicarboxylate, which was recycled by using di(acetoxy)iodobenzene as a stoichiometric oxidant, in combination with two equivalents of triphenylphosphine (Fig. 1C) (*22*). Further work reported by Taniguchi, Košmrlj, and co-workers in 2013 and in 2016 resulted in a more efficient recycling protocol using a modified arylazocarboxylate that was elegantly regenerated through aerobic oxidation with an iron phthalocyanine cocatalyst by using molecular oxygen as the terminal oxidant (Fig. 1C) (*23*, *24*). These processes were successful in rendering the Mitsunobu reaction catalytic with respect to the oxidant, but stoichiometric phosphine was still required. Protocols catalytic in phosphine or both species suffered from limited output (*25*, *26*). Although these catalytic variants are valuable, any catalytic Mitsunobu reaction based on redox recycling will always require a stoichiometric oxidant and reductant, which places a ceiling on the level of atom economy that can be achieved (*27*).

Conscious of these limitations, we questioned whether an alternative catalysis manifold could be developed in which the oxidation state of phosphorus was invariant (*28*, *29*). Such a manifold would require the unconventional step of generating a Mitsunobu-active phosphorus species from phosphorus(V) in a catalytic sense. We therefore designed a cycle based on phosphine oxide catalyst **1** (Fig. 1D), which we reasoned would be activated by the acidic pronucleophile and undergo cyclization and dehydration to afford oxyphosphonium salt **2**. Although this transformation, which involves cleavage of the strong phosphorus-oxygen formal double bond, appears very challenging, we were aware that phosphine oxides containing two hydroxyaryl groups had been observed to undergo thermal dehydration at 200°C to afford isolable pentavalent phosphoranes (*30*). As in the classical Mitsunobu reaction, the counteranion associated with phosphonium salt **2** may engage in nonproductive, reversible bonding and exchange at phosphorus (*11*), but ultimately, ring-opening by the alcohol would afford the conventional intermediate, the alkoxyphosphonium-nucleophile ion pair **3**. Subsequent nucleophilic substitution between the alkoxyphosphonium salt and associated counter anion should then afford the substitution product and regenerate phosphine oxide **1**, closing the catalytic cycle. This approach was particularly attractive because there is no redox change and water is generated as the sole by-product. Furthermore, if this catalytic dehydration system could be validated, it would expand the field of phosphorus-based organocatalysis (*31*–*37*) and allow further reaction development. Herein, we demonstrate phosphine oxide **1** functions as an efficient catalyst for Mitsunobu inversion in the designed manifold.

We began our investigation by examining the role of the acidic pronucleophile, which in our proposed cycle (Fig. 1D), participates in the initial dehydration step. Experiments were performed with catalyst **1** (a bench-stable solid, prepared on a multigram scale in two steps without chromatography; see materials and methods) and (+)-2-octanol [>99% enantiomeric excess (e.e.)] as a representative nonactivated alcohol. Azeotropic removal of water from either toluene or xylenes by using a Dean-Stark trap is critical to the cycle because the phosphonium salt intermediates are kinetically and thermodynamically unstable with respect to hydrolysis, which returns the phosphine oxide. Pronucleophiles with low Brønsted acidity [for example, benzoic acid, $pK_a(H_2O) = 4.2$] did not promote measurable catalysis, but as acidity increases [for example, 4-nitrobenzoic acid, $pK_a(H_2O) = 3.4$], the catalysis manifold becomes active. Presumably, dehydration requires sufficient protic activation of the strong phosphorus-oxygen bond. However, with increasing acidity, elimination reactions and acid-promoted coupling, which occurs with retention of configuration, also become increasingly competitive. This leads to a second acidity boundary, and optimization identified dinitrobenzoic acid [$pK_a(H_2O) = 1.4$] as an efficient coupling partner for inversion (tables S1 and S2). The inverted ester product was formed in a yield of 84% and an e.e. of 98%.

