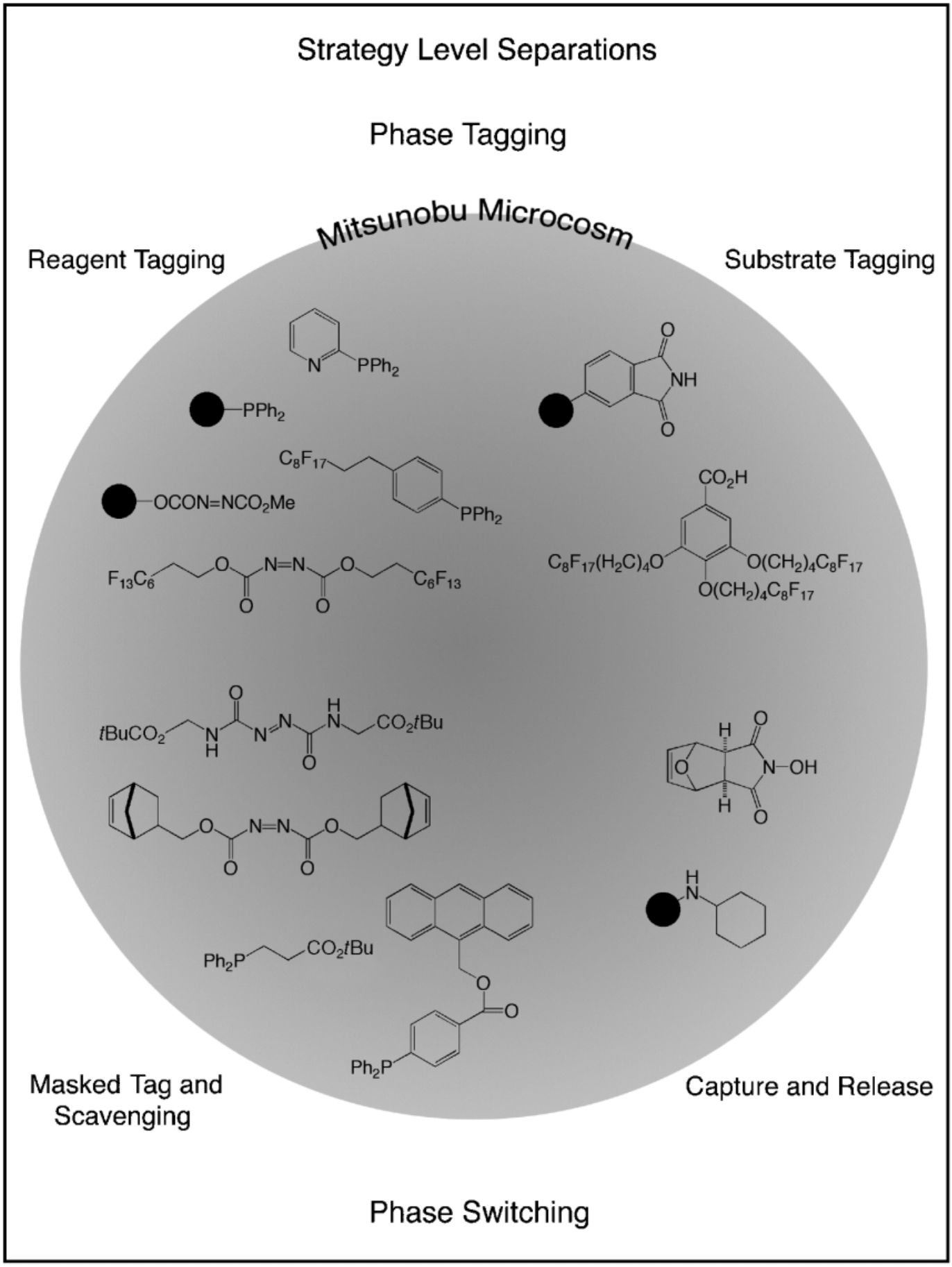

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Separation-Friendly Mitsunobu Reactions: A Microcosm of Recent Developments in Separation Strategies

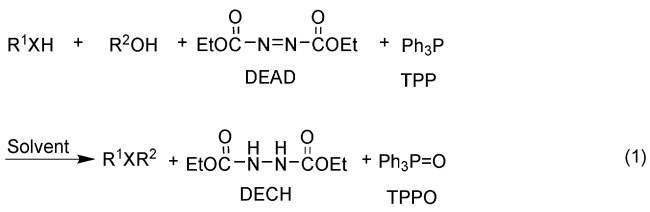
Sivaraman Dandapani* and Dennis P. Curran*[a]

Abstract: The Mitsunobu reaction is famous for its scope and power, but infamous for its separation headaches. Typically, the target product is enticed away from the reagent-derived byproducts by careful chromatography. The use of polymer-bound Mitsunobu reagents solves only half of the problem, because polymer-bound diethyl azodicarboxylate (DEAD) and phosphine reagents cannot be employed simultaneously. This article classifies, compares, and contrasts various emerging strategies for product isolation in Mitsunobu reactions. Because so many different strategies have been used, the Mitsunobu reaction is a microcosm for the new field of strategy level separations.

