Tag Strategy for Separation and Recovery

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Contents

I. Introduction

The purpose of organic synthesis is to produce useful organic compounds with high efficiency. Organic chemists have tended to focus on the efficiency of reactions and competence of synthetic strategies. It is important to recognize, however, that total efficiency of synthesis is also limited by the ability to separate and isolate products in a pure form. Although substantial efforts have been made to develop new efficient reactions, it is highly necessary to develop strategic separation protocols that are generally applicable for various structural types of compounds.[1]

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With the advent of high-throughput chemistry,[2] the importance of separation protocols has been increasingly recognized in laboratory synthesis. Paradigm shift from the synthesis of mixtures of millions of compounds to the parallel synthesis of libraries that constitute pure compounds facilitates this trend. It should also be kept in mind that high-throughput synthesis relies on the automation of synthesis.[3] This means separations should be automated as well as reactions. Separation of products from unchanged starting materials, excess reagents, and catalysts is the key issue of high-throughput synthesis. Separation protocols, which are easily automated to enable rapid purification by simple operations, are highly called for.

In the development of industrial processes, separation is also important. Efficient separation of catalysts and reagents to enable their reuse for subsequent cycles of reactions are key challenges. Especially in the stream of green chemistry, separation protocols that allow for effective recovery of reagents and catalysts have been increasingly appreciated.

Thus, separation is one of the central issues of organic synthesis in this century, and several fundamental approaches have been studied to propose a solution to this problem. Among these approaches, the concept of phase tag has emerged as a powerful tool for strategic separation and recovery.[4] This article will provide an outline of the principle of phase tag and its applications, with special emphasis on recovery of reagents and catalysts.

II. Background

A. Phase Separation

Separation is an operation that moves a certain chemical entity apart from other chemical entities. In organic synthesis, separation is a molecular-level operation and, therefore, it is not a technical issue but a scientific issue. Generally, it is not an easy task to separate a certain kind of molecules from other kinds of molecules in a homogeneous system. To separate a certain kind of molecules in a homogeneous mixture, molecular recognition is necessary. Therefore, separation is usually carried out in multiphase system.

Phase can be defined as a discrete homogeneous part of a material system that is mechanically separable from the rest. If two phases are present, they are easily separated mechanically by simple operation (Scheme 1). For example, a solid phase can be separated from a solution phase by simple filtration. It should be noted that filtration is an operation

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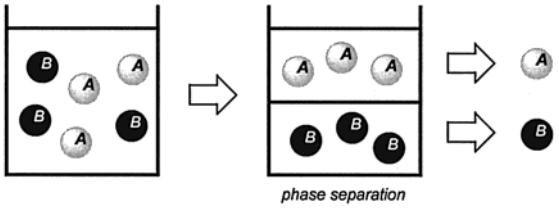
Scheme 1

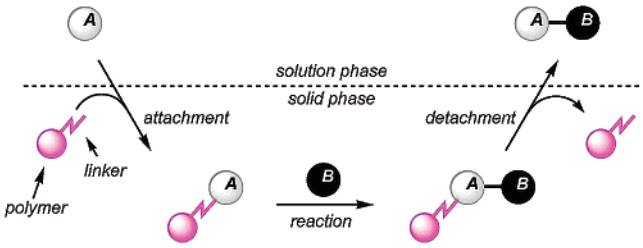


of phase separation that separates a solid phase from a solution phase. Generally, in phase separation, a certain chemical entity that is predominantly or exclusively present in one phase is separated by mechanical operation from other chemical entities in the other phase. In other words, phase separation makes the molecular-level separation into a macroscopic mechanical separation of two phases.

B. Solid-Phase Synthesis

Although phase separation is a powerful method for separation and recovery, its effectiveness lies in the natural phase affinity of compounds to be separated. Phase affinity of molecules, however, varies significantly with structural change, and therefore, it is rather difficult to develop a general method for separation that is applicable to a wide variety of compounds. Solid-phase synthesis has emerged as a key strategy to overcome this problem (Scheme 2).[5]

Scheme 2



In solid-phase synthesis, substrate molecules are bound to insoluble polymer resins by covalent bonds, and reactions are performed on the resins using soluble reagents and catalysts. The product is always present in the solid phase irrespective of the nature of the product molecule, because it is bound to the insoluble polymer backbone. Thus, the polymer-bound product can be easily separated from catalysts, excess reagents, or byproducts in the solution phase by simple filtration. This key advantage of solid-phase synthesis enables automated synthesis of peptide, DNA, and a variety of organic molecules in a combinatorial way. However, solid-phase synthesis often suffers from disadvantages of limited scale, high price of solid support, low reactivity in the resin-bound media, and difficulties on product analysis. Therefore, a new solution-phase protocol to overcome the problem of product separation has been strongly desired.

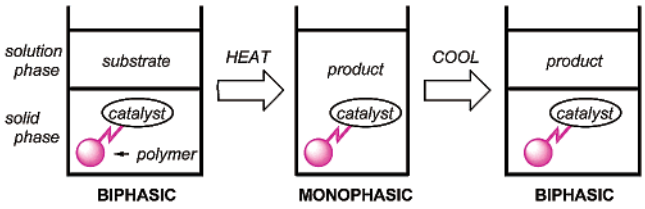
C. Polymer-Assisted Solution-Phase Synthesis

Recently, new solution-phase protocols having the advantages of easy separation like that of solid-phase synthesis have been developed. For example, polymer-assisted synthesis has emerged as a promising approach in solution-phase synthesis and enjoys fast-growing applications. This section provides a brief outline of such protocols.

Soluble polymer-supported synthesis (liquid-phase synthesis)[6] utilizes a polymer that is soluble in a variety of organic solvents for conducting reactions in solution phase but can be precipitated out of solution for purification purposes after a reaction.[7] Poly(ethylene glycol) (PEG) polymers have been found to be effective for this purpose because they are soluble in DMF, CH_2Cl_2, toluene, CH_3CN, water, and MeOH, but insoluble in Et_2O, *tert*-butyl methyl ether, *i*-PrOH, and cold EtOH. Polymer supports in

catalysis are especially effective for catalyst separation and reuse.[7] The reactivity of catalysts is controlled through the temperature- or solvent-dependent phase separation of the polymeric ligand. Such phase separation also facilitates the recovery of catalysts from reaction mixtures. Thermomorphic catalyst[8,9] is one of the most intriguing examples of this approach (Scheme 3). Related to soluble polymer-

Scheme 3

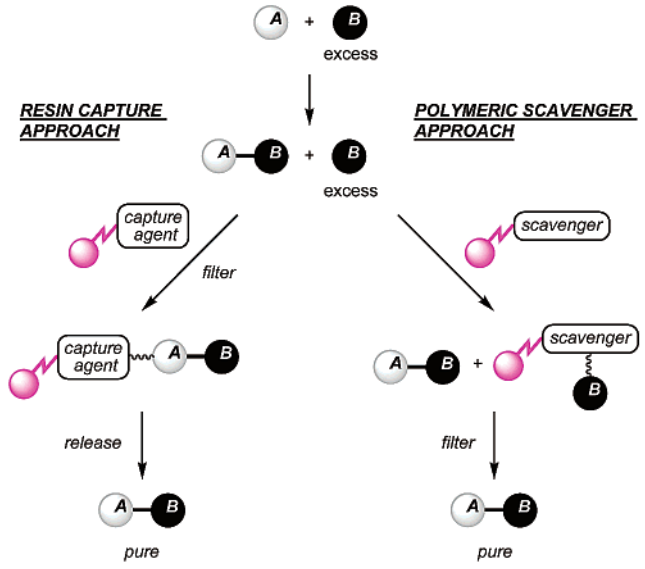


supported synthesis, dendrimer-supported synthesis has been developed[10] in which the purification is effected by size-based separation techniques such as size-exclusion chromatography.

Polymer-aided solution-phase synthesis that utilizes insoluble polymer is also an effective approach. For example, polymer-supported reagents[11] and catalysts[12] have been developed, enabling easy separation of products. Products in solution phase are separated from excess reagents, byproducts derived from reagents, and catalysts by simple filtration. Microencapsulation,[13] which utilizes a polymer to physically envelop, support, and immobilize a catalyst or a reagent, is also a fascinating approach for polymer-assisted solution-phase synthesis.

In the polymeric scavenger approach,[14] byproducts and excess reagents are selectively removed from solution via binding, such as covalent bond formation, to an insoluble polymer (Scheme 4, right). The resin

Scheme 4



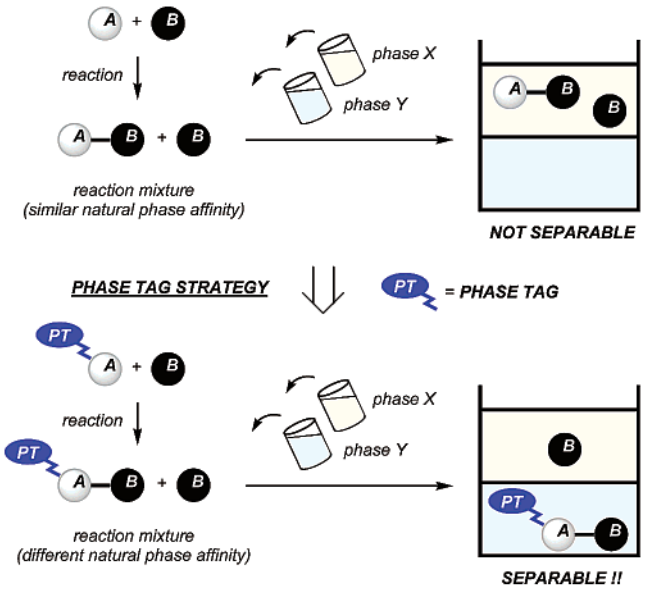
capture approach[15] involves capture of products rather than reagents or catalysts (Scheme 4, left). Products are formed in solution-phase reaction. After the reaction, they are captured on a polymer resin to separate them from reagents or catalysts by filtration. In the final stage, the products are released from the polymer resin back into solution by suitable transformation. Sometimes subsequent solid-phase transformations are carried out on the polymer resin before cleaving.

III. Tag Strategy for Phase Separation

Polymer-aided solution-phase synthesis, described above, utilizes polymers as the aid for solid/solution phase separation. Polymers constitute a solid phase on the occasion of separation. Therefore, the substance bound to the polymer can be easily separated from other substances by simple filtration. There is, however, another type of approach that utilizes relatively small functional groups to facilitate phase separation. Such functional groups are called tags for phase separation or phase tags.[16]

In general, a tag[17] is a group of atoms or a molecular fragment that is attached to a molecule for identification. But in some cases a tag is used to give a particular nature to a molecule. Several types of tags, such as affinity tags and fluorescent tags, have been widely used in the field of chemistry and biochemistry. A tag that facilitates phase separation is called a phase tag (Scheme 5). A phase tag is a

Scheme 5

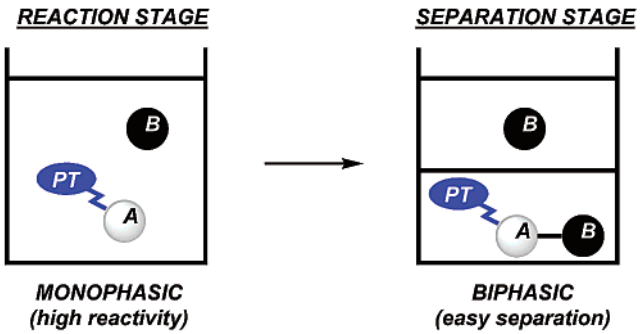


functional group attached to a molecule to control the favorable phase of the parent molecule in phase separation. In other words, a phase tag changes the natural phase affinity of the molecule. Therefore, it is easy to separate tagged molecules, that have strong interaction to a phase determined by the tag, from other untagged molecules, which have natural phase affinity (Scheme 5). Such phase separation includes liquid/liquid extraction, solid/liquid extraction, and filtration. In the phase tag protocol, a range of reactions can be conducted under homogeneous traditional conditions because all chemical entities that participate in reactions are relatively small molecules, yet the products can still be easily separated by a simple phase separation. Easy monitoring of reactions by routine methods such as TLC, GC, and

HPLC is also an advantage of tag strategy. Easy identification of intermediate products by conventional spectroscopy such as solution-phase NMR during the course of multistep syntheses is also advantageous.

Generally, a monophasic system is advantageous for reactions although a biphasic (or multiphasic) system is essential for phase separation (Scheme 6).