Having optimized the conditions, we then explored the scope of the catalytic Mitsunobu coupling reaction. Stoichiometric esterification

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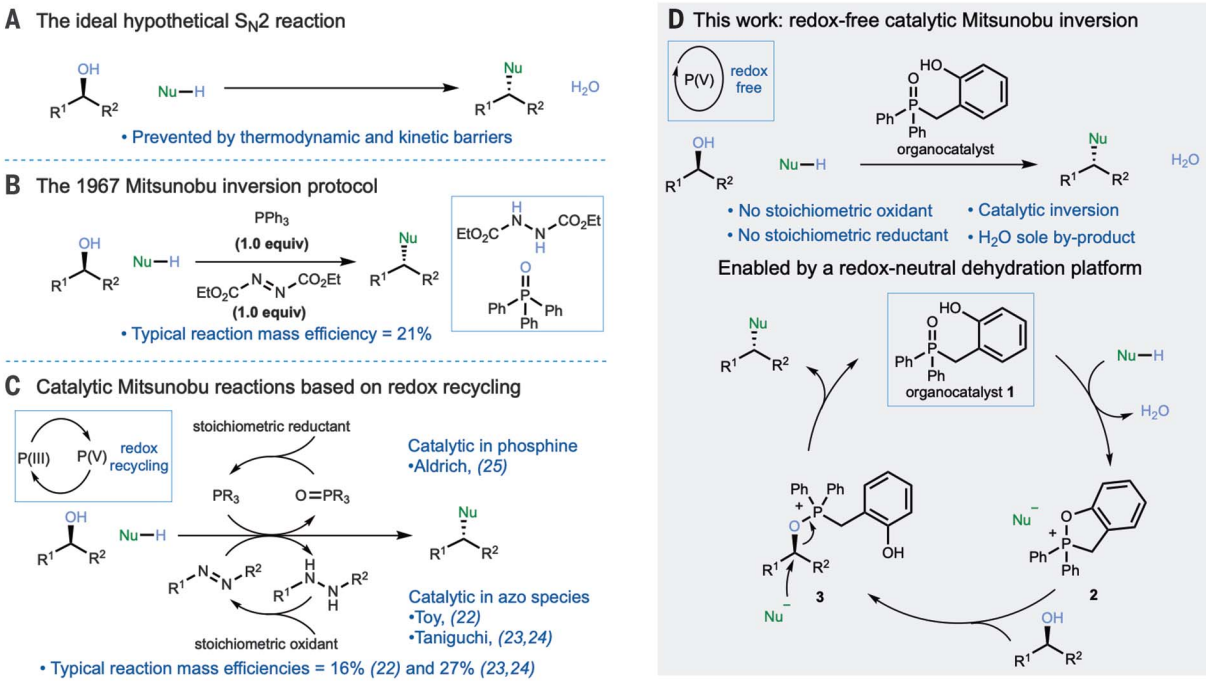

Fig. 1. Approaches to bimolecular nucleophilic substitution reactions of alcohols. (**A**) The ideal hypothetical S_N2 reaction involving direct displacement of the leaving group, inversion of stereochemistry, and generation of water as the sole by-product. (**B**) The 1967 Mitsunobu protocol for nucleophilic substitution of alcohols with inversion of stereochemistry. equiv, equivalent. (**C**) Catalytic variants of the Mitsunobu reaction based on recycling with exogenous redox reagents. (**D**) Design of a redox-free catalytic Mitsunobu inversion based on a phosphorus organocatalysis platform.

methods generally require activated carboxylic acid derivatives, coupling reagents, or strongly acidic conditions. As such, catalytic access to substitution products of both primary and secondary alcohols is valuable. As shown in Fig. 2, primary alcohols bearing functional groups potentially sensitive to strong acid, including ester (**5a**), amide (**5b**), phthalimide (**5c**), and nitrile (**5d**), were esterified under the reaction conditions. β-Citronellol also afforded the desired ester product (**5e**) with little isomerization of the sensitive trisubstituted alkene. Notably, substrates containing a phosphine-sensitive alkyl bromide (**5h**) and azide (**5i**) coupled efficiently, which would likely be problematic when using a catalytic P(III) redox-cycling strategy. It was also possible to use *p*-toluenesulfonic acid monohydrate as a pronucleophile (**5j**). This provides access to a valuable alkyl tosylate electrophile, avoiding use of a toxic sulfonyl chloride and the associated stoichiometric base.