Keywords: azo compounds · combinatorial chemistry · Mitsunobu reaction · perfluorinated compounds · solid-phase synthesis

Introduction

The Mitsunobu reaction: The Mitsunobu reaction involves the condensation of an acidic pronucleophile (R^1XH) and an alcohol (R^2OH) promoted by triphenylphosphine (TPP) and diethyl azodicarboxylate (DEAD) or diisopropyl azodicarboxylate (DIAD) [Eq. (1)].[1,2] This reaction produces the coupled product (R^1XR^2) along with diethoxycarbonylhydrazine (DECH) and triphenylphosphine oxide (TPPO).



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Despite the lack of atom economy, the Mitsunobu reaction is popular in organic synthesis and medicinal chemistry because of its scope, stereospecificity, and mild reaction conditions. However, careful chromatography is usually required to isolate the pure target product from the unreacted reagents and byproducts. This limits the direct application of the Mitsunobu reaction in combinatorial library syntheses. This article provides an overview of the separation-friendly strategies that have recently been introduced to facilitate product isolation in Mitsunobu reactions. Complementing the strategy separation focus of this article, a concurrent review by Dembinski provides a more comprehensive account of new Mitsunobu reagents.[2b]

Separation strategy: Separation has recently become a strategy-level concern in synthetic planning at all scales.[3] Speed and efficiency in chemical separation are at the heart of parallel synthesis and combinatorial chemistry, and are increasingly important in traditional synthesis as well. Today, workup-level separations are often performed to avoid chromatography by using various methods of phase tagging.[3–5] Briefly, one of the reaction components is attached to a "separation tag" (sometimes called a "phase tag", "phase label" or "affinity tag") which controls the behavior of the component in a simple binary separation technique that is used to separate tagged reaction components from untagged ones. Examples of separation tags and their complementary separation methods include polymers/filtration, fluorous tags/fluorous solid-phase extraction (FSPE), and ionizable tags/acid–base extraction. In a technique called phase switching, the tag is sometimes added or created after the reaction, thereby switching the behavior of a reaction component from one phase to another. Effectively, synthesis controls separation in these techniques.

Scheme 1 provides a high-level summary of strategic separations that are used in the Mitsunobu reaction.[6] In "reagent tagging", the substrates are untagged. One or both of the Mitsunobu reagents gets a separation tag, and its derived byproducts are removed by the appropriate tag-based separation. In "substrate tagging", the roles are reversed, as

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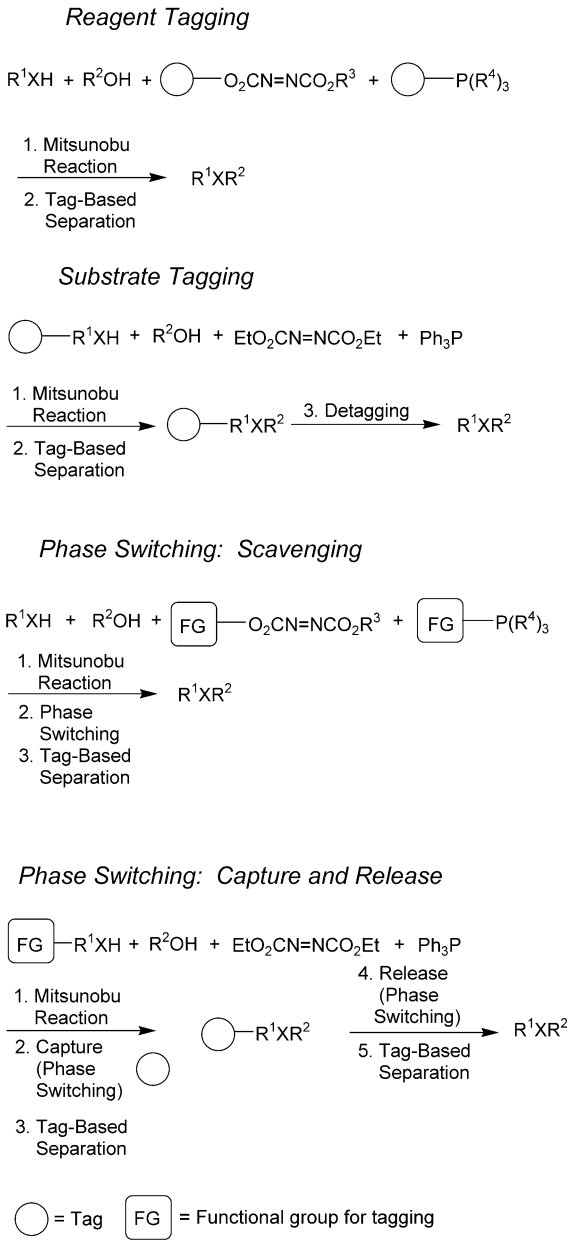


Scheme 1. Strategies for product isolation in Mitsunobu reactions.