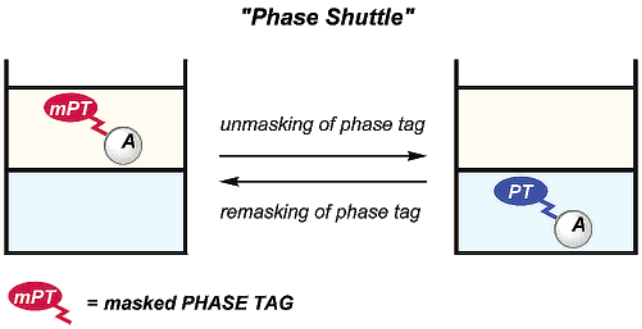
Scheme 6



Heterogeneous reactions usually proceed less effectively than the homogeneous counterparts. One of the most popular approaches to solve this problem is the use of a solvent that dissolves both tagged compounds and untagged compounds. After the reaction is finished, the solvents are changed to form a biphasic system. Sometimes temperature-dependent miscibilities or solubilities are used to switch from monophasic systems to a biphasic system.[7−9]

Another approach to this issue is masking of tags (Scheme 7). In some cases, tags are masked so that

Scheme 7



tagged compounds retain their natural phase affinity. Thus, reactions can be conducted under homogeneous conditions in organic solvents. After the reaction, however, the tag is converted into its active form to effect separation of the tagged compound from untagged compounds. A typical example of this case is acid/base extraction. For example, an ammonium ion tag is unmasked by protonation of the corresponding amine tag and the tagged compound is extracted from the organic phase into acidic aqueous phase. Remasking of the tag by neutralization enables reextraction of the tagged compound into the organic phase (phase switching). In such a case, the tag is not a simple tag, but a phase-trafficking tag[18] or "phase shuttle", because it facilitates the back-and-forth movement of molecules from one phase to the other.

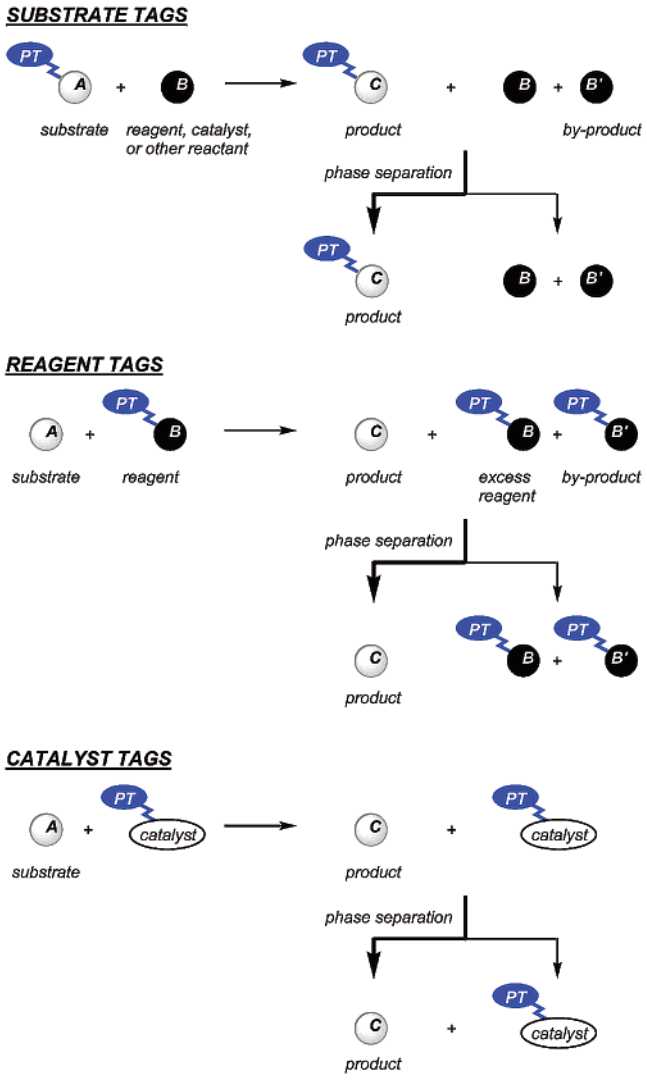
In some other cases, tags are introduced after the reaction. Thus, the reaction can be conducted under homogeneous conditions. In this case, however, highly chemoselective tagging is needed to discriminate the compound to be tagged and other compounds (Section V-B).

IV. Classification of Phase Tags Based on Parent Reaction Component

To understand the utility of tag strategy in organic synthesis, it is convenient to classify phase tags. Based on parent reaction components, phase tags can be classified into three categories, i.e., (1) substrate tags, (2) reagent tags, and (3) catalyst tags.

Substrate tags are tags that are introduced to substrate molecules or starting materials of particular reactions or transformations (Scheme 8). This

Scheme 8



approach is quite similar to solid-phase synthesis, where substrate molecules are bound to insoluble polymer beads. In the substrate tag approach, an appropriate tag is introduced (tagging) to a substrate, which is then subjected to some chemical transformation(s). The tagged product thus obtained is separated by phase separation. In the last stage, the

tag is cleaved (detagging) by a suitable chemical reaction to obtain the final desired product. It is important to note that the substrate tag approach is effective for reagent and catalyst recovery, because untagged reagents and catalysts can be easily separated from tagged products by phase separation (vide infra).

Reagent tags are tags that are introduced to reagent molecules (Scheme 8). This approach is related to polymer-supported reagents. After the reaction is finished, excess reagents and used reagents are separated from products by phase separation with the aid of the tag. The recovered reagents may be reactivated by some chemical transformation to be used for the next cycle of the reaction.

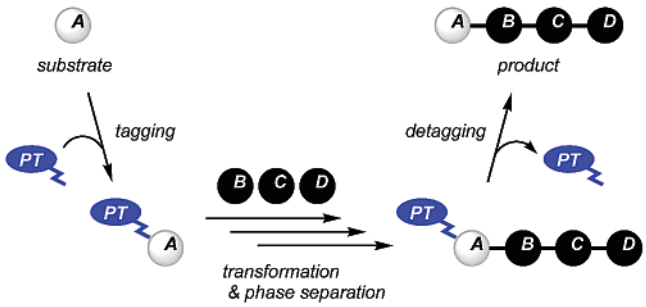
Although in organic chemistry it is often very hard to draw a distinct line between substrate and reagent, substrate tags and reagent tags are distinctly defined in this article as follows. Substrate tags are the tags that are still bound to the desired organic product after reaction. Reagent tags are the tags that are not bound to the desired product.

Catalyst tags are the tags that are attached to catalyst molecules (Scheme 8). This approach has an analogy with supported catalysts. After the reaction, the tagged catalyst is separated from a reaction mixture by phase separation and recovered for the next cycle of the reaction.

A. Substrate Tags

A number of synthetic transformations using tagged substrates have been developed to enable purification by simple phase separation. By using a substrate tag, multistep synthesis can be conducted in a fashion similar to that of solid-phase synthesis (Scheme 9).

Scheme 9



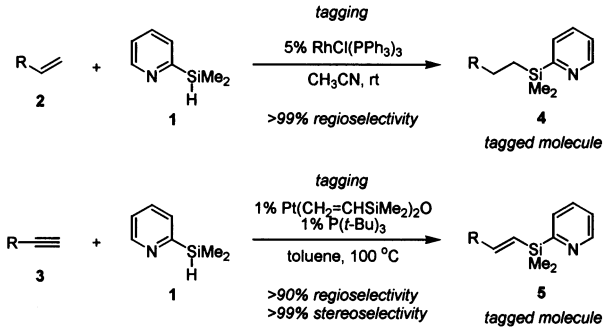
In the first step, a suitable tag is introduced to a substrate (tagging). In the second step, some transformations are carried out. After each step of the transformation, an intermediate product is purified by phase separation with the aid of the tag. In the last step, the tag is removed to liberate the final desired product (detagging).

1. Requirements for Substrate Tags

It should be pointed out that substrate tags should meet, in general, the following requirements: (1) it should be easily introduced to a starting molecule (tagging); (2) it should be stable under the conditions of desired chemical transformation(s); (3) it should not interfere with or disturb desired chemical transformation(s); (4) it should effectively change the phase affinity of the molecule to ensure effective phase separation; and (5) after the transformation is completed, a tag should be removable from the product without affecting other functional groups in the molecule (detagging).

Let us briefly touch an example of substrate tags to see how these requirements are fulfilled in reality. Dimethyl(2-pyridyl)silyl (2-PyMe$_2$Si) tag[19,20] is an acid/base phase tag (see Section VI-B) which enables the easy purification of the tagged compounds by simple acid/base extraction process. The tagging of 2-PyMe$_2$Si group can be easily accomplished by the metal-catalyzed hydrosilylation reaction using 2-PyMe$_2$SiH (**1**) as a tagging agent. For example, the hydrosilylation of alkenes **2** can be achieved with the aid of Rh catalyst to afford the corresponding tagged molecule **4** in excellent regioselectivity (Scheme 10).[19,21,22] The hydrosilylation of alkynes **3** was

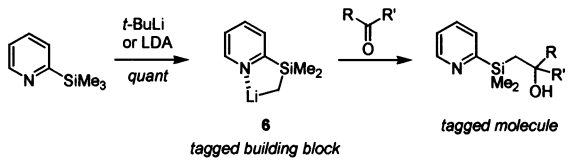
Scheme 10



achieved with Pt/P(*t*-Bu)$_3$ catalyst to yield alkenylsilane-type tagged molecule **5** in good regioselectivity (Scheme 10).[22] These are the very general and straightforward ways to introduce the 2-PyMe$_2$Si acid/base phase tag into organic molecules.

The most straightforward means of tagging is to simply attach a tag to a parent molecule. Hydrosilylation is an example of such cases. There is, however, another approach that utilizes synthetic building blocks having a tag. Tagged molecules can be synthesized by some transformation(s) using such building blocks. For example, 2-PyMe$_2$Si tag can be introduced using 2-PyMe$_2$SiCH$_2$Li (**6**) as a building block (Scheme 11).[23]

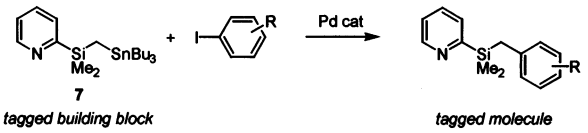
Scheme 11



The following cases also serve as examples of the use of a tagged building block.

Organostannane 2-PyMe$_2$SiCH$_2$SnBu$_3$ (**7**) was found to react with aromatic halides in the presence of Pd catalyst.[24] 2-PyMe$_2$SiCH$_2$ group was selectively transferred onto Pd and coupled with the aromatic group (Scheme 12). This reaction serves as an effective

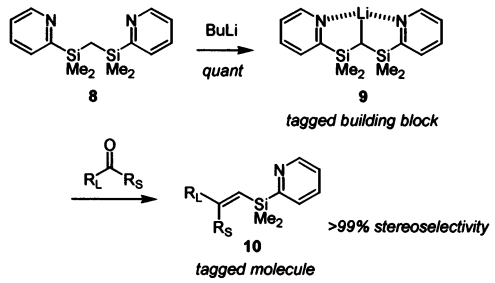
Scheme 12



method for the introduction of a tagged methylene, 2-PyMe$_2$SiCH$_2$ group, into organic compounds.

Organolithium (2-PyMe$_2$Si)$_2$CHLi (**9**) generated from (2-PyMe$_2$Si)$_2$CH$_2$ (**8**) was found to react with various carbonyl compounds giving the corresponding alkenylsilanes **10** by the well-known Peterson-type elimination process (Scheme 13).[25] The reaction

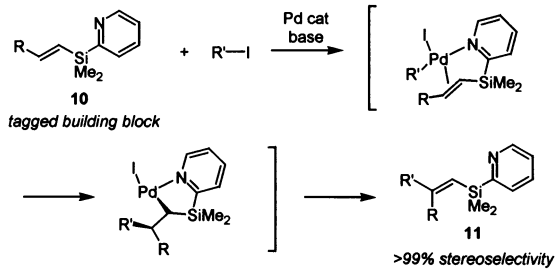
Scheme 13



proceeds in a virtually complete stereoselective fashion.

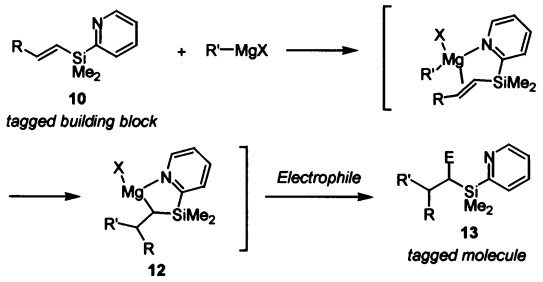
Thus obtained alkenyldimethyl(2-pyridyl)silanes **10** also serve as useful building blocks bearing a 2-PyMe$_2$Si group. For example, Mizoroki−Heck-type reactions proceed with the aid of a Pd catalyst to give substituted alkenyldimethyl(2-pyridyl)silanes in a regio- and stereoselective fashion (Scheme 14).[26,27]

Scheme 14



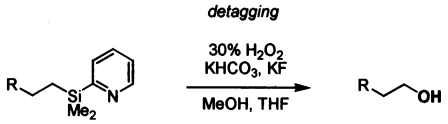
Grignard reagents also add to such alkenyldimethyl(2-pyridyl)silanes **10** under very mild conditions, and the thus-obtained α-silyl organomagnesium compounds **12** react with various electrophiles to afford a highly functionalized molecule having a 2-PyMe$_2$Si tag (Scheme 15).[28]

Scheme 15



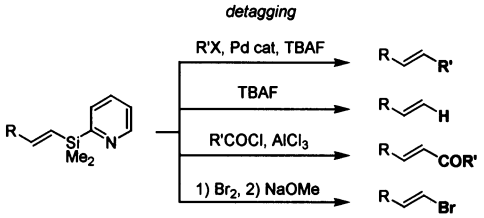
In tag strategy, it is essential that the tag is removed from the final product (detagging). Otherwise it cannot be used as a tag. Detagging of the 2-PyMe$_2$Si group can be accomplished in several ways. For example, detagging of a 2-PyMe$_2$Si group from alkyl groups can be achieved effectively by H_2O_2 oxidation (Tamao−Fleming-type oxidation)[29,30] which affords the corresponding alcohol as the final product (Scheme 16).