A hallmark of the Mitsunobu reaction is secondary alcohol inversion. Acyclic, cyclic, and benzylic chiral nonracemic secondary alcohols were found to undergo efficient inversion reactions with either 2,4-dinitrobenzoic acid or 2-nitrobenzoic acid. Substrates containing ether (**5l**), alkene (**5m**), aryl chloride (**5o**), sulfone (**5q**), and silyl ether (**5r**) functional groups afforded the corresponding inverted esters in good to excellent yields. Benzylic alcohols **4t** and **4u** gave the desired ester products with excellent yields and high levels of inversion when the less acidic 2-nitrobenzoic acid was used as the coupling partner. In these more sensitive cases, competing elimination erodes the yield, whereas loss of stereochemical integrity presumably occurs from Fischer esterification or racemizing first-order nucleophilic substitution (S_N1) reactions. Electron-deficient alcohols were also challenging substrates; however, in the case of alcohol **4l**, low reactivity could be overcome by increasing the catalyst loading, which gave **5l** with excellent yield and selectivity. The desired inverted ester was also obtained when natural 5α-cholestan-3β-ol (**4v**) was subjected to the reaction conditions. In the case of cholesterol (**5x**) and *exo*-norborneol (**5w**), the corresponding esters were formed with retention of configuration due to anchimeric participation of the alkene and the nature of the bicyclic ring system, respectively (*38*).

We next sought to extend the method to encompass carbon-nitrogen and carbon-sulfur bond formations. Using dibenzenesulfonimide as a pronucleophile allowed access to a range of *N*,*N*-bis-sulfonamide derivatives (**5y** to **5ab**). The *N*,*N*-bis-sulfonamide moiety can be deprotected to afford either the sulfonamide or primary amine (*39*). The utility of this reaction was demonstrated in the efficient synthesis of the orthogonally protected diamine **5z** from amino alcohol precursor **4z**. Critically, reaction with (+)-2-octanol was shown to occur with excellent inversion of stereochemistry (**5ab**). Thioester (**5ac**) was also accessed by using thiobenzoic acid and 1-decanol as coupling partners, demonstrating the viability of carbon-sulfur bond formation, albeit with lower efficiency.

Often, the ester products formed by Mitsunobu inversion are immediately hydrolyzed to yield the inverted alcohol. The non-natural isomer of steroid 5α-cholestan-3β-ol, **7**, was synthesized on scale (4.37 g, 56%) in two steps by using a catalytic Mitsunobu esterification protocol followed by ester hydrolysis, with only a solvent exchange between the steps. Catalyst **1** and the carboxylic acid were recovered from the final mixture in 91 and 87% yield, respectively, and subsequently reused in catalytic esterification of substrates **5f** and **5g** with no loss of yield. In principle, this recycling strategy could be considered an effective implementation of the ideal inversion reaction depicted in Fig. 1A.

To further demonstrate the scope and applicability of the new Mitsunobu protocol, we next investigated the use of phenols as coupling partners. Although phenol itself is not acidic enough to participate in catalytic Mitsunobu couplings directly as a pronucleophile, we reasoned that a one-pot tosylation-etherification protocol could be developed. This was exemplified through the synthesis of the antituberculosis agent thiocarlide **10** (Fig. 2). A catalytic Mitsunobu reaction between isoamyl alcohol and *p*-toluenesulfonic acid monohydrate afforded isoamyl tosylate, which was reacted with 4-nitrophenol in situ to afford the ether product **9**. This one-pot etherification protocol provides a convenient and atom-economical alternative to existing phenol alkylation reactions and avoids stoichiometric and toxic alcohol-activating agents such as *p*-toluenesulfonyl chloride or phosphorus tribromide.