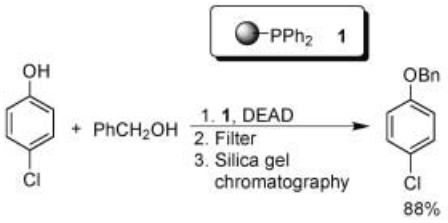
shown in Scheme 1 with a tagged pronucleophile. Of course, the alcohol can also be tagged. In the two analogous phase-switching modes, reagents or a substrate bear a functional group that can be attached to or fashioned into the phase tag after the reaction. Phase switching of reagents and undesired byproducts is often called scavenging, while phase switching of the target product is often called capture and release.[7]

Below we classify separation strategies for the Mitsunobu reaction by whether or not additional reactions are required after the Mitsunobu reaction itself.

Product Isolation Strategies Requiring No Additional Reactions—Reagent Tagging

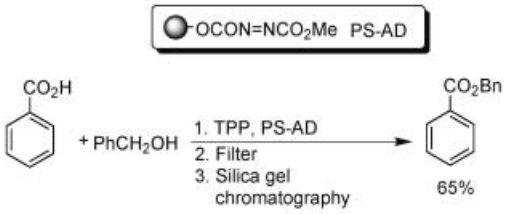
In general, polymer-supported reagents[8] and soluble reagents carrying a separation tag are employed in combinatorial chemistry under solution-phase conditions.[3–6] The facile separation of the tagged compounds from the untagged ones by phase or affinity separation dictates the success of these approaches. When Mitsunobu reagents carrying suitable phase or affinity tags are used, the coupled Mitsunobu product can be isolated by phase separation or affinity chromatography. This reagent-tagging strategy is inherently attractive, since it is the only one in which no additional reactions are required to effect a separation.

Mitsunobu reactions with polymer-supported reagents: When phosphine bound to an insoluble polymer support is used in Mitsunobu reactions, the derived phosphine oxide can be removed by filtration at the end of the reaction.[9] For example, *p*-chlorophenol and benzylalcohol have been coupled by using soluble DEAD and polymer-bound triphenylphosphine **1** [Eq. 2].[9a] At the end of the reaction, the



(2)

polymer-bound phosphine oxide was removed by filtration. The filtrate was evaporated to give a mixture containing *p*-chlorophenyl benzyl ether and DECH. This was separated by silica-gel chromatography to give the desired ether in 88% yield. Alternatively, Vederas and co-workers have paired soluble TPP with a polymer-supported azodicarboxylate (PS-AD) to promote the Mitsunobu reaction.[10] For example, after the reaction of benzyl alcohol and benzoic acid with PS-AD and TPP [Eq. 3], the solution was filtered to



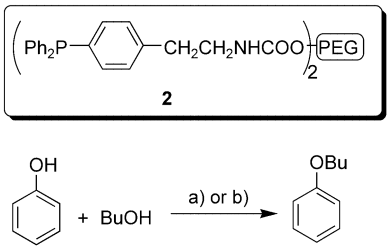
(3)

remove the polymer bound DECH, and chromatography was carried out to separate benzyl benzoate from TPPO.

Insoluble, polymer-supported phosphines and azodicarboxylates cannot be employed simultaneously because reactions do not readily occur between isolated polymer beads. Also, Mitsunobu reactions employing polymer-bound re-

agents are slower than the corresponding solution-phase reactions,[11] and large excesses of the polymer-bound reagent are typically used.

Phosphines attached to soluble polymers offer easy separation without sacrificing reaction rate. For example, Janda and co-workers have used PEG-supported (PEG = polyethyleneglycol) phosphine **2** along with DEAD to promote the Mitsunobu reaction between *n*-butanol and phenol in dichloromethane (Scheme 2).[11] After 3 h, the reaction mixture was concentrated to half the volume and DECH was removed by filtration. The filtrate was then poured onto diethyl ether, and the precipitated PEG-bound phosphine oxide was removed by filtration to give the analytically pure butyl phenyl ether in 85% yield. The same reaction with cross-linked polystyrene-bound phosphine **1** in place of soluble **2** took 8 h to complete and gave the product in 87% yield.



Phosphine	time	yield
2	3 h	85%
1	8 h	87%

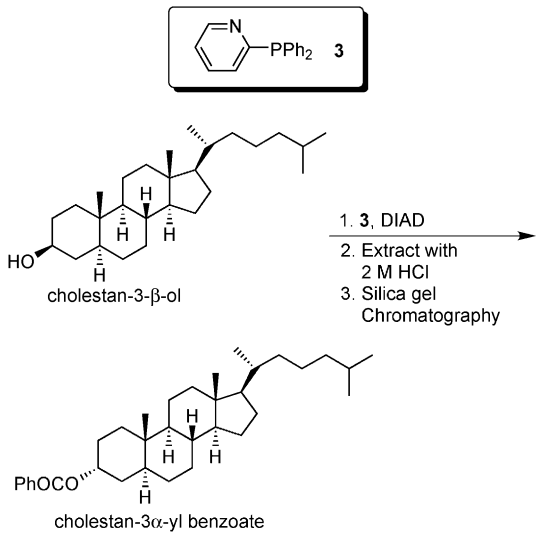
Scheme 2. Mitsunobu reactions with soluble polymer-supported phosphine. a) 1) **2**, DEAD; 2) concentrate, filter; 3) add diethyl ether, filter. b) 1) **1**, DEAD; 2) filter; 3) concentrated, filter.