Scheme 16



There are other options for detagging when the 2-PyMe$_2$Si group is attached to an alkenyl group (Scheme 17). For example, Pd-catalyzed Hiyama-type

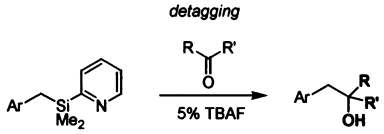
Scheme 17



coupling proceeds smoothly in the presence of fluoride to cleave the C−Si bond, providing the substituted olefins as the final products.[27,31] This example demonstrates the possibility that useful chemical transformation can be achieved on the occasion of detagging. It is also important to note that treatment of alkenyldimethyl(2-pyridyl)silanes with fluoride leads to simple protodesilylation. This is an example of traceless detagging. Detagging can also be accomplished by the reaction with other electrophiles such as acid chlorides or bromine (Scheme 17).[25]

The benzyldimethyl(2-pyridyl)silanes, obtained in the Pd-catalyzed Stille-type coupling (Scheme 12), add to the carbonyl compounds in the presence of a catalytic amount of fluoride ion giving the secondary and tertiary alcohols in good yields (Scheme 18).[24]

Scheme 18



This method is also useful for the detagging of a 2-PyMe$_2$Si group.

The chemical stability of a tag is a crucial factor. If a tag is destroyed during the course of a synthetic transformation, phase separation cannot be performed with the aid of the tag. The inactiveness of a tag is also an important factor. If a tag kills a catalyst or a reagent, it cannot be used as a tag any more. It should, however, be kept in mind that there could be tags that affect the reactions in a positive manner. In such cases, tags activate substrate and facilitate reactions that are otherwise difficult to achieve efficiently. For example, the 2-PyMe$_2$Si group dem-

onstrated in this section not only serves as a phase tag but also functions as a reagent- and catalyst-directing group[19−28,32] by taking advantage of pyridyl-to-metal coordination (complex-induced proximity effect, CIPE).[33]

The requirement for detagging is somewhat contradictive to the stability of tags. The easy removal of a tag (detagging) under mild conditions is required because undesirable side reactions which destroy the desired product should be avoided in the last part of synthesis. The tag, however, should not be removed under the conditions of chemical transformations prior to detagging. Therefore, the conditions for detagging should be quite different from those used for the transformation.

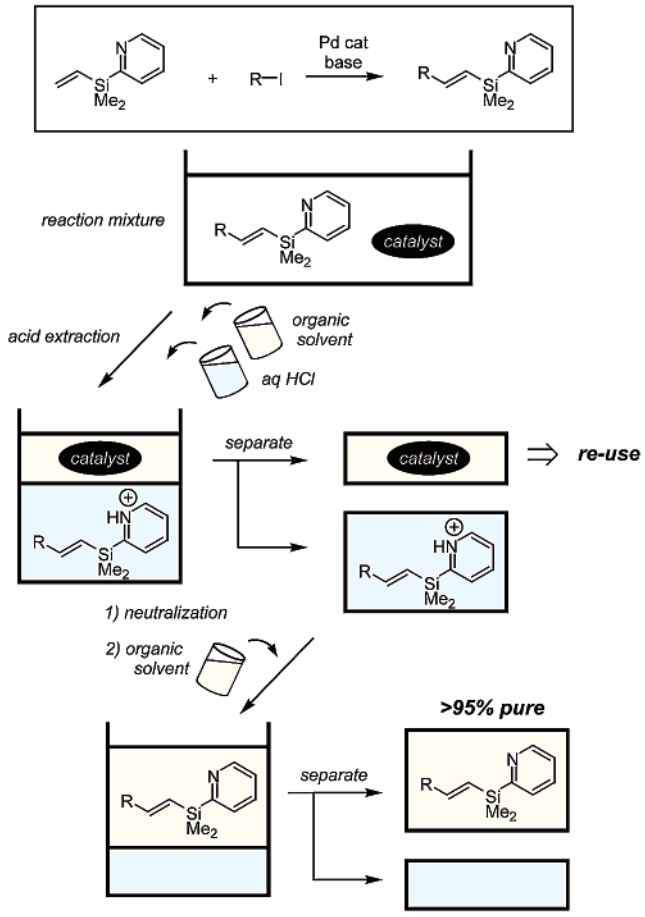
The loading capacity of a tag for phase separation is also a very important factor. There are no tags of infinite capacity. The ability of a tag should depend on the size of the attached molecule and the nature and the number of functional groups in the molecule. Therefore, it is important to choose a suitable tag by taking these factors into account.

2. Catalyst Recovery Using a Substrate Tag

It should be noted that the substrate tag approach is effective for the recovery and reuse of reagents and catalysts, because easy separation of products means easy separation of reagents and catalysts.

The following Mizoroki−Heck-type reaction using a 2-PyMe$_2$Si tag serves as a good example of this case (Scheme 19).[26,27] Alkenes having a 2-PyMe$_2$Si tag

Scheme 19



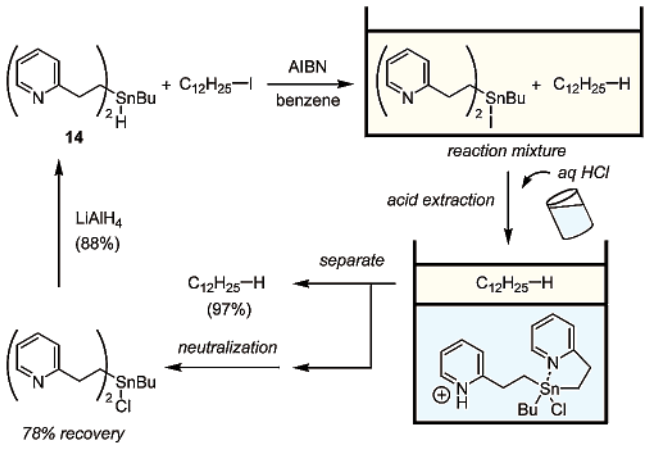
cross-coupled with a variety of aryl, heteroaryl, and alkenyl iodides in the presence of a Pd catalyst (Scheme 14). By taking advantage of the phase tag property of the 2-PyMe$_2$Si group, products were isolated by simple acid/base extraction. Acid extraction of the reaction mixture transferred the product to the aqueous phase, while the catalyst and excess reagent (organic iodide) remained in the organic phase. Neutralization of the aqueous phase and subsequent extraction with organic solvent retransferred the product to the organic phase. Finally, evaporation of the organic solvent afforded the products. The important fact is that the Pd catalyst was recovered from the initial organic phase in the acid extraction purification process, leading to the consecutive use for the next run. In fact, the Pd catalyst recovered in this manner was used in the second, third, and fourth runs without eroding the catalytic activity. This example demonstrates the effectiveness of substrate tags for the recovery of catalyst. The catalyst in hydrosilylation reaction of alkenes with 2-PyMe$_2$SiH was also recovered by acid/base extraction.[22]

B. Reagent Tags

Requirements for reagent tags are somewhat different from those for substrate tags. Factors of easy introduction and removal are not so important. There is no need for removing the tag from the reagent after the reaction. Stability under the reaction conditions and inactiveness toward substrate molecules are, however, essential factors. The following tin hydride reagent having pyridyl groups demonstrates the utility of reagent tags.

Tin hydride **14** having two pyridyl groups was reported to reduce organic iodides effectively (Scheme 20).[34] The resulting tin halide was completely sepa-

Scheme 20



rated by acid extraction and recovered by the follow-up base extraction. The reduction of the recovered tin halide regenerated tin hydride **14**, which could be reused for the next run. It is noteworthy that the tin halide having only one pyridyl group could not be separated in a similar fashion. This is probably because the first pyridyl group was utilized for the

coordination to tin and only the second pyridyl group participated in the protonation that was required for acid extraction.

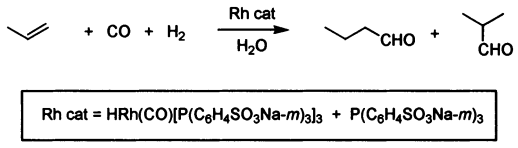
4-Pyridylethyldiphenyl tin hydride is also known, but this compound was reported not to be fully extracted from ether solutions by 6 N *aq* HCl.[35] High polarity due to the pyridyl group, however, facilitates chromatographic separation.

C. Catalyst Tags

In the system using catalyst tags, the organic product remains usually in the organic solution phase and the catalyst is present in another phase that is determined by the nature of the tag. Thus, phase separation enables easy separation of the product from the catalyst as well as easy recovery of the catalyst, which would be recycled for further use.[36] Similar to reagent tags, there is no need to remove catalyst tags from the parent catalyst molecules. The chemical bond between the tag and the parent catalysts should be strong so that tagged catalysts survive during cycles of use.

There are quite a few examples of catalyst tags. Aqueous biphasic catalysis systems have been widely utilized, not only in laboratory synthesis but also as industrial product.[37] The "Ruhrchemie/Rhône-Poulenc (RCH/RP) process", which has been enjoying industrial practice since 1984, is one of the most popular aqueous biphase catalyst systems. In this process, water-soluble Rh catalyst bearing phosphine ligands tagged with hydrophilic groups, $HRh(CO)[P(C_6H_4SO_3Na\text{-}m)_3]_3$, is used for the hydroformylation of alkenes (Scheme 21).[38] The use of an aqueous/

Scheme 21

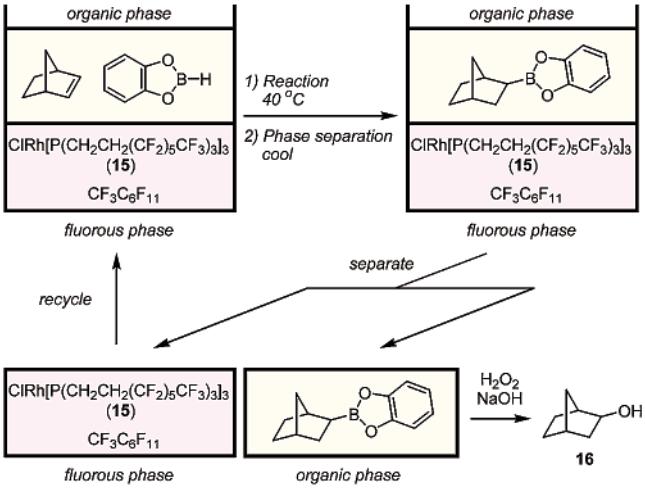


organic biphasic system, in which the aqueous phase contains the dissolved catalyst, affords a straightforward separation of the organic products. The reaction is considered to take place in the interphase region, not in the bulk aqueous phase.

An epoch-making example of catalyst tags is the use of fluorous biphase catalysts. Horváth and coworkers developed fluorous transition metal catalysts by appending perfluoroalkyl groups as tags to phosphine ligands.[39] The fluorous Rh(I) catalyst, which bears $P(CH_2CH_2(CF_2)_5CF_3)_3$ ligand, is soluble in $CF_3C_6F_{11}$ but insoluble in virtually all common organic solvents. A typical example of the use of fluorous catalyst tag is demonstrated by the following Rh-catalyzed hydroformylation of 1-decene. The reaction was carried out with $CF_3C_6F_{11}$ as the fluorous phase and toluene as the organic phase under CO/H_2 pressure at 100 °C. After the reaction was completed, the two phases were separated under N_2. Hydroformylation products (undecanals) were isolated from the upper organic phase. The lower fluorous phase containing the catalyst can be reused for the next hydroformylation reaction without eroding catalytic activity.

Hydroboration of alkenes catalyzed by the fluorous Rh catalyst $ClRh[P(CH_2CH_2(CF_2)_5CF_3)_3]_3$ (**15**) developed by Horváth and Gladysz also demonstrates the effectiveness of catalyst tags (Scheme 22).[40] A solu-

Scheme 22



tion of the fluorous Rh catalyst **15** in $CF_3C_6F_{11}$ was combined with catecholborane and an alkene with or without organic solvent, and the reaction was carried out at 40 °C. After the reaction, the product was extracted with THF. The remaining $CF_3C_6F_{11}$ solution of catalyst was reused for the next reaction. The organoborane product extracted to THF was oxidized to the desired alcohol **16**.

