Redox Neutral Organocatalytic Mitsunobu Reactions

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Abstract: Nucleophilic substitution reactions of alcohols are amongst the most fundamental and strategically important transformations in organic chemistry. For over half a century these reactions have been achieved 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 within 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.

One Sentence Summary: A phosphine oxide organocatalyst promotes redox-neutral, stereospecific Mitsunobu coupling reactions of alcohols generating water as the sole by-product.

Alcohols are important feedstocks *(1-5)* for chemical synthesis because they are abundant, inexpensive and can be converted into a wide range of additional functional groups using, amongst 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 there are kinetic and thermodynamic barriers that prevent direct substitution and, therefore, additional chemical activating agents must be used. Unfortunately, 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 non-activated chiral alcohols remains a major challenge *(19-20).* Although some progress has been made using cyclopropenone catalysis *(21),* the majority of effort to date has been focused on modifying the original Mitsunobu protocol by redox recycling of the stoichiometric reagents. Although this approach is intuitive, it is challenging to implement 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 sub-stoichiometric (10 mol%) azodicarboxylate, which was recycled 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 co-catalyst 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 both species *(25)* suffered from oxidation/reduction incompatibilities and limited output *(26).* Although these catalytic variants are valuable, any catalytic Mitsunobu reaction based upon 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 upon 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 counter anion associated with phosphonium salt **2** may engage in non-productive, 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 within 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 using catalyst **1** (a bench-stable solid, prepared on a multigram scale in 2 steps with no chromatography, see supplementary materials, pages 4-5) and (+)-2-octanol (>99% enantiomeric excess (e.e.)) as a representative non-activated alcohol. Azeotropic removal of water from either toluene or xylenes using a Dean-Stark trap is critical to the cycle as the phosphonium salt

intermediates are kinetically and thermodynamically unstable with respect to hydrolysis, which returns the phosphine oxide. Pronucleophiles with low Brønsted acidity (e.g. benzoic acid, pK_a(H_2O) = 4.2) did not promote measurable catalysis but, as acidity increases (e.g. 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 (see supplementary materials, table S1 and table S2). The inverted ester product was formed in a yield of 84% and an enantiomeric excess of 98%.

With optimized conditions in hand we then explored the scope of the catalytic Mitsunobu coupling reaction. Stoichiometric esterification 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. Pleasingly, β-citronellol also afforded the desired ester product (**5e**) with little isomerization of the sensitive trisubstituted alkene. Significantly, substrates containing a phosphine-sensitive alkyl bromide (**5h**) and azide (**5i**) coupled efficiently, which would likely be problematic 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. Importantly, acyclic, cyclic and benzylic chiral non-racemic 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, whilst loss of stereochemical integrity presumably occurs from direct coupling or racemizing 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** - **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 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, 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 re-used 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 anti-tuberculosis 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. 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 employed with phosphine oxide **1** as a co-catalyst (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 co-catalyst (see supplementary materials, page 57). This phosphine oxide/co-catalyst 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 Figure 1D we carried out mechanistic studies beginning with an isotope labelling 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 almost complete ^{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 due to a combination of a Fischer esterification and a racemizing S_N1 mechanism (or elimination/addition racemization of the alcohol). 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 5-membered phosphonium species **2** is

precluded. Catalyst **14** has a ^{31}P shift (39.4 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 NMR spectroscopy. However, the only phosphorus species observed during the catalytic reaction was the phosphine oxide **1** (see supplementary materials Fig. S6 and Fig. S7). Given that phosphonium intermediates are typically hydrolytically sensitive and that phosphine oxide activation requires dehydration at elevated temperature, we designed an alternative method to access and characterize 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 new species, whose ^{31}P, ^{13}C and ^{1}H NMR data were consistent with phosphonium triflate **2**. Subsequent addition of decanol resulted in ring-opening to afford 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. The phosphine oxide is the likely resting state of the catalyst, with dehydration to afford phosphonium intermediates appearing to be turnover limiting and dependent on a geometrically important hydroxyl group; hydrogen bond availability is insufficient alone to account for the reactivity. The labelling 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% (see supplementary materials, Fig. S9) *(41)*. The established organophosphorus-catalyzed dehydration manifold has potential applications in a range of other transformations, such as the Wittig and Staudinger reactions.