Charette and co-workers have also developed a soluble, non-cross-linked polystyrene-supported phosphine and applied it to Mitsunobu reactions.[12] In this protocol, the derived phosphine oxide was removed by filtration after adding methanol to the crude reaction mixture.

Mitsunobu reactions with basic phosphines: Jenkins and Camp introduced diphenyl(2-pyridyl)phosphine (**3**) as an alternative to triphenylphosphine in Mitsunobu reactions [Eq. 4].[13] The crude mixture from the reaction of cholestan-3β-ol and benzoic acid promoted by **3** and DIAD was washed with 2 M HCl to remove the basic phosphine oxide derived from **3**. Column chromatography was conducted to separate the desired cholestan-3α-yl benzoate from diisopropoxycarbonylhydrazine.

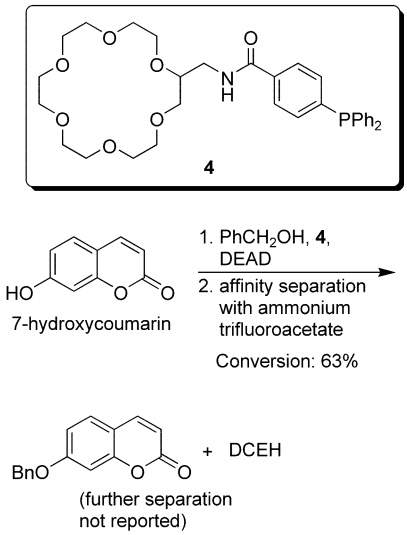
In a similar fashion, von Itzstein and Mocerino have used (*p*-dimethylamino-phenyl)diphenylphosphine in Mitsunobu reactions.[14] The derived phosphine oxide was removed by an acidic wash.

Mitsunobu reactions with a crown ether tagged phosphine: Routledge and Jackson have used [18]crown-6-tagged triarylphosphine **4** in Mitsunobu reactions and separated the derived phosphine oxide by exploiting the interaction of the



(4)

crown ether with ammonium ions [Eq. (5)].[15] For example, 7-hydroxycoumarin was benzylated by using [18]crown-6-tagged phosphine **4** and DEAD. The crude reaction mixture was loaded onto an ArgoPore™ ammonium trifluoroacetate column (ArgoPore-NH_2 is a highly cross-linked macroporous resin) and eluted with dichloromethane. Although the first-pass eluent was free of any phosphorous-containing impurity as assayed by ^{31}P NMR spectroscopy, it must have been a mixture of the Mitsunobu product and DECH. Further separation of this mixture was not reported. Second-pass elution of the column with dichloromethane containing 2% triethylamine gave the crown ether-tagged phosphine oxide (not shown) in 80% yield.

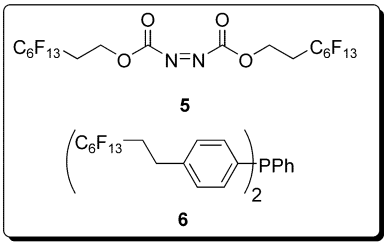


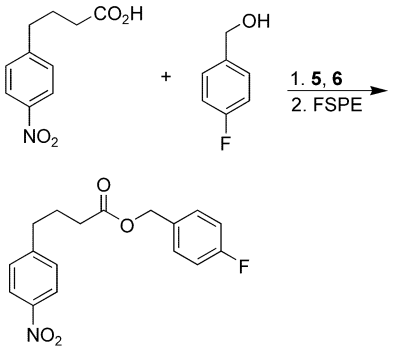
(5)

Mitsunobu reactions with fluorous reagents: Fluorous compounds with a high fluorine content (60% or more by weight) can be separated from non-fluorous (organic) compounds by partitioning a mixture between a fluorous and an organic liquid.[3] For compounds with lower fluorine content, filtration over fluorous silica gel (silica gel with fluorocar-

bon-bonded phase) is more effective.[16] This technique is referred to as fluorous solid-phase extraction (FSPE) and it is carried out in three stages, that is, loading, fluorophobic wash, and fluorophilic wash. A mixture of fluorous and organic (non-fluorous) compounds is loaded onto fluorous silica gel and eluted with a fluorophobic solvent system (typically 80% MeOH). This elutes organic compounds from the column, while retaining fluorous-tagged compounds. A second wash with a fluorophilic solvent (typically ether or THF) elutes the fluorous compounds. FSPE's are easy to conduct in parallel and, hence, are suited for combinatorial chemistry applications.[17]

Curran[18] and Dobbs[19] have independently reported the synthesis of the fluorous DEAD reagent **5** and its applications in Mitsunobu reactions. Dandapani and Curran paired the fluorous DEAD **5** with the fluorous phosphine **6** for



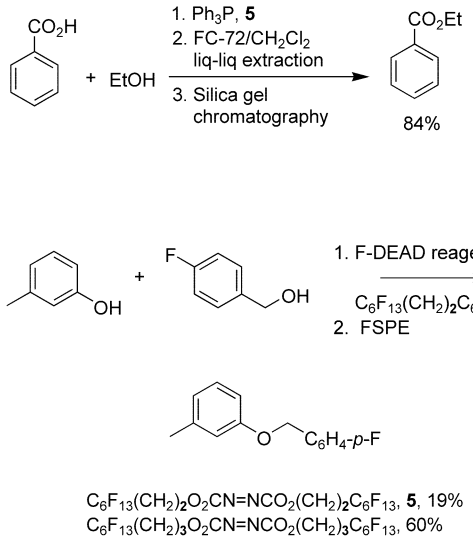


(6)