V. Classification of Phase Tags Based on Usage

A. Tagging Prior to Reaction

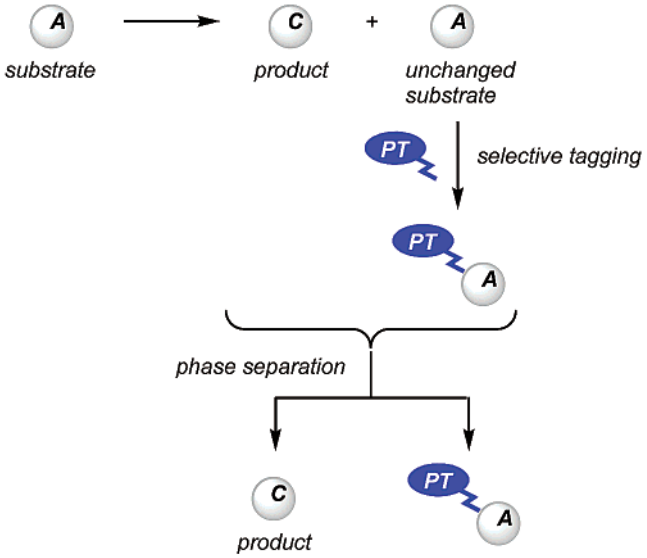
Tags are usually introduced to parent reaction components such as substrates, reagents, and catalysts prior to reaction as described above. Therefore, reactions are carried out with tagged molecules. This means that the tag should be inert to reaction conditions and should not interfere with the desired reaction. Sometimes tags are masked to avoid undesirable side reactions and unmasked after the reaction.

B. Tagging Posterior to Reaction

There is another approach in the usage of phase tags. In some cases, tags can be introduced selectively to a specific reaction component posterior to the reaction. For example, using chemoselective tagging of a starting substrate without affecting a product, the product can be separated from the unchanged substrate (Scheme 23). Some examples will be discussed in this section. This tactic might also be applied to reagent tags, although few examples have been reported in the literature.

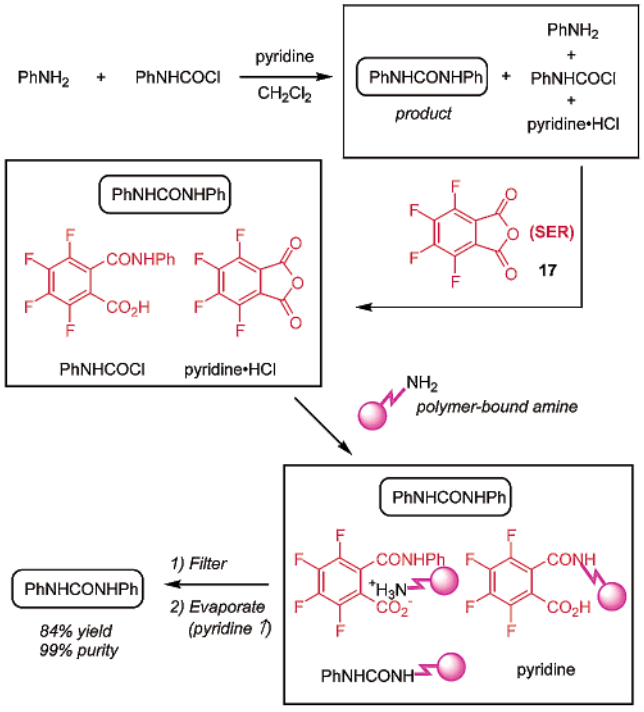
It is often necessary to remove excess substrate from a reaction mixture. Substrate tags discussed in the previous section are not effective for this purpose,

Scheme 23



because they are attached to both substrates and products. To solve this problem, Parlow and co-workers have reported an interesting approach that involves tagging after the reaction (Scheme 24).[41]

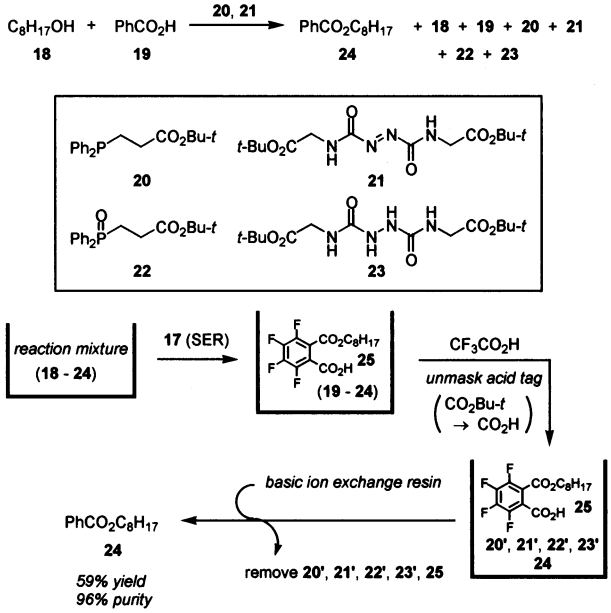
Scheme 24



They focused on the removal of amines from reaction mixtures. The tagging of amines is accomplished with tetrafluorophthalic anhydride **17** (sequestration enabling reagent, SER) to give the carboxylic acid-tagged compounds, which are removed (scavenged) by the treatment with the polymer-bound amine (see Scheme 4). It is important to note that the excess tetrafluorophthalic anhydride (**17**) and electrophile can also be scavenged by the polymer-bound amine by covalent bond formation. This method is successfully applied to the reaction of amines with acid halides, arenesulfonyl halides, and isocyanates.

Tetrafluorophthalic anhydride is also effective for tagging compounds having a hydroxy group (Scheme 25).[42] In the Mitsunobu reaction, unchanged hydroxy-

Scheme 25



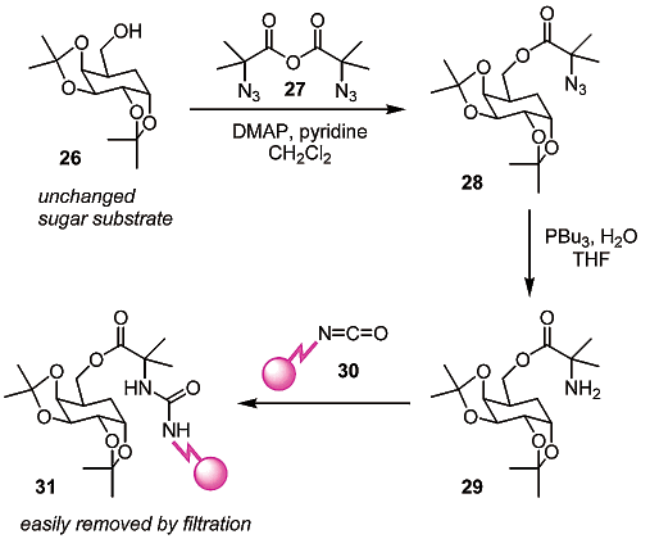
substituted substrate **18** was converted into the corresponding carboxylic acid-tagged compound **25**, which was easily removed (scavenged) by the treatment with basic ion-exchange resin. Excess nucleophile **19** was also removed by this process. The use of a phosphine and a carbodiimide, tagged with *tert*-butyl esters, was quite effective for the Mitsunobu reaction. The *tert*-butyl ester tag was then unmasked by the treatment with trifluoroacetic acid after the reaction. The Mitsunobu products **24** were easily removed from all other carboxylic acid-tagged byproducts.

Seeberger has developed an α-azidoisobutyric ester tag (A-tag) for the separation of unchanged sugar substrate in polysaccharide synthesis.[43] The treatment of the reaction mixture with the anhydride of α-azidoisobutyric acid **27** led to the formation of the ester **28** with unchanged sugar glycosyl acceptor **26**, which was removed effectively by the conversion of azide to amine by treatment with tributylphosphine followed by the treatment with an isocyanate silica gel scavenger **30** (Scheme 26). The product, which did not contain a free hydroxyl group, remained in the solution phase. This method has been successfully combined with solid-phase oligosaccharide synthesis.

VI. Classification of Phase Tags Based on the Nature of Preferred Phase

Let us turn our attention to the nature of phase that is used for phase separation. Usually organic molecules are soluble in organic solvents according to the principle of "like dissolves like", which means that the natural phase of organic compounds is organic solution phase. Therefore, the role of a phase

Scheme 26



tag for organic (or organometallic) substrates, reagents, and catalysts is to push the attached molecule to move into an unnatural phase such as solid phase, aqueous phase, or solution phase that is immiscible with the organic solution phase. Organic molecules tagged with such phase tags can be separated from other untagged organic molecules by simple phase-separating operations such as filtration and extraction.

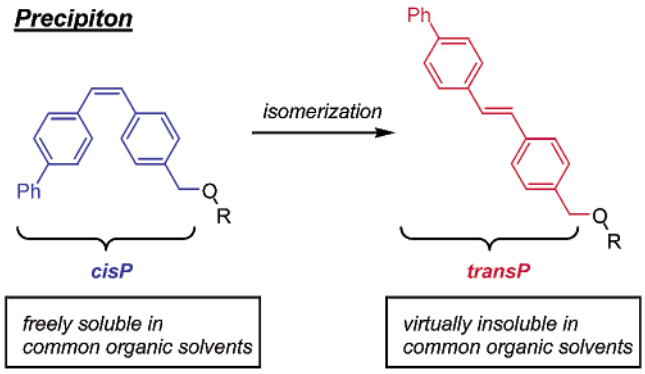
A. Tags for Solid Phase

Tags that make the attached molecules move to the solid phase can be utilized for solid/solution phase separation. The solid phase that contains the tagged compound is easily separated from the solution phase containing other untagged organic compounds by simple filtration. After the separation, the tagged molecule should be liberated from the solid phase by a suitable reaction. There are two types of tags in this category. One is the tag for precipitation. Such tags enforce precipitation of the attached molecule under some conditions. The other type is the tag for solid-phase (resin) capture. Such tags are used for binding of the attached molecules to solid support. Various interactions including covalent bond formation, coordination to polymer-bound metals, ionic interaction, hydrogen bonding, and van der Waals interaction have been used for such purposes.

1. Tags for Precipitation

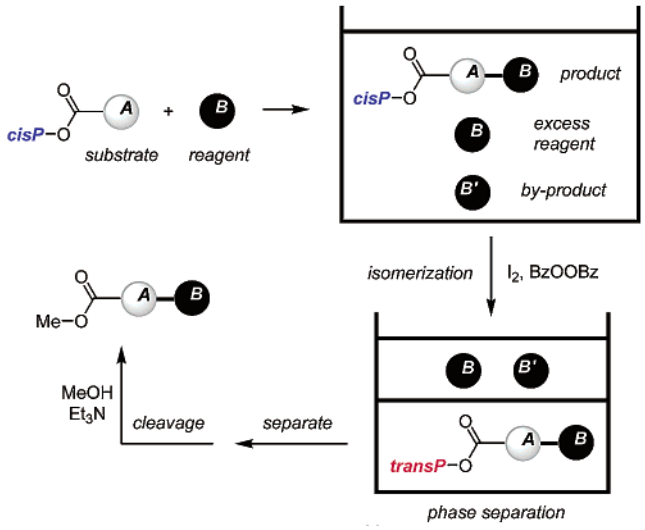
Wilcox developed a tag that changes the solubility of the attached molecule in common organic solvents upon isomerization and enforces precipitation.[44] He named this tag "precipiton". It is important to note that a precipiton behaves just like a normal organic group during a reaction (freely soluble in a given organic solvent) but it can be isomerized after the reaction to facilitate precipitation (quite insoluble in that solvent). Thus, a molecule attached to such precipiton can be isolated by simple filtration or centrifugation. A striking example of a precipiton is

Scheme 27



stilbene, because *cis*-stilbenes (**cisP**) are more soluble than *trans*-stilbenes (**transP**) in common organic solvents (Scheme 27). So, reactions are carried out with a molecule having **cisP** unit as a tag (Scheme 28). The tag is connected to the substrate molecule

Scheme 28



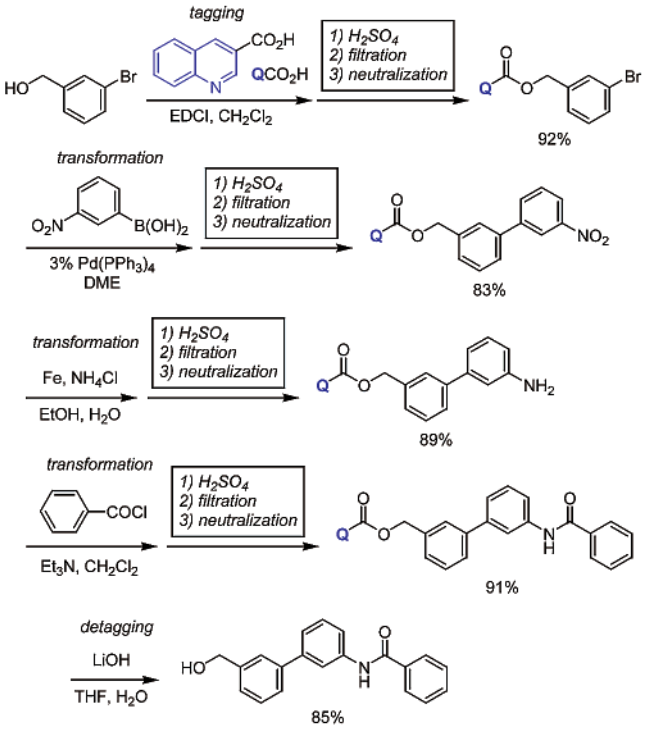
by ester linkage. After the reaction is completed, the carbon−carbon double bond in the tag is isomerized to trans with the aid of diphenyl disulfide or iodine/benzoyl peroxide. After the isomerization, the crude product is washed with Et_2O, MeOH, or hexanes to remove byproducts, and the sparingly soluble pure product is isolated by filtration.