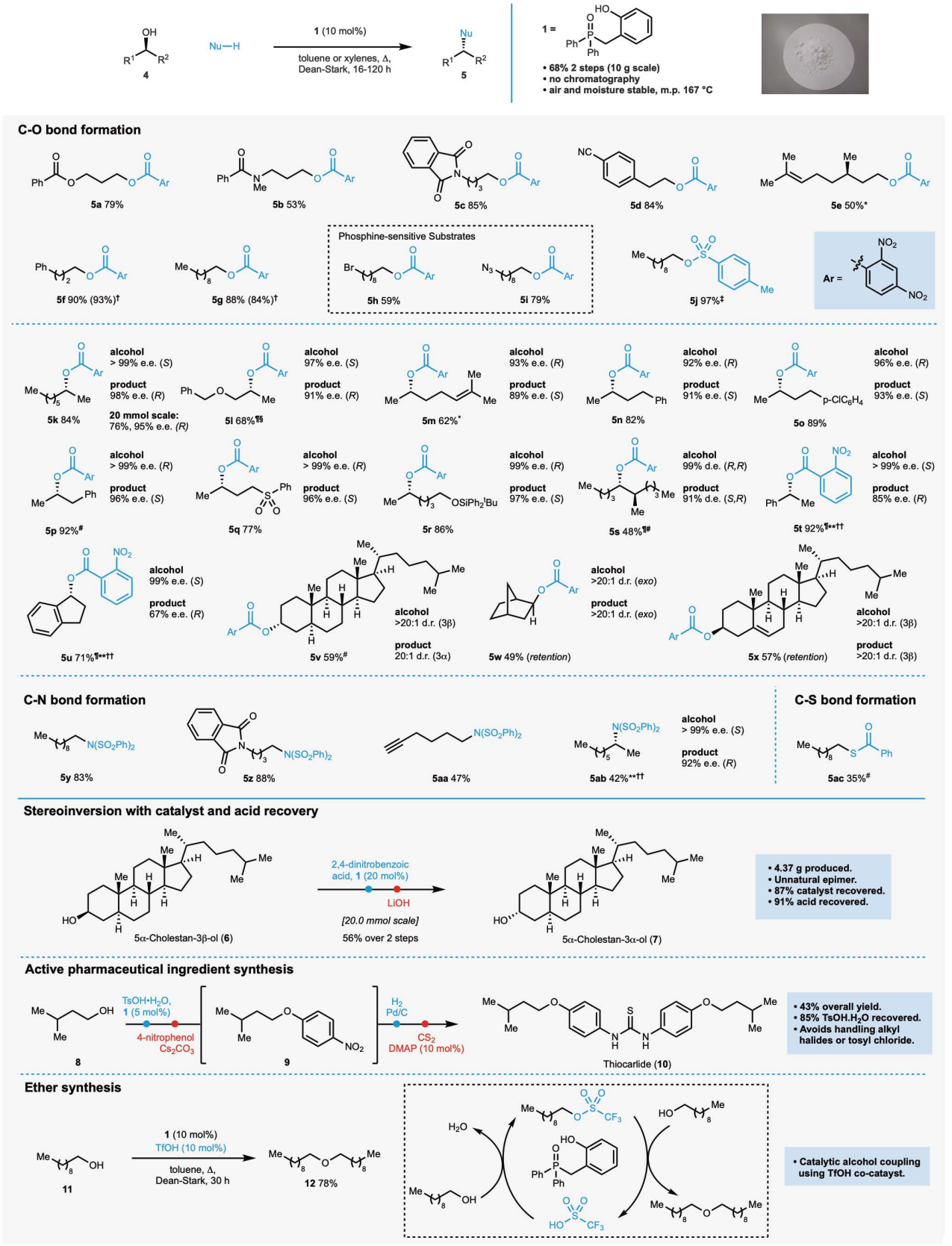

Fig. 2. Substrate scope of the catalytic Mitsunobu inversion reaction. Reactions carried out in either toluene or xylenes (1- to 2-mmol scale with respect to the alcohol unless otherwise stated); all yields are isolated yields. *Isomerization of alkene accounts for ~10% of the yield. †Reaction performed with reclaimed acid and catalyst. ‡5 mol % of catalyst used. §40 mol % catalyst used. ¶Portion-wise addition of the acid. #20 mol % of catalyst used. **25 mol % of catalyst used. ††2 equivalents of alcohol used. DMAP, 4-dimethylaminopyridine; d.e., diastereoisomeric excess; d.r., diastereoisomeric ratio; m.p., melting point.