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Author contributions: RMD designed the experiments. RHB, KGA, VM, JDC, JS and ASL carried out the experiments. All of the authors analyzed the data. RMD, RHB and KGA drafted the manuscript.

Competing interests: Authors declare no competing interests **Data and materials availability:** All data is available in the main text or the supplementary materials.

Supplementary Materials:

Materials and Methods

Figures S1-S14

Tables S1-S3

References (*42-80*)

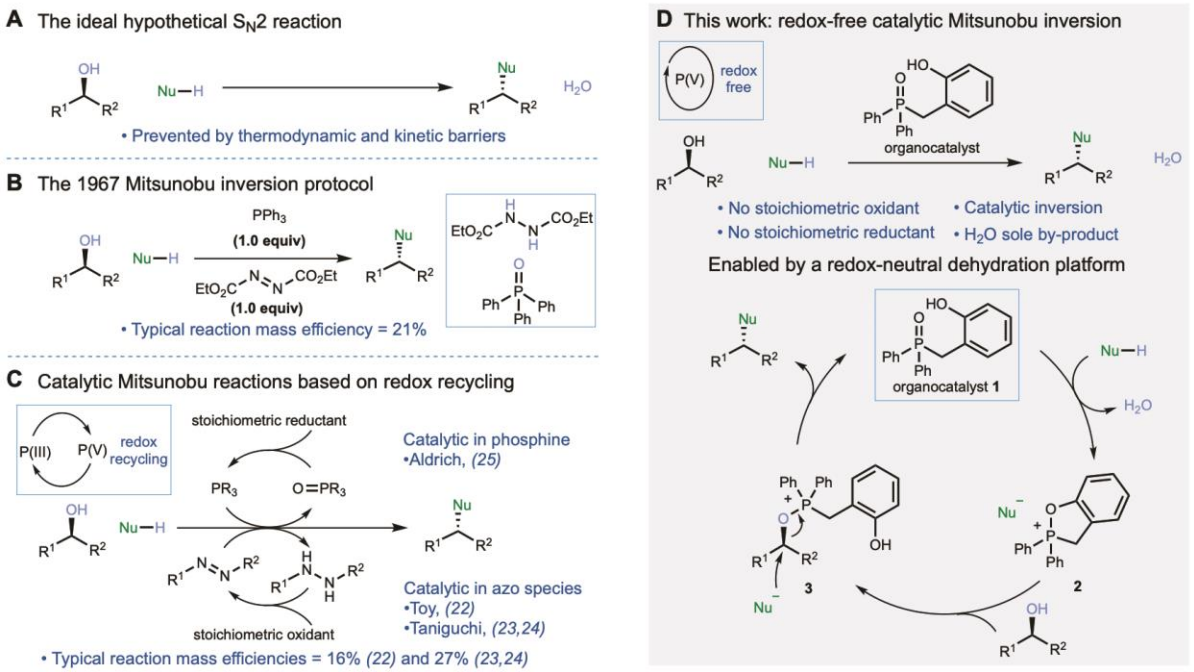
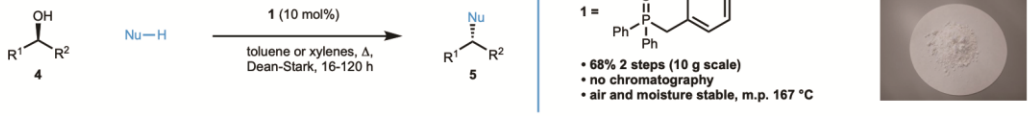
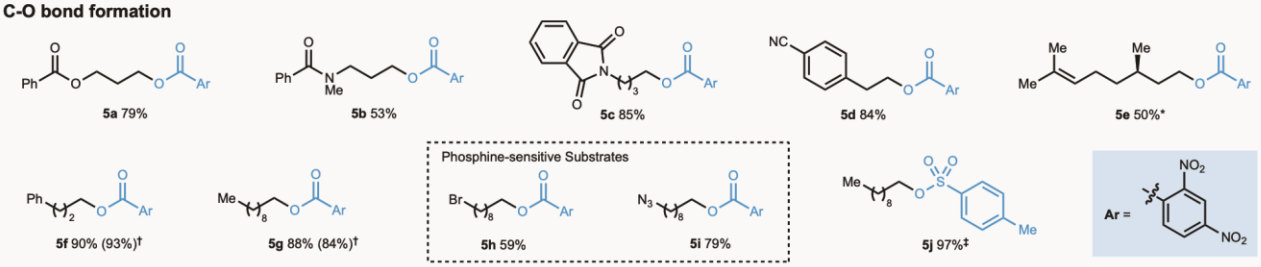
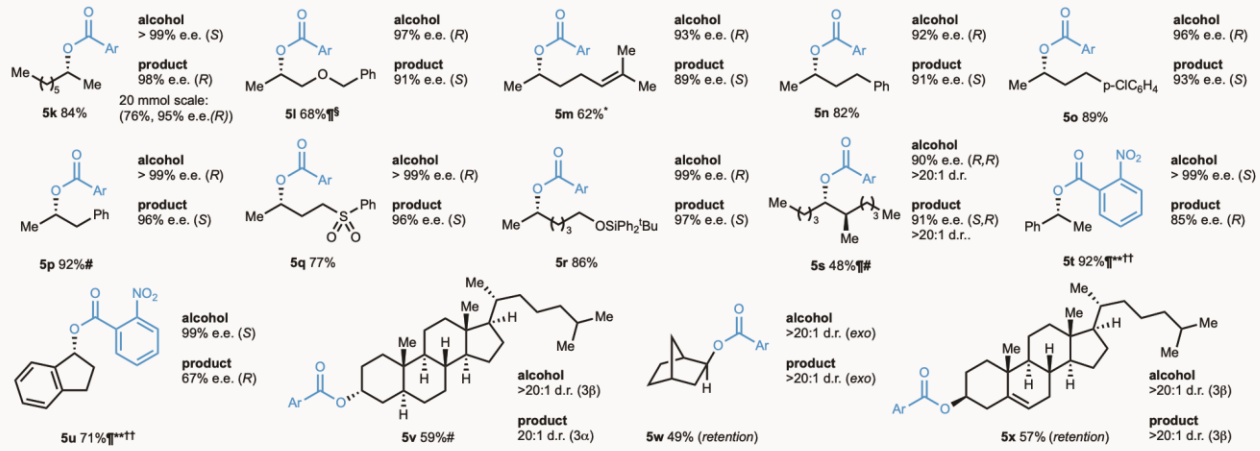