The **transP**-bound products are, however, sufficiently soluble in THF to allow cleavage of the precipiton from the products by methanolytic transesterification in THF. Treatment with MeOH/Et_3N cleaves the ester linkage to afford the corresponding methyl ester (Scheme 28). To demonstrate the effectiveness of this method, nitrile oxide cycloaddition,[44] alkylation of β-ketoesters,[45] and Baylis−Hillman reaction[46] have been studied.

Recently, Wilcox has extended this precipiton method to reagent scavenging strategy in solution-phase synthesis.[47]

Perrier and Labelle developed a new strategy using a quinoline carboxylate (**Q**CO_2−) tag to effect separation of the desired reaction products from the reaction mixture by simple precipitation (Scheme 29).[48] The

Scheme 29



tag was attached to a substrate molecule by the ester linkage. After the transformation was completed, the addition of H_2SO_4 to a solution of the tagged product in organic solvents such as AcOEt and CH_2Cl_2 under rapid stirring deposited a precipitate, which was easily separated by filtration. Then, the precipitated quinolinium salt was neutralized to return the molecule back to the soluble form, which was used for the next transformation. The following example illustrates the utility of this method (Scheme 29).

Bromobenzene derivative tagged with quinoline carboxylate was coupled with 3-nitrobenzeneboronic acid in the presence of a Pd catalyst (Suzuki coupling). In the next step, the nitro group was reduced by Fe/NH_4Cl and the resulting amine was allowed to react with benzoyl chloride. In each step, the product was purified by acid precipitation/filtration protocol. In the final step, the tag was removed by hydrolysis of the ester linkage.

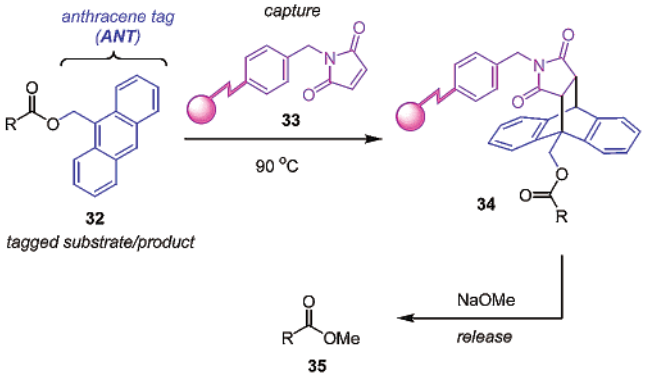
Recently, Tietze reported an interesting method for precipitation based on the formation of a betaine.[49] He carried out multicomponent domino reactions. The products thus obtained contained a 1,3-dicarbonyl unit with an acidic methylene group and an amino group; this led to the formation of a betaine, which could be precipitated by the addition of Et_2O. Although this is not a tag approach, this concept might provide a basic principle of new tags for precipitation.

2. Tags for Solid-Phase Capture

Another approach to solid/solution phase separation is the capture of a molecule to solid support such as polymer beads (Scheme 4). To bind the tagged molecule to solid support, covalent bond formation, coordination, ionic interaction, hydrogen bonding, and van der Waals interaction are used.

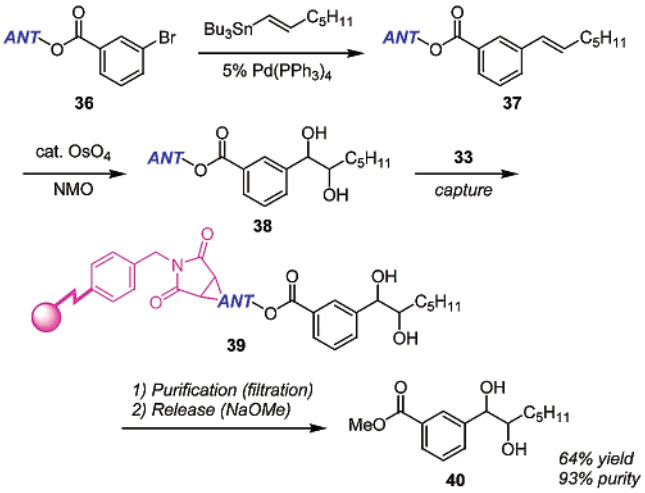
Proco developed a tag to facilitate product sequestration and overall purification by Diels−Alder resin capture/release processes (Scheme 30).[50] To accomplish resin capture, compound **32** having a tag containing anthracene moiety is allowed to react with a polymer-bound maleimide dienophile **33**. The release from the resin can be done easily by simple ester cleavage.

Scheme 30



The multistep transformation using this tag was carried out to demonstrate the utility of this method (Scheme 31). Pd-catalyzed Stille coupling followed by Os-catalyzed dihydroxylation afforded the tagged diol **38**. This diol was incubated with excess maleimide resin **33** to provide the resin-captured diol **39**. After resin washing and subsequent detagging (transesterification), the product **40** was obtained in high purity.

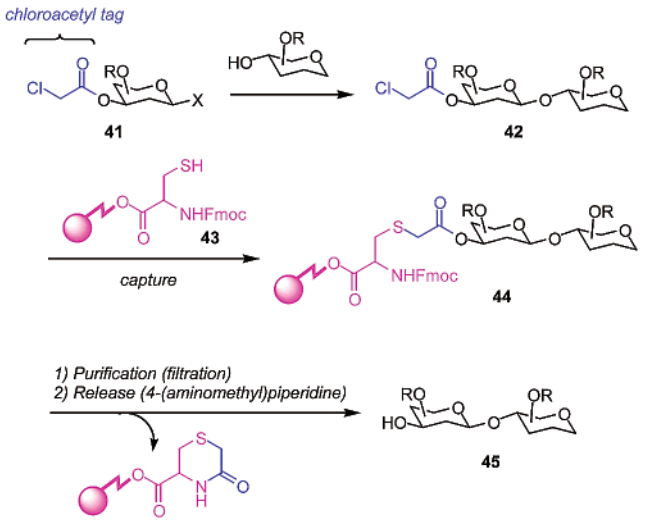
Scheme 31



Similar tags based on cycloaddition reactions have been developed. Keana reported a 1,3-diene-containing phase-transfer catalyst and its capture with triazolinedione dienophile bound to silica.[51]

Chloroacetyl group, which is used as a protecting group in oligosaccharide synthesis, can be utilized for solid-phase capture (Scheme 32).[52] Ito and co-workers reported that saccharides **42** tagged with chloroacetyl group were effectively captured by thiol-containing resin **43** (cystein-loaded Wang resin). Release of the product **45** was effected by treatment with 4-(aminoethyl)piperidine. This solid-phase capture/release

Scheme 32

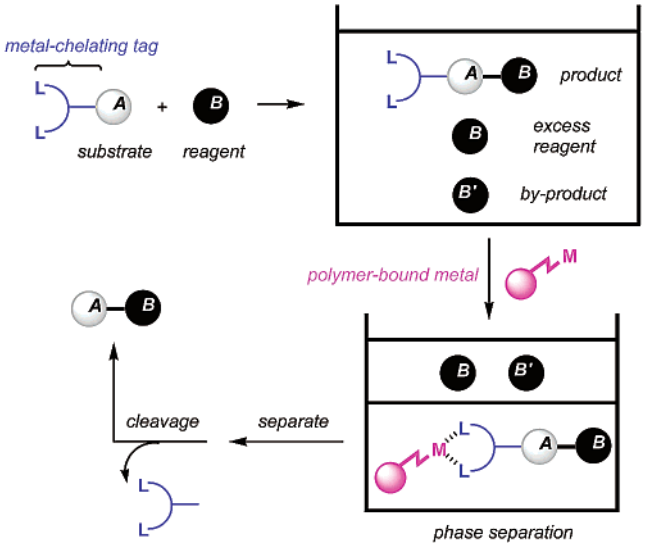


strategy combined with a low-molecular-weight polymer tag (vide infra) serves as a powerful method for oligosaccharide synthesis.

Fukase and Kusumoto have reported that products having a 4-azido-3-chlorobenzyl (ClAzb) tag could be selectively isolated (captured) from a reaction mixture by using a polymer-bound phosphine as a capturing agent.[53] After purification with filtration, detagging was easily accomplished by treatment with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ). Application to several oligosaccharide syntheses is also described.

Coordination to a polymer-bound metal is also effective for binding a molecule on solid phase. This approach has an advantage of reversible binding because the interaction is noncovalent. For this purpose a polymer-bound metal and a metal-chelating tag are used (Scheme 33). Thus, upon completion

Scheme 33

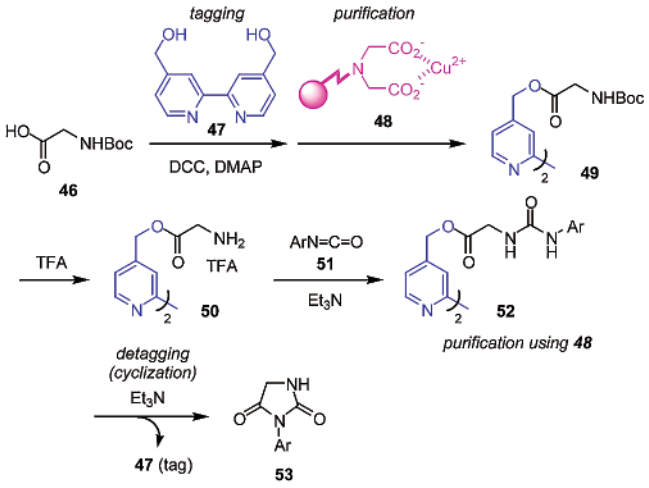


of the solution-phase reaction, the immobilization of the tagged product is realized by the addition of a polymer-bound metal to the reaction media. The resin is washed to remove excess reagents and byproducts, and finally the purified product is easily obtained after release from the resin.

Ley and co-workers evaluated a variety of transition metals, metals bound to solid supports, and metal-chelating organic molecules, and found that the preferred resin with respect to optimal loading of Cu(II) ions was the inexpensive solid support IRC-718 which contains iminodiacetic acid.[54] They also found that bidentate pyridine-containing ligands such as 1,10-phenanthroline and 2,2′-bipyridine were optimal, not only with respect to their good affinity for Cu(II) ions but also in regard to their moderately low reactivity to a wide range of reaction conditions.

The following synthesis of hydantoins illustrates the utility of this approach (Scheme 34).[54] In the first

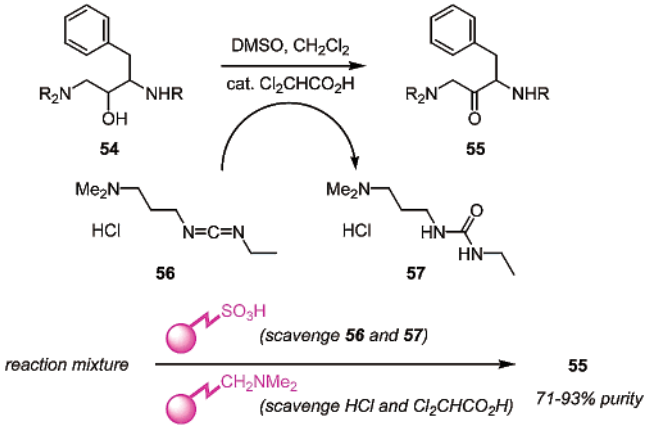
Scheme 34



step, compound **46** was tagged with **47**, and the resulting **49** was purified with the resin-bound Cu(II) ions **48** (vide infra). The subsequent deprotection of the amino group afforded compound **50**. After the urea formation with the tagged amine **50** was completed, the beads of resin-bound Cu(II) ions **48** were added to the crude solution of the product **52**. The resin was then washed to remove excess reagents and other byproducts. The product was released from the beads by the addition of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) and shaking the suspension. Filtration and concentration of the filtrates afforded the desired **52**. Thereafter, the treatment with Et_3N induced cyclization (detagging) to afford hydantoins **53** in greater than 95% purity.

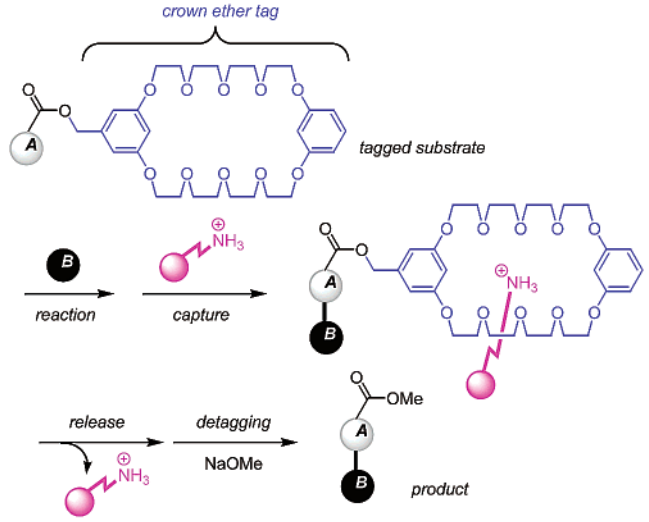
Ion−ion interaction is also effective for solid-phase capture. Flynn and co-workers developed a tertiary-amine-tagged carbodiimide **56** for the Moffat oxidation of alcohols **54** to the corresponding carbonyl compounds **55** (Scheme 35).[55] After the reaction, tagged urea **57** thus formed and unchanged carbodiimide **56** are removed (scavenged) by the sulfonic acid-substituted resin. It is interesting that the acids (HCl and Cl_2CHCO_2H) in the reaction mixture can also be removed by the amine-substituted resin. Because acidic resin and basic resin do not interfere with one another, both processes can be accomplished simultaneously by employing two ion-exchange resins.