88% yield, 100% purity

promoting Mitsunobu reactions. For example, 4-(4-nitrophenylbutyric acid) was coupled with *p*-fluorobenzyl alcohol using **5** and **6** [Eq. (6)] and the crude reaction mixture was purified by FSPE to separate the target organic product from the fluorous reagent-derived products.[18] On the other hand, Dobbs and McGregor-Johnson paired the fluorous DEAD **5** with TPP for promoting Mitsunobu reactions. For example, the crude reaction mixture from the reaction of benzoic acid with ethanol promoted by TPP and **5** was partitioned between the fluorous liquid FC-72 (a mixture of perfluorinated hexanes) and dichloromethane [Eq. (7)].[19] This fluorous–organic liquid extraction completely removed the fluorous DECH (structure not shown). However, silica-gel chromatography was required to separate the desired ethyl benzoate from TPPO.[20] The recovered fluorous phosphine and hydrazine products are readily reconverted to the starting reagents for reuse.[18a]

Very recently it has been discovered that fluorous DEAD reagent **5** with the ethylene spacer underperforms relative



(7)

to the standard DEAD reagent in some reactions with sterically hindered alcohols or weakly acidic nucleophiles (like phenols). Adding a methylene group provides the propylene-spaced reagent $C_6F_{13}(CH_2)_3CO_2N{=}NCO_2(CH_2)_3C_6F_{13}$, which in early experiments seems to be a much better mimic of DEAD in its reactivity profile.[18c] In addition, SPE separation media have improved since the original publication, and the lighter fluorous phosphine *p*-$(C_8F_{17}CH_2CH_2)C_6H_4P(C_6H_5)_2$ can now be used in place of **6**. A representative example of this improved second-generation fluorous Mitsunobu protocol is shown in the lower part of Equation (7).[18c]

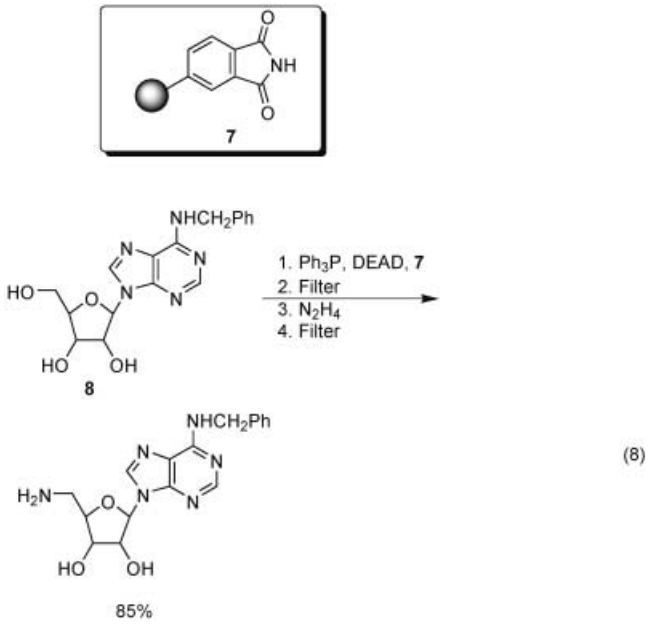
Product Isolation Strategies Requiring Additional Reactions

Strategies based on substrate tagging and phase switching require additional reactions after the Mitsunobu reaction. These reactions add effort and can impose their own set of limitations, but they can return dividends as well. For example, substrate tagging is often used in multistep settings, so the tags find use in more than one step. In phase switching, the solubilization of reaction components during the reaction can be an advantage.

Substrate tagging in Mitsunobu reactions: When either the alcohol or the pronucleophile substrate involved in a Mitsunobu reaction has a phase tag, the coupled Mitsunobu product can be easily separated from the untagged byproducts by a phase or affinity separation. However, an additional reaction is needed to remove the phase tag and bring the coupled product back to the desired organic/liquid phase.

Mitsunobu reactions on polymer-supported substrates: When an insoluble polymer-bound alcohol or pronucleophile is employed in a Mitsunobu reaction, the resulting product is tagged (attached) to the polymer support and can be readily purified by filtration. The desired product is then released

from the polymer by a suitable detagging reaction. For example, Gelb and Aronov have used the phthalimide resin **7** for carrying out Mitsunobu amino dehydroxylations [Eq. (8)].[21] The nucleoside **8** was coupled with phthalimide