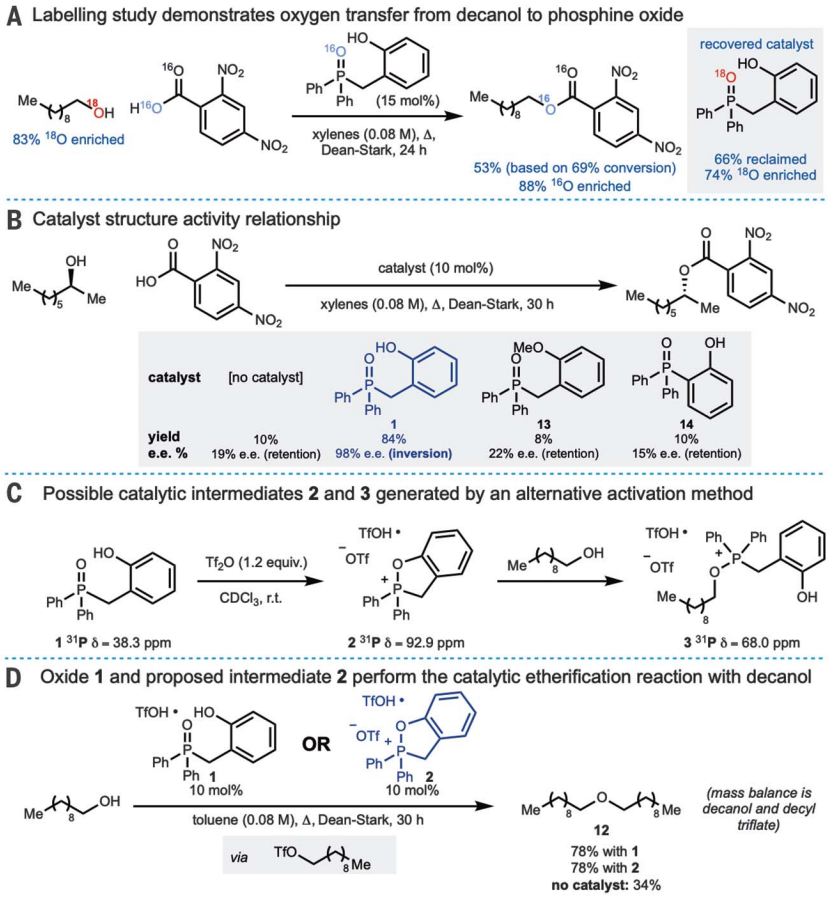

Fig. 3. Mechanistic investigation. (**A**) Oxygen-18 labeling demonstrates transfer of oxygen from the alcohol substrate to the catalyst. (**B**) Catalyst analogs, which cannot engage in cyclization and formation of proposed phosphonium intermediate **2**, are not active catalysts. (**C**) Synthesis of possible catalytic intermediates **2** and **3**. (**D**) Phosphonium intermediate **2** catalyzes etherification of decanol in analogy to phosphine oxide **1**. r.t., room temperature.

The tosic acid was recovered (87%) from the crude reaction mixture. Subsequent reduction and thiourea formation afforded the active pharmaceutical ingredient **10**. This synthesis demonstrates that the catalytic Mitsunobu protocol is valuable in contexts other than inversion and that alternative acidic pronucleophiles can be used.

Finally, we were able to demonstrate a manifold in which the coupled alcohol product can act directly as an electrophile. When triflic acid is used with phosphine oxide **1** as a cocatalyst (Fig. 2), the Mitsunobu-generated alkyl triflate (*40*) is reactive enough to undergo in situ alkylation with remaining alcohol to afford the symmetrical ether **12** and regenerate the triflic acid cocatalyst (materials and methods). This phosphine oxide–cocatalyst manifold (Fig. 2) may allow the development of reactions in which toxic alkylating agents are formed and reacted with a range of nucleophiles in situ, avoiding the need to handle such species.