Scheme 35



Fukase and Kusumoto found that the interactions between ammonium ions and crown ethers are also effective for immobilization of the tagged product (Scheme 36).[56] They developed a crown ether-based

Scheme 36

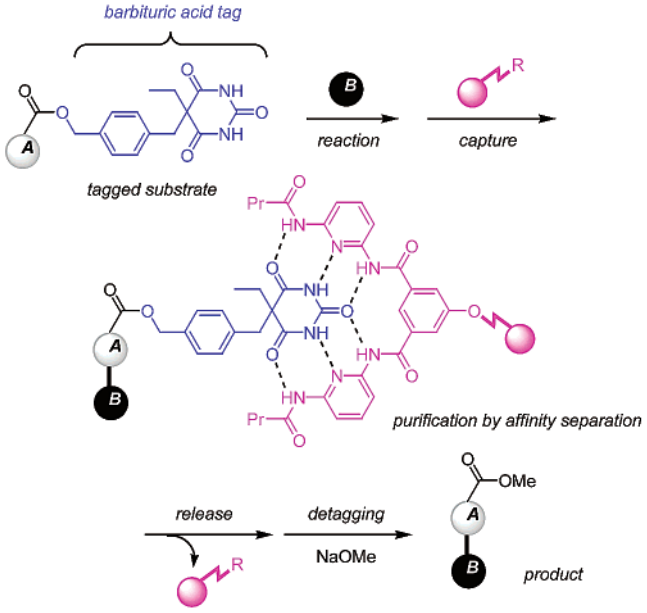


tag and used anion-exchange resin having a quaternary ammonium group as the capture resin. Solvents such as CH_2Cl_2 and $CHCl_3$ were used for binding compounds having a crown ether tag to the resin. To desorb the compound, polar solvents such as MeOH, EtOH, or DMF were found to be effective.

Lepore also reported the use of a crown ether tag for separation.[57] A silica-supported propylbenzenesulfonic acid ion-exchange column (after treatment with potassium carbonate solution) was used to capture organic molecules tagged with an 18-crown-6 moiety.

Hydrogen bonding provides an effective interaction for solid-phase capture. A tag based on barbituric acid was selectively bound to the polymer-supported bis-(2,6-diaminopyridine)amide of isophthalic acid by forming a tight complex via six hydrogen bonds (Scheme 37).[58] In the solid-phase extraction, tagged compounds were effectively retained in a column containing the supported receptor by using eluents such as CH_2Cl_2, $CHCl_3$, and toluene. Untagged compounds in the reaction mixture were eluted from the column. Because polar solvents disfavor the

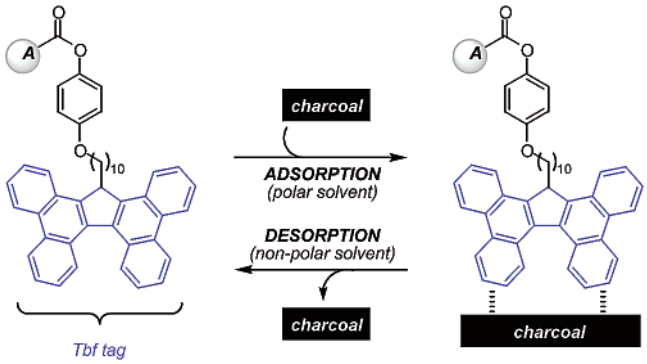
Scheme 37



complex formation, the tagged compounds were readily desorbed from the column by using CH_2Cl_2/MeOH as an eluent. This tag was applied to the synthesis of small peptides and oligosaccharides.

Strong affinity of aromatic groups for charcoal was also utilized for the immobilization of tagged molecules. The affinity of tetrabenzo[ac,c,g,i]fluorene (Tbf) for charcoal was used in the purification of peptides,[59] proteins,[60] and DNA.[61] Adsorption/desorption can be controlled by the choice of suitable solvent. Ramage found that this protocol can be applied for the synthesis of general organic molecules (Scheme 38).[62] Organic compounds, covalently bound

Scheme 38



to Tbf via a suitable linker group, are allowed to react in conventional solution phase, and the tagged products are purified by exploiting the affinity of Tbf group for charcoal. Untagged compounds are then removed in the filtrate. The Tbf-tagged product can be desorbed from the charcoal by a suitable solvent and used for the next transformation. In the final step of the synthesis, the cleavage of the linker liberates the product.

Recently, the tagging of polyaromatic hydrocarbon tags such as pyrene to tin hydride reagents[63] or amine scavenger agents[64] has been reported.

Ito and co-workers have reported that low-molecular-weight poly(ethylene glycol) (PEG) (average

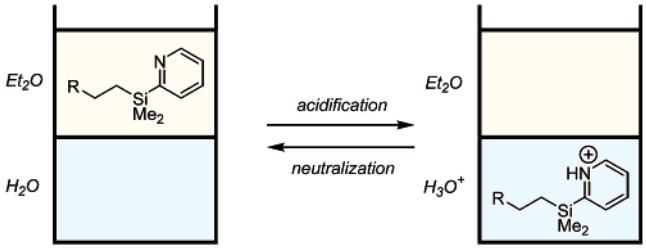
molecular weight 550) serves as a tag for separation in oligosaccharide synthesis.[65] Separation of tagged oligosaccharide products can be achieved simply by direct chromatography of the reaction mixture on silica gel. The tagged product stays at the top of the column during the elution with AcOEt, while other untagged compounds move rapidly through the column. After the column is washed with AcOEt, the tagged product is eluted with a mixture of AcOEt and MeOH. One of the intriguing aspects of this tag is that glycosylation reaction of the tagged acceptor can be monitored by MALDI-TOF MS, because PEG-bound materials are easily distinguished from others by their mountain-like shape in MS spectra, which are derived from statistical distribution of the PEG chain length.

B. Tags for Aqueous Phase

It is naturally considered that hydrophilic groups serve as tags for aqueous phase, but simple hydrophilic groups cannot be used for the recovery of tagged compounds. After reaction in organic solvents, tagged molecules are extracted into aqueous phase. To recover the tagged molecules, it is neccesary to re-extract them with organic solvent from water. Therefore, the nature of the tag should be switched from hydrophilic to hydrophobic (or less hydrophilic) in order to accomplish the re-extraction (phase shuttle, Scheme 7). This switching is often realized by acid/base reaction. Ionized forms such as ammounium ions and carboxylate ions are hydrophilic, whereas their nonionized forms such as amines and carboxylic acids are less hydrophilic (masked form of aqueous tags). As a matter of fact, such phase switch involving aqueous acidic and basic extractions has been extensively used in traditional organic synthesis for many years.[66]

The greatest flaw of this traditional protocol, however, is that the compounds to be extracted must possess an acidic or a basic functional group. This issue poses a big disadvantage to the separation of products. Substrate phase tags for the aqueous phase, however, provide a general scheme that can be applicable to compounds of various structural types without acidic or basic functional groups. In this case, tags must be easily introduced to substrate and removed from products after separation. The following acid/base phase switch (phase shuttle) using a 2-PyMe$_2$Si tag, which has been already mentioned in Section IV-A, is representative (Scheme 39).

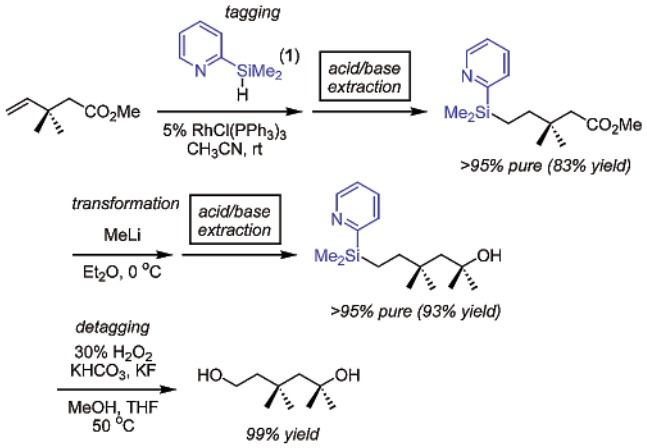
Scheme 39



Acid extraction (1 N *aq* HCl) of a solution of a 2-PyMe$_2$Si-tagged organic molecule in organic solvents such as Et$_2$O and toluene transfers the tagged molecules into the aqueous phase. Other organic compounds, which do not have the tag, remain in the organic phase and they are easily separated from the tagged compound by phase separation. Neutralization of the aqueous phase to deionize (or re-mask) the tag followed by the extraction with an organic solvent transfers the tagged compound to the organic phase.

The following example using a 2-PyMe$_2$Si group as a tag demonstrates the utility of aqueous phase tags (Scheme 40).[19] The 2-PyMe$_2$Si tag was introduced to

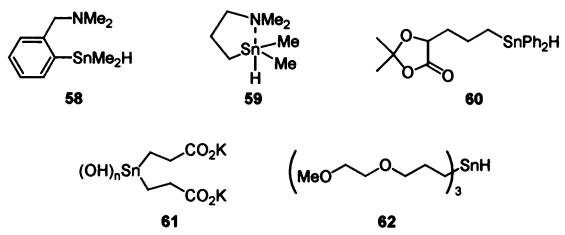
Scheme 40



methyl 3,3-dimethyl-4-pentenoate by the hydrosilylation with 2-PyMe$_2$SiH (**1**) in the presence of RhCl(PPh$_3$)$_3$. The tagged compound was purified by simple acid/base extraction based on protonation/deprotonation of the pyridyl group. In the next step, this tagged ester was treated with MeLi to obtain tertiary alcohol, which was also purified by acid/base extraction process. In both of the steps, 2-PyMe$_2$Si-tagged compounds were obtained in greater than 95% purity. In the final step, H_2O_2 oxidation was used to remove 2-PyMe$_2$Si tag to obtain the corresponding diol as the final product.

In the previous part of this review, it was demonstrated that 2-pyridylethyl group is effective as a reagent tag for aqueous phase (Scheme 20). Several other organotin reagents having hydrophilic tags have also been developed (Scheme 41). For example,

Scheme 41

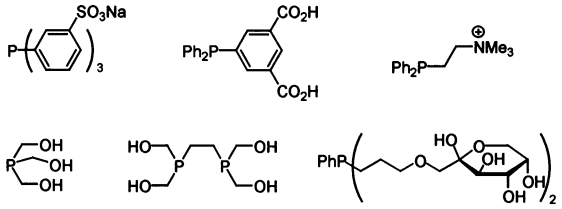


the tin hydride having an amino group (**58**[67] or **59**[68]) or an ester group (**60**)[69] have been developed and utilized for ionic and radical reductions. The organotin reagent having carboxylate units (**61**) has been synthesized and used for radical reduction and cyclization.[70] Polyether functionality is also effective as

a tag. Breslow has developed a water-soluble tin hydride reagent **62** carrying three methoxyethoxypropyl groups.[71] This tin hydride reduces various alkyl halides in water or in organic solvents. The tin species are easily recovered. The treatment with *aq* HCl converts the tin residue to the tin chloride, which is extracted into $CHCl_3$ and reduced with BH_3 to regenerate the tin hydride.

There are a number of examples of catalyst tags for aqueous phase. Some of them have already been discussed in the previous section (Section IV-C). Catalysis in aqueous/organic biphasic system is playing an increasingly important role in the manufacturing of organic compounds.[72] The biphasic system facilitates separation of organic products from organic phase and recovery and reuse of catalysts from aqueous phase. To achieve such a biphasic catalyst system, various catalyst tags have been developed so far. Most frequently used tags are hydrophilic tags for phosphine ligands.[73] Some examples are shown in Scheme 42.

Scheme 42



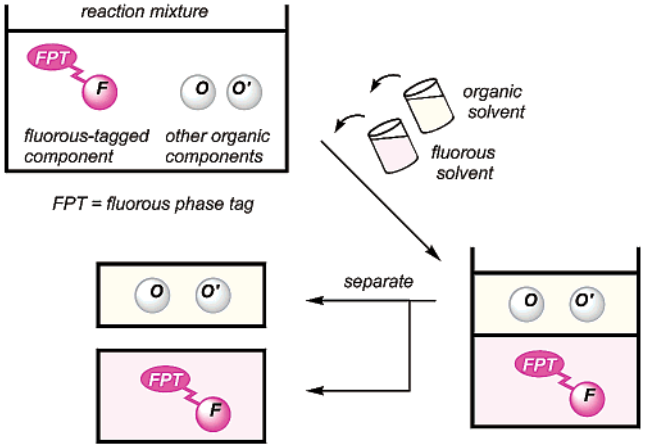
C. Tags for Fluorous Phase

Fluorous techniques have been recognized as increasingly useful methods for high-throughput synthesis of small organic molecules, because fluorous media constitutes a liquid phase orthogonal to other liquid phases (organic and aqueous liquid phases). Thus, the fluorous techniques are attractive for strategic separation of reaction mixtures because fluorous-tagged compounds can be quickly separated from untagged compounds in binary liquid/liquid and solid/liquid extractions. There are excellent reviews on chemistry in fluorous media,[74] and therefore the objective of this section is to provide a current overall picture of this fast-growing field.