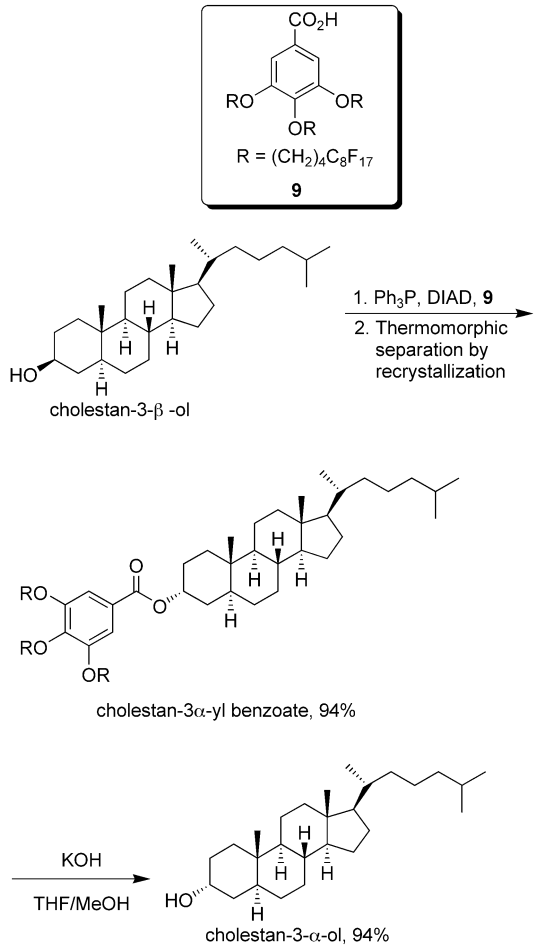


(8)

resin **7** by using TPP and DEAD. The crude reaction mixture was then purified by filtration to remove TPPO and DCEH. The polymer-bound product was finally released by hydrazinolysis.

When a Mitsunobu reaction is carried out as one of the steps in a sequence of solid-phase organic transformations on polymer-bound substrates, the polymer-bound Mitsunobu product can be purified by filtration and taken to the next step. Mitsunobu reactions have been reported on solid-supported alcohol,[22] imide,[23] phenol,[24] sulfonamide,[25] sulfamide,[26] carboxylate,[27] and ammonium moieties.[28]

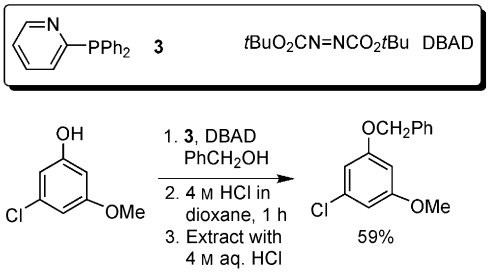
Mitsunobu reactions on fluorous substrates: When a Mitsunobu reaction is used to invert the configuration of secondary alcohols, the ester product is subjected to hydrolysis. In such cases, it is advantageous to use a tagged acid for the Mitsunobu reaction, since the ester product can be readily separated and the tag can be removed at the hydrolysis stage. Dembinski and Markowicz have employed fluorous acid **9** for carrying out Mitsunobu reactions (Scheme 3).[29] For example, the coupling of cholestan-3β-ol and fluorous acid **9** was promoted by TPP and DIAD. The product was isolated directly from the crude reaction mixture in 94% yield by a simple recrystallization from $CHCl_3$/MeOH (1:1). The generality of this recrystallization procedure was demonstrated by five other examples. Such a ready separation of a fluorous solid by recrystallization or precipitation forms the basis of thermomorphic (temperature-dependent properties like solubility) separations in fluorous media.[30] The fluorous cholestan-3α-yl ester was saponified to give the inverted alcohol (cholestan-3-α-ol) in 94% yield.



Scheme 3. Mitsunobu inversion of a secondary alcohol employing fluorous acid.

Byproduct removal by phase-switching: When Mitsunobu reagents are used with latent functional groups that offer easy phase switching, the coupled Mitsunobu product can be isolated after unmasking of the latent functional group. Alternatively, a byproduct can be separated by phase switching after the reaction if it possesses a suitable functionalized tag. These approaches require additional reactions for enabling separation.

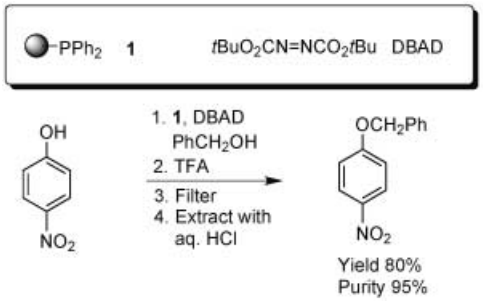
Mitsunobu reactions with acid-labile di-tert-*butyl azodicarboxylate*: Kiankarimi and co-workers have used diphenyl(2-pyridyl)phosphine **3** and di-*tert*-butyl azodicarboxylate (DBAD) to allow easy product isolation in Mitsunobu reactions [Eq. (9)].[31] For example, when this reagent combina-



(9)

tion was used to couple 3-chloro-5-methoxyphenol and benzylalcohol, the desired product could be isolated free from reagent byproducts after treating the crude reaction mixture with 4 M HCl. Di-*tert*-butoxycarbonylhydrazine decomposes under acidic conditions to give gaseous isobutylene and carbon dioxide, and water-soluble hydrazine. The basic phosphine oxide derived from **3** is also extracted into the acidic aqueous layer, leaving only the desired product in the organic layer. Concentration and purification of the crude product by short flash column chromatography gave the Mitsunobu adduct in 59% yield.