To assess the catalytic dehydration platform depicted in Fig. 1D, we carried out mechanistic studies beginning with an isotope labeling experiment, whereby 2,4-dinitrobenzoic acid and ^{18}O-enriched 1-decanol were subjected to the reaction conditions (Fig. 3A). The ester product was obtained with high ^{16}O incorporation, and the recovered catalyst was found to contain 74% ^{18}O. This result, along with the excellent enantioselectivities obtained for secondary alcohol substrates, is consistent with the expected oxygen transfer from the alcohol to the catalyst. We next examined structural changes to the catalyst. An initial control experiment in the absence of the catalyst yielded the benzoic ester product in 10% yield after 30 hours with 19% e.e. for the retention product (Fig. 3B). We presume that the loss of stereochemical integrity during the reaction arises through a combination of a Fischer esterification and a racemizing S_N1 mechanism. We next probed the posited role of the hydroxyl group using phosphine oxides **13** and **14**, neither of which were catalytically active (Fig. 3B). In both cases, formation of the proposed five-membered phosphonium species **2** is precluded. Phosphine oxide **14** has a ^{31}P shift [39.4 parts per million (ppm)] similar to the active catalyst **1** (38.3 ppm), indicating a similar amount of phosphoryl activation (phosphonium character) and demonstrating a role for the hydroxyl group beyond simple hydrogen-bond activation of the phosphorus-oxygen bond.

We next sought to identify reaction intermediates by monitoring the reaction using ^{31}P and ^{1}H nuclear magnetic resonance (NMR) spectroscopy. However, the only phosphorus species observed in aliquots of the catalytic reaction was the phosphine oxide **1** (figs. S8 and S9). Given that activated phosphonium intermediates are typically hydrolytically sensitive and that phosphine oxide activation requires dehydration at elevated temperature under Dean-Stark conditions, we designed an alternative method to access possible catalytic intermediates avoiding the generation of water. To this end, activation of phosphine oxide **1** with triflic anhydride at room temperature (Fig. 3C) resulted in a species, whose ^{31}P, ^{13}C, and ^{1}H NMR data were consistent with phosphonium triflate **2**. Subsequent addition of decanol afforded the acyclic alkoxyphosphonium triflate **3**. Finally, phosphonium triflate **2** was demonstrated to be catalytically active and promoted etherification in analogy to phosphine oxide **1** (Fig. 3D). In summary, the experiments described above and in the supplementary material are congruous with the catalytic cycle depicted in Fig. 1D, where dehydration to afford phosphonium intermediates is likely to be turnover-limiting and dependent on a geometrically important hydroxyl group; hydrogen-bond availability alone is insufficient to account for the reactivity. The labeling study and stereochemical inversion are consistent with the carbon-nucleophile bond formation occurring from an alkoxyphosphonium salt–nucleophile ion pair in accord with the classical Mitsunobu reaction.

The elimination of redox chemistry in our catalytic Mitsunobu protocol obviates the need for terminal oxidants and reductants and results in substantially increased reaction mass efficiency of 65% (fig. S14) (*41*). The established organophosphorus-catalyzed dehydration manifold has potential applications in a range of other classical phosphorus-mediated transformations.

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SUPPLEMENTARY MATERIALS

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Materials and Methods
Figs. S1 to S14
Tables S1 to S3
HPLC and SFC Traces
NMR Spectra
References (*42*–*80*)

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Redox-neutral organocatalytic Mitsunobu reactions

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Displacing OH groups catalytically

The Mitsunobu reaction is widely used to invert the configuration of alcohols. However, its major drawback is the need to activate the alcohol with a full equivalent of phosphine, thereby generating a phosphine oxide co-product. Beddoe *et al.* report a phosphine oxide compound that achieves the same result catalytically (see the Perspective by Longwitz and Werner). The key is a phenol substituent that can reversibly bond through its oxygen to phosphorus, forming a ring that the alcohol opens. The phosphorus thus remains in the +5 oxidation state throughout the reaction, and water is the only by-product.

Science, this issue p. 910; see also p. 866