There are a number of fluorous solvents commercially available and they commonly exhibit temperature-dependent miscibility with organic solvents. Therefore, reactions of fluorous-tagged compounds (substrates, reagents, and catalysts) with organic compounds are often carried out at higher temperature (monophasic) and the separations are pursued at lower temperature (biphasic). Separation and recovery in fluorous techniques commonly utilize fluorous/organic liquid extraction but fluorous/organic/aqueous liquid extraction is also used in some cases (Scheme 43).

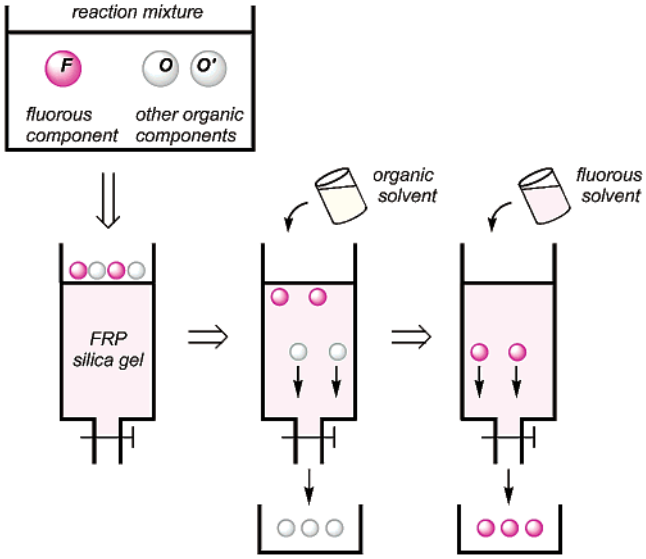
Although fluorous/organic or fluorous/organic/aqueous liquid extraction is useful, a large number of fluorine atoms are required for fluorous tags to induce tagged molecules to partition into fluorous solvent. Curran has elegantly demonstrated that

Scheme 43



solid/liquid extraction over fluorous reverse-phase (FRP) silica gel can be used to reduce the number of fluorine atoms required for fluorous synthesis (Scheme 44).[75] By using this solid/liquid extraction protocol,

Scheme 44



fluorous-tagged molecules that are essentially insoluble in fluorous solvent and fully soluble in organic solvents can still be separated from untagged molecules with ease. There are commercially available FRP columns for this purpose (e.g., Fluofix, FluoSep-RP).

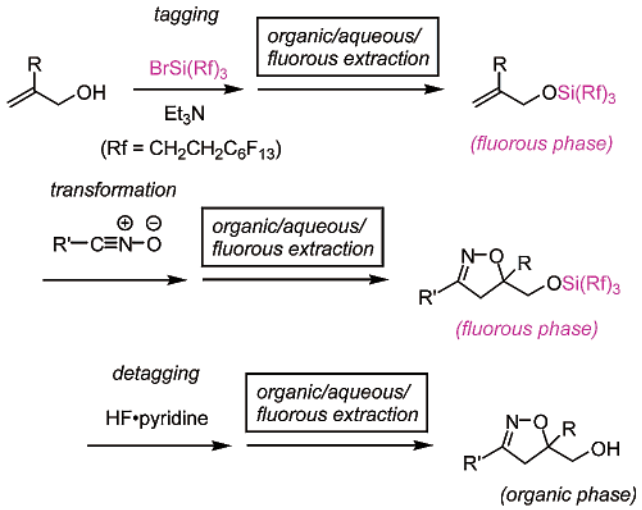
Another intriguing tactic in fluorous-tagging strategy is separating compounds of different fluorous content using FRP column.[76] A series of substrate molecules is tagged with a series of fluorous tags of different fluorous content (different chain length of perfluoroalkyl group). The compounds are then mixed and multistep syntheses are performed. The resulting products are separated (demixed) with fluorous chromatography.

Fluorous tags are also categorized into catalyst tags, reagent tags, and substrate tags. Recent extensive studies in these fields have uncovered a rich variety of synthetic applications as shown in the following sections.

1. Fluorous Substrate Tags

A silicon-based fluorous substrate tag has been developed by Curran and this tag has been widely utilized in organic synthesis.[77] For example, the tag is easily introduced to allylic alcohols, and the cycloaddition with nitrile oxides provides the corresponding isoxazolines, which are purified by simple liquid/liquid extraction (Scheme 45).[78]

Scheme 45



The fluorous silyl group can also be introduced to a benzyl protecting group, which is utilized as an effective substrate tag for disaccharide synthesis.[79] Similarly, fluorous silyl-substituted benzoic acids have been utilized for Ugi and Biginelli multicomponent condensation.[80] (Perfluoroalkoxy)silyl groups have also been developed as highly acid-stable tags for liquid/liquid or liquid/solid extraction with fluorous reverse-phase silica gel.[81] It is interesting to note that transportative deprotection of fluorous silyl ethers (H_2SO_4 or H_2SiF_6 in *aq* MeOH) with concomitant purification was achieved by fluorous triphasic reaction using a U-shaped tube reactor.[82]

Perfluoroalkyl alcohols are also utilized as tags, which are introduced to substrates by forming acetals[83] and esters.[84] A fluorous THP protecting group has also been developed.[85] Fluorous Boc (^{F}Boc) containing perfluoroalkoxy group has been developed as amine protecting groups for fluorous synthesis.[86] A fluorous acyl protecting group has also been devised and applied in oligosaccharide synthesis.[87]

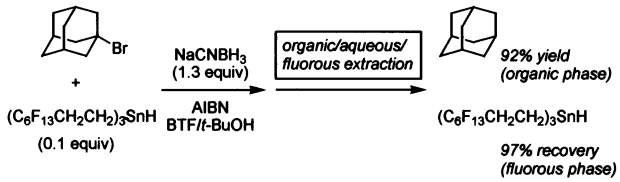
Theil has reported that a fluorous ester can be utilized as a fluorous acyl donor to a lipase-catalyzed kinetic resolution of a racemic alcohol.[88] Fluorous/organic extraction afforded acylated alcohol from the fluorous phase (98% ee) and unchanged alcohol from the organic phase (>99% ee).

2. Fluorous Reagent Tags

Fluorous-tagging strategy is also effective for reagent separation and recovery.[89] Fluorous organotin reagents have been most extensively studied, probably because conventional organotin compounds, especially organotin halides, are known to be difficult to separate from other organic compounds by silica gel column chromatography.

Radical-mediated reduction of organic halides and related compounds with fluorous organotin hydride has been developed by Curran.[90] The reaction can be performed with a catalytic amount of the fluorous tin hydride with a stoichiometric amount of $NaCNBH_3$ in a 1/1 mixture of benzotrifluoride (BTF, $C_6H_5CF_3$) and *tert*-butyl alcohol at reflux. Three-phase liquid extraction between water, CH_2Cl_2, and a fluorous solvent (PFMC, perfluoromethylcylohexane) is used for the separation of products and recovery of the tin hydride (Scheme 46). Intramolecular and intermolecular radical-mediated carbon−carbon bond formation has also been achieved with the fluorous tin hydride and an application to combinatorial synthesis has been demonstrated. Very recently, a new fluorous/organic amphiphilic solvent, F-626, has been introduced and used as a solvent for fluorous radical reduction reactions.[91]

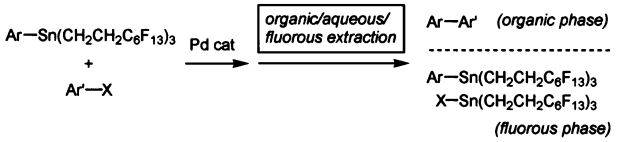
Scheme 46



Ryu and co-workers applied fluorous tin hydride to radical-mediated carbonylation.[92] Products were isolated by three-phase separation.

Allyltin reagents can also be tagged with perfluoroalkyl groups and used for thermal, radical, and metal-catalyzed reactions.[93] Pd-catalyzed Stille coupling of fluorous organotin compounds with organic halides takes place smoothly in a 1/1 mixture of DMF and THF.[94] Fluorous/organic extraction enables easy separation of the coupling product from the organic phase and recovery of the organotin halide from the fluorous phase (Scheme 47). The organotin halide is allowed to react with a Grignard reagent to regenerate the starting fluorous organotin reagent.

Scheme 47



It is interesting to note that microwave irradiation promotes the radical and metal-catalyzed reactions of fluorous-tagged organotin reagents.[95] The advantage probably stems from rapid heating, superheating of the solvent, smaller temperature gradients, and the absence of wall effects.

Fluorous-tagged organotin azide was shown to be a useful reagent for the synthesis of tetrazoles from nitriles.[96] In this case, the initial product, which contains the fluorous organotin group, was easily separated from unchanged nitrile by phase separation. It is also reported that fluorous organotin reagents have been successfully used in the synthesis of organometallic compounds such as Cp^*TaCl_4 and

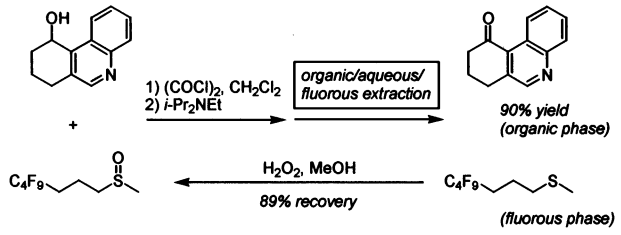
Cp^*NbCl_4, where the product isolation is accomplished by simple extraction.[97]

Fluorous-tagged triphenylphosphine was used as a precursor for fluorous ylides for Wittig reaction. Easy separation of product (alkene) from the phosphine oxide and the regeneration of fluorous triphenylphosphine by simple reduction of crude oxide have been demonstrated.[98] Fluorous-tagged triphenylphosphine was applied in a fluorous biphasic system for the efficient parallel synthesis of 3*H*-quinazolin-4-ones via an aza-Wittig reaction.[99] The products were isolated by solid/liquid extraction using fluorous reverse-phase silica gel.

Very recently, Dobbs and Curran have prepared fluorous dialkylazodicarboxylates and used as fluorous Mitsunobu reagents in combination with fluorous or nonfluorous phosphines.[100]

Organosulfur and organoselenium compounds serve as useful reagents in organic synthesis, but their use on a large scale is rather limited by environmental problems. Crich developed dimethyl sulfoxide tagged with a perfluoroalkyl group and used it in Swern oxidation (Scheme 48).[101] After the reaction in CH_2Cl_2, the crude mixture was partitioned between toluene and a fluorous solvent to recover the sulfide, which was reoxidized with hydrogen peroxide to regenerate the sulfoxide. A fluorous version of the Corey−Kim reaction has also been demonstrated using the same fluorous DMSO.[101b] Fluorous-tagged organoselenium reagents have also been developed.[102]

Scheme 48



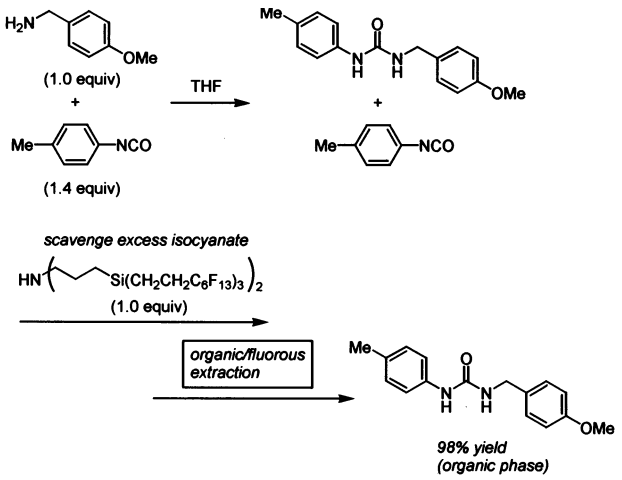
Enantioselective protonation of samarium enolates has been accomplished with fluorous chiral BINOL as a proton source.[103] The fluorous diols can be recovered by liquid/liquid extraction with fluorous solvents or solid/liquid extraction with fluorous reverse-phase silica gel and reused.