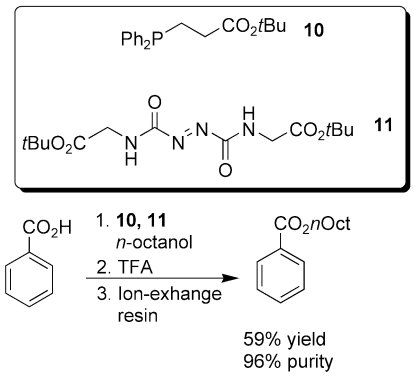
Pelletier and Kincaid paired di-*tert*-butyl azodicarboxylate with polymer-supported phosphine for use in Mitsunobu reactions.[32] By using this combination of reagents, 4-nitrophenol was coupled with benzyl alcohol [Eq. (10)]. The crude



(10)

reaction mixture was treated with trifluoroacetic acid for 1 h and filtered. The filtrate was washed with aqueous HCl. The desired product was isolated from the organic layer in 80% yield and 95% purity.

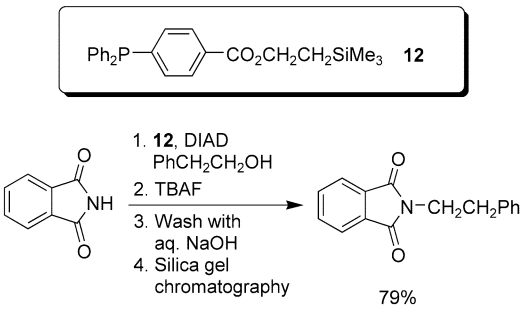
Mitsunobu reagents with masked acids: Flynn and co-workers have designed modified reagents **10** and **11**, carrying a *tert*-butyl ester as the masked acid tag [Eq. (11)].[33] A Mitsunobu reaction was carried out between benzoic acid and



(11)

octanol by using **10** and **11**. Trifluoroacetic acid was added to hydrolyze the *tert*-butyl esters releasing the masked acids. The mixture was then passed through a basic ion-exchange resin to sequester the acid-tagged Mitsunobu byproducts, and pure octyl benzoate was collected.

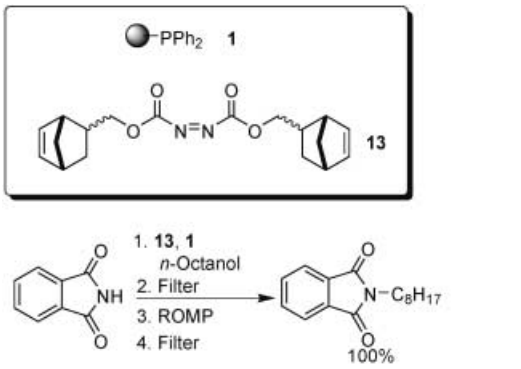
Yoakim and co-workers have used phosphine **12** containing a trimethylsilyl ethyl ester as the masked acid tag [Eq. (12)].[34] For example, phthalimide was alkylated with phenethylalcohol by using **12** and DIAD. After completion of the reaction, a solution of tetrabutylammonium fluoride in THF was added to release the carboxylic acid functional



(12)

group after loss of ethylene. The crude mixture was washed with aqueous sodium hydroxide to remove the acid-tagged phosphine oxide (structure not shown). After silica-gel chromatography to remove dicarboisopropyloxyhydrazide, *N*-phenethylphthalimide was isolated in 79% yield.

Impurity annihilation strategy for Mitsunobu reactions: Barrett and co-workers have introduced a new technique named "impurity annihilation" for removing the Mitsunobu byproducts by filtration after polymerization.[35] Modified azodicarboxylate **13**, incorporating two norbornene groups, was used along with polymer-bound triphenylphosphine for promoting the Mitsunobu reaction of phthalimide and octanol [Eq. (13)]. The polymer-bound phosphine oxide was sep-



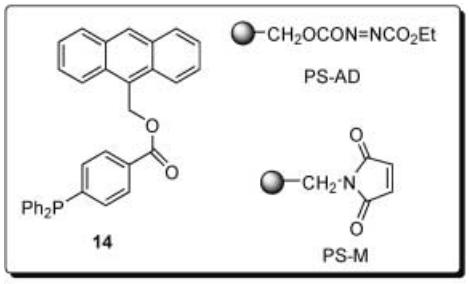
(13)

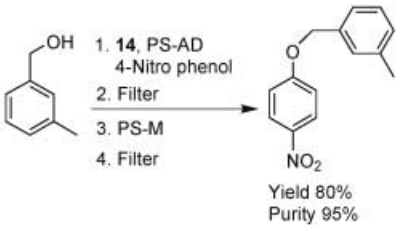
arated by filtration, and the crude reaction mixture was then treated with Grubbs catalyst [PhCH=Ru(PCy$_3$)$_2$Cl$_2$] to effect ring-opening metathesis polymerization (ROMP) of the norbornene-tagged hydrazide derived from **13**. The new polymer was then separated by filtration to give the pure Mitsunobu adduct in 100% yield.

A homogeneous Mitsunobu reaction could be performed with **13** and a norbornenyl-tagged phosphine, but under those conditions the subsequent ROMP failed, presumably due to inhibition of polymerization by the soluble phosphine.