Fig. 1. Approaches to bimolecular nucleophilic substitution reactions of alcohols. (**A**) The ideal hypothetical S_N2 reaction involving direct displacement of the leaving group, inversion of stereochemistry and generation of water as the sole by-product. (**B**) The 1967 Mitsunobu protocol for nucleophilic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



C-O bond formation





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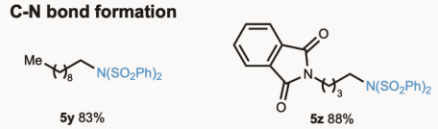
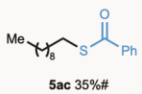
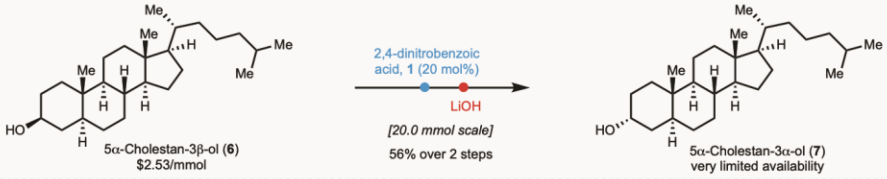


C-S bond formation

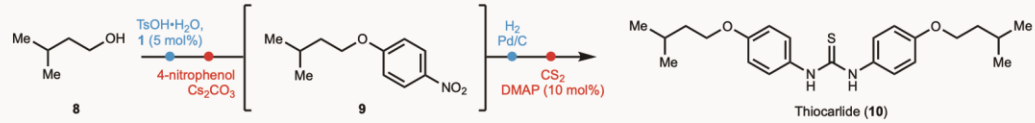


Stereoinversion of Chiral Pool Substrate



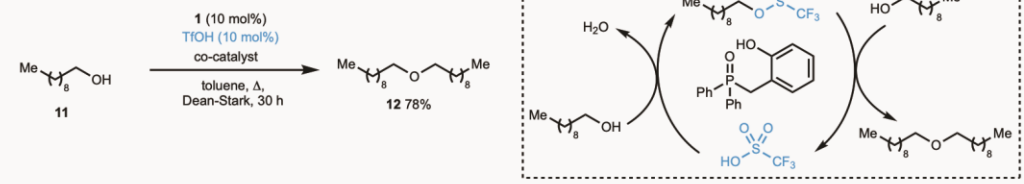
- 4.37 g produced.
- Unnatural epimer.
- 87% catalyst recovered.
- 91% acid recovered.

Active Pharmaceutical Ingredient Synthesis



- 43% overall yield.
- 85% TsOH.H2O recovered.
- Avoids handling alkyl halides or tosyl chloride.

Ether synthesis



- Catalytic alcohol coupling using TfOH co-catayst.

Fig. 2. Substrate scope of the catalytic Mitsunobu inversion reaction. Reactions carried out in either toluene or xylenes (1-2 mmol scale with respect to the alcohol unless otherwise stated); all yields are isolated yields. * Isomerization of alkene accounts for approximately 10% of the yield. † Reaction performed using 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.

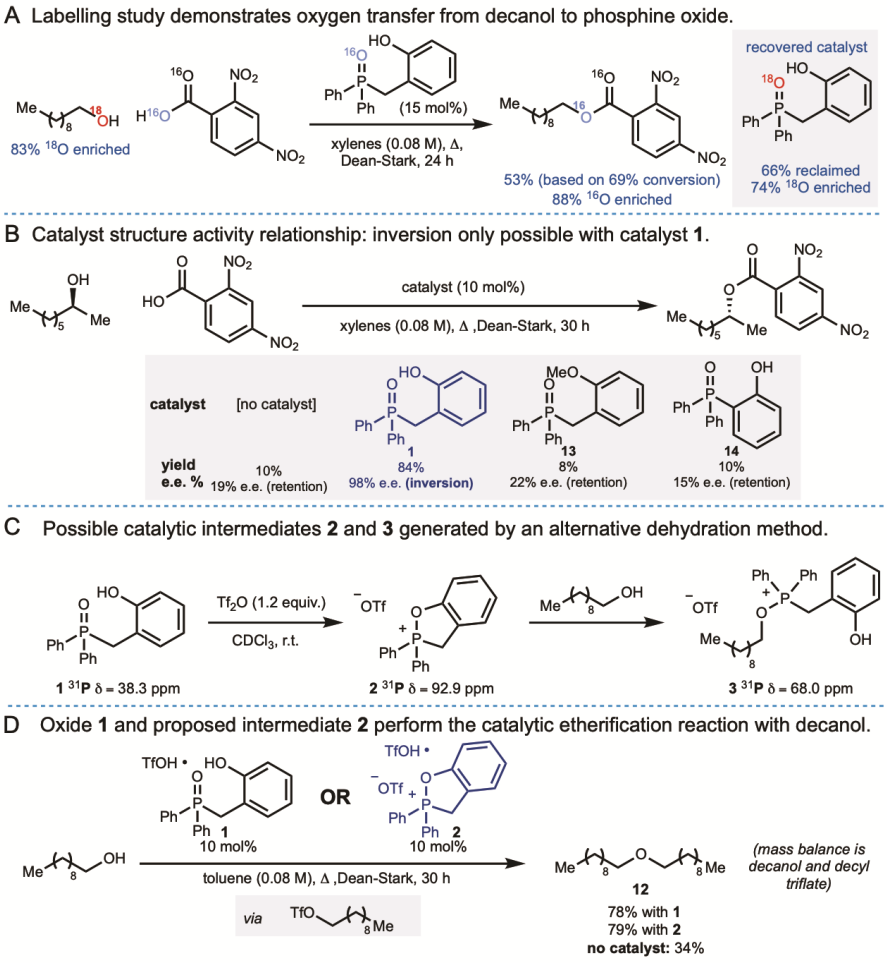


Fig. 3. Mechanistic investigation. **(A)** Oxygen-18 labelling demonstrates transfer of oxygen from the alcohol substrate to the catalyst. **(B)** Catalyst analogs which cannot engage in cyclization and formation of proposed phosphonium intermediate **2** are not active catalysts. **(C)** Synthesis of

possible catalytic intermediates **2** and **3**. **(D)** Phosphonium intermediate **2** catalyzes etherification of decanol in analogy to phosphine oxide **1**.