Capture of a Mitsunobu byproduct onto a polymer support: Recently, Parlow and co-workers have introduced anthra-

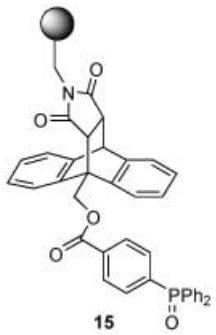
cene-tagged phosphine **14** for use in separation-friendly Mitsunobu reactions [Eq. (14)].[36] The Mitsunobu reaction of 4-nitrophenol and *m*-methylbenzyl alcohol was promoted by anthracene-tagged phosphine **14** and polymer-supported





(14)

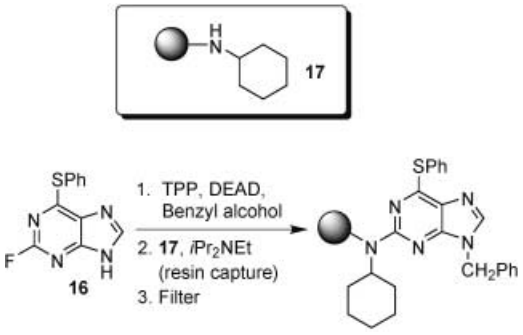
azodicarboxylate (PS-AD). After filtration to remove the polymer-supported hydrazide byproduct, the filtrate was treated with polymer-supported maleimide (PS-M) to capture the anthracene-tagged phosphine oxide by a Diels–Alder reaction. The polymer-bound Diels–Alder adduct **15**



was then removed by filtration to give the desired Mitsunobu ether in 82% yield and 95% purity. A library of 20 Mitsunobu products was synthesized and purified by this protocol.

Product purification by capture and release: The Mitsunobu product obtained by using untagged reagents can be purified by "capture and release" principle when suitable functional motifs are introduced in one of the substrates (alcohol or the pronucleophile). Such an approach necessitates at least two additional reactions—one for capture and one for release. However, if additional reactions are conducted on the solid phase subsequent to capture, then the capture and release reactions do double duty.

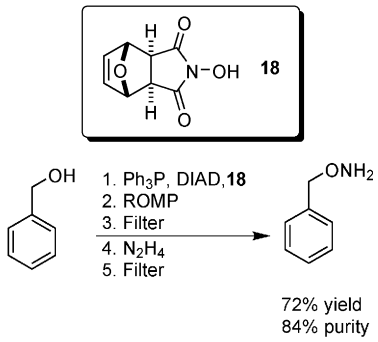
Schultz and co-workers conducted a Mitsunobu reaction between the fluoropurine derivative **16** and benzyl alcohol in solution by using TPP and DEAD [Eq. (15)].[37] The Mitsunobu product (not shown) was captured by an amino-defluorination reaction employing polymer-supported amine **17** and the reaction mixture was then purified by filtration.



(15)

The polymer-bound purine derivative was taken through other steps on solid phase before it was released (not shown). A library of substituted purines was prepared by a combination of solution-phase Mitsunobu reactions followed by solid-phase capture. The extra effort involved in carrying out additional reactions is partially offset by the introduction of diversity at the capture stage. Since the captured Mitsunobu product serves as the starting point for solid-phase combinatorial synthesis, an extra step for attaching the substrate to the solid support is not needed.

Hanson and co-workers have used a ROMP-based separation strategy by tagging the substrate [Eq. (16)].[38] Modified *N*-hydroxysuccinimide **18** was reacted with benzyl alcohol by employing TPP and DIAD. Subjection of the crude reaction mixture to ROMP generated a solid polymer that was separated by filtration. *O*-Benzylhydroxylamine was then released by treating the polymer with hydrazine. The generality of this approach was tested by preparing seven other *O*-alkylhydroxylamines.



(16)

Conclusions and Outlook

The various strategies available for product isolation in Mitsunobu reactions are presented in this article. The strategies are classified based on the type of separation tag that is

used, the species that is tagged, and the protocol for separation. Reagents with suitable separation tags including polymers and fluorous tags allow Mitsunobu products to be isolated with no additional reactions. However, since two insoluble polymeric reagents cannot be used simultaneously, the use of one polymeric reagent is often coupled with another type of tagged soluble reagent. This approach illustrates an ability to "mix-and-match" that is inherent in most of the methods in this overview. Several modified Mitsunobu reagents render ready separation of the product after a phase-switching reaction. When substrates are tagged, standard soluble organic reagents like DIAD and triphenylphosphine can be used, and a detagging reaction is required to release the desired product. Although two additional reactions are required, strategies based on "capture and release" have also found use in specific cases of Mitsunobu reactions.

Efforts to design separation tags for facilitating purification of reaction mixtures have gained considerable momentum in the recent years, and the Mitsunobu reaction has begun to serve as a focal point. Since a large number of tags have been tested for their applicability in Mitsunobu reactions, it makes sense to test new tags in Mitsunobu reactions as well to provide a touchstone to prior work. Perhaps more importantly, the methods, tags, and concepts highlighted in this article on the Mitsunobu reaction are generalizable and can be directly applied to many other transformations.

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