The fluorous approach is also effective for tagging posterior to reaction. For example, Curran has developed perfluoroalkyl-substituted amines as fluorous scavenger and used them to scavenge excess isocyanates in the synthesis of urea derivatives (Scheme 49).[104] This method was successfully applied to automated parallel synthesis. Very recently, a fluorous thiol scavenger ($C_6F_{13}CH_2CH_2SH$) has been devised and used as a scavenger agent in *N*-alkylation reactions.[105,106] Fluorous acid chloride, sulfonic acid, sulfonyl chloride, and epoxide are also reported as fluorous scavenging agents.[106]

Wipf has developed fluorous vinyl ether as a fluorous capturing agent and used it to achieve rapid purification of a mixture library of analogues of the antimitotic marine natural product curacin A.[107]

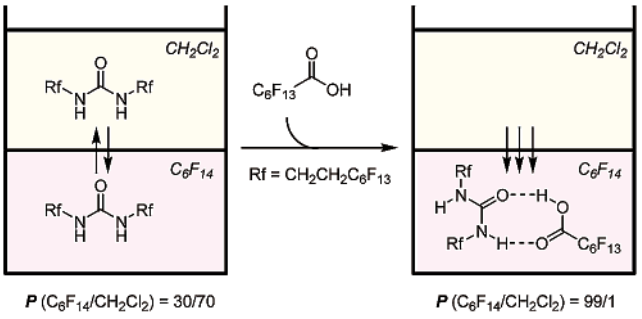
Fluorous tin hydride scavenger has been also reported.[90]

Scheme 49



Fluorous-phase extraction with the aid of hydrogen bonding is interesting. Palomo and Aizpurua noticed that solubility of *N*,*N*-di(perfluoroalkyl)ureas in fluorous solvents increases dramatically when hydrogen bonding complexes are formed with perfluoroalkanoic acid (Scheme 50), and applied it to the peptide

Scheme 50



synthesis.[108] The reaction was carried out using fluorous-tagged carbodiimides in a biphasic CH_2Cl_2/C_6F_{14} medium and peptides were isolated by washing with a solution of perfluoroheptanoic acid in C_6F_{14}.

3. Fluorous Catalyst Tags[109]

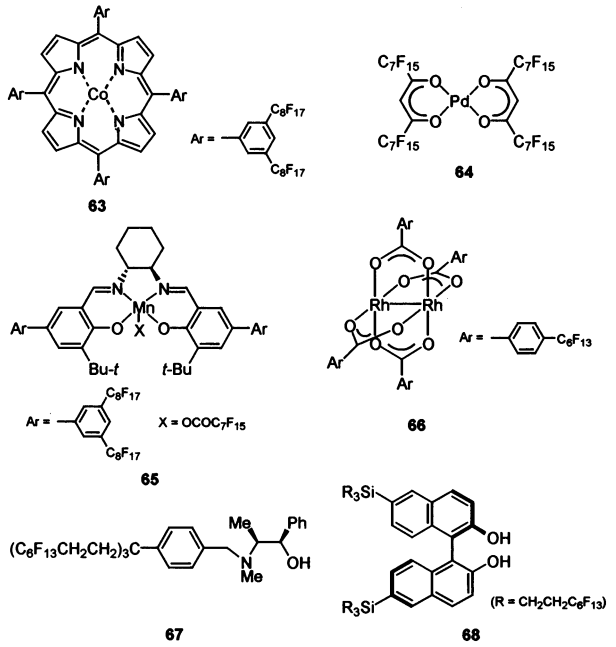
Transition metal complexes can be made fluorous-soluble through ligand modification by attaching fluorous tags. Various phosphorus-based ligands[110] including fluorous trialkylphosphines,[111] fluorous triarylphosphines,[112] fluorous bidentate phosphines,[113] enantiomerically pure fluorous phosphines,[114] and fluorous phosphites[115] have been reported so far. Reactivity patterns of some transition metal complexes with such phosphine ligands in fluorocarbons have also been investigated.[116]

With these fluorous phosphine ligands, various transition metal complex-catalyzed reactions have been exploited. Hydroformylation with Rh catalyst, tagged by fluorous phosphine ligands,[39] is one of the most popular examples. Fluorous catalysts are also effective for hydrogenation of alkenes,[117] hydroboration of alkenes and alkynes,[40] and hydrosilylation of ketones[118] and alkenes.[119] Allylic substitution,[120] Stille coupling,[121] Suzuki coupling,[122] Heck reac-

tion,[123] and cyclodimerization of conjugated enynes[124] are also catalyzed by fluorous Pd catalysts.

Fluorous tags are also introduced to various other types of ligands (Scheme 51). For example, fluorous-

Scheme 51



tagged Co-porphyrins such as **63** are effective for epoxidation of alkenes by dioxygen and 2-methylpropanal under fluorous biphasic conditions.[125] The reaction was carried out at room temperature in a mixture of perfluorohexane and CH_3CN under atmospheric pressure of dioxygen with vigorous stirring. After the reaction, the two phases were easily separated to recover the catalyst. It was also reported that fluorous-tagged Mn-porphyrins can be used for epoxidation.[126] A related Co-phthalocyanine complex was also synthesized and used for catalytic oxidation.[127]

As to nitrogen-containing ligands, macrocyclic triazacyclononane[128] and tetraazacyclotetradecane,[129] pyridine,[130] bipyridine,[131] and bis(aminomethyl)phenyl group[132] are tagged with perfluoroalkyl groups.

Haddleton reported that a fluorous-tagged amine ligand was effective for Cu(I)-mediated living radical polymerization.[133] The polymerization of methyl methacrylate was carried out with ethyl 2-bromoisobutyrate as polymerization initiator in perfluoromethylcyclohexane at 90 °C with efficient stirring, although the system was not monophasic. After polymerization, the reaction mixture was cooled to ambient temperature to reveal two phases, and the catalyst was recovered by phase separation and reused.

It is interesting that Pd complexes with fluorous dialkyl sulfide ligands have been prepared and used as catalysts for Suzuki coupling reaction.[134]

The Wacker oxidation of olefins was found to proceed under fluorous biphasic conditions using fluorous Pd catalyst **64**. The Pd catalyst can be recovered and reused several times.[135]

Chiral salen ligands were also tagged with perfluoroalkyl groups. Epoxidation of alkenes was carried out with chiral fluorous Mn(salen) complex **65** under fluorous biphasic conditions.[136] Fluorous salen ligands have also been used for Ir-catalyzed asymmetric hydrogen transfer reduction of ketones.[137] Very recently, fluorous chiral Co(salen) complexes have been tested as catalysts for hydrolytic kinetic resolution of terminal epoxides.[138]

It is also reported that fluorous-tagged carboxylic acids[139] were utilized as ligands in metal-catalyzed reactions such as Rh-catalyzed cyclopropanation of alkenes with diazoacetates[140] and silylation of alcohols under fluorous biphasic conditions.[141]

Cyclopentadienyl ligands, which also form complexes with a variety of transition metals, can be tagged with perfluoroalkyl groups.[142] With such ligands, ferrocenes, manganese carbonyl, rhenium carbonyl, and cobalt carbonyl complexes have been prepared. These complexes dissolve in fluorous solvents.

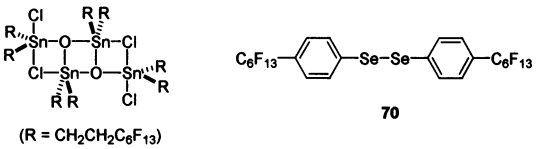
Fluorous-phase soluble Pd nanoparticles are also developed and used for various Pd-catalyzed reactions under fluorous biphasic conditions.[143]

Fluorous-tagging is also effective for the enantioselective addition of dialkylzincs to aldehydes.[144] For example, the reaction mediated by fluorous amino alcohols such as **67** was performed in nonfluorous solvent toluene/hexane (2:1) and the resulting mixture was subjected to solid/liquid extraction with fluorous reverse-phase silica gel.[145] Perfluoroalkyl-substituted BINOLs such as **68** were also synthesized and utilized for Ti-catalyzed addition of dialkylzincs to aldehydes.[146]

Fluorous lanthanide complexes such as $Yb[N(SO_2C_4F_9)_2]_3$, $Yb[C(SO_2C_8F_{17})_3]_3$, and $Sc[C(SO_2C_8F_{17})_3]_3$ have also been developed and used for esterification, Diels−Alder reactions, Friedel−Crafts reactions, and Mukaiyama-aldol reactions.[147] The reactions are carried out in fluorous (perfluoromethylcyclohexane)/organic (toluene or CH_2Cl_2) mixed solvent systems. After the reaction, the two phases are separated and the catalyst in the fluorous phase is recovered and reused without isolation.

Fluorous dialkyldistannoxane **69** has been developed and found to catalyze transesterification (Scheme 52).[148] The reaction takes place efficiently with the

Scheme 52



employment of a carboxylic acid and an alcohol in a 1:1 ratio by heating a mixture with the catalyst and fluorous solvent at 150 °C. After the mixture cools, the two phases are separated. The catalyst can be recovered from the fluorous phase and can be reused directly in the next reaction. The use of fluorous tin oxide for selective sulfonylation of 1,2-diols has also been reported.[149]

Diaryldiselenides tagged with fluoroalkyl groups such as **70** are used for tin-mediated radical reaction[150] and reductive elimination of vicinal dimesylates.[151] A method for effective recovery of selenium-

containing compounds by continuous extraction has also been developed. Fluorous aryl butylselenide is reported to catalyze the epoxidation of various olefins with hydrogen peroxide in a fluorous biphasic system.[152] Catalytic oxidation of carbonyl compounds with hydrogen peroxide is also reported.[153]

Fluorous arylboronic acid was found to be a good catalyst for the direct amide condensation reaction under fluorous biphasic conditions.[154] Recovery and reuse of boronic acid catalyst were also demonstrated.

Fluorous ketones have been reported to catalyze selective epoxidation of alkenes with hydrogen peroxide.[155] The reaction was performed in organic solvent such as CH_2Cl_2 with anhydrous hydrogen peroxide in EtOAc. After the reaction completed, simple cooling of the reaction mixture to 0 °C gave rise to crystallization of the catalyst. Filtration and washing with a small amount of cold solvent gave the pure catalyst. The recovered catalyst was still active for epoxidation. Stoichiometric and catalytic epoxidation reactions using Oxone as primary oxidant and fluorous ketones as reagents that can be regenerated in situ are also reported.[156]

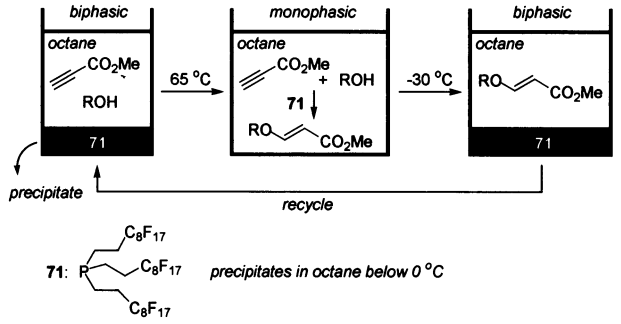
Perfluoroalkylated cinchona derivatives are prepared and used as base catalyst for Diels−Alder reaction in fluorous solvents.[157]

Fluorous tags are effective for photosensitizers. A fluorous porphyrin is used for singlet oxygenation of allylic alcohols.[158] The reaction is carried out in a mixture of perfluorohexane and CH_3CN. A relatively long lifetime of $^1O_2$ in perfluoroalkanes is advantageous. After the reaction, two phases are separated and the sensitizer solution can be used directly for the next cycle.

Very recently, fluorous nicotinamide adenine dinucleotide (NAD) has been prepared and used as a soluble coenzyme for enzymatic chemistry in fluorous solvent.[159]

Although the fluorous catalysts described above are commonly used in fluorous solvents for both reactions and recovery of catalyst, Gladysz has developed a new thermomorphic property-based protocol that does not use fluorous solvents (Scheme 53).[160] He

Scheme 53



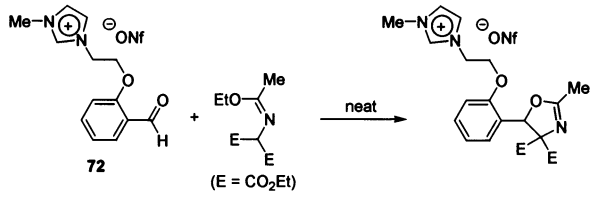
reported that fluorous phosphine **71** catalyzed the addition of alcohols to methyl propiolate. The reaction was carried out in octane at 65 °C. At this temperature the mixture became homogeneous. After the reaction, the mixture was cooled to −30 °C. The catalyst that precipitated was easily separated from the product by simple decantation. The recovered catalyst could be used for the next cycle without deterioration in yield. This intriguing example indicates the effectiveness of fluorous tags as tags for precipitation, and opens a new aspect of fluorous chemistry.

D. Tags for Ionic Liquid Phase

Room-temperature ionic liquids have received significant interest from both academia and industry because of their ability to form biphasic systems with organic product mixtures, which enables easy isolation of products and easy recovery of reagents and catalysts.[161] The following examples demonstrate the potential of tag strategy in this field.

Dipolarphile **72** having an imidazolium salt tag has been synthesized and used for the cycloaddition reactions (Scheme 54).[162] It is noteworthy that the

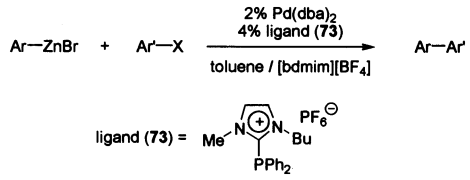
Scheme 54



reaction of the tagged dipolarphile **72** was found to be faster than that of 2-ethoxybenzaldehyde without tag in ionic liquid. Although the reaction using **72** was performed without any added solvent (ionic liquid), such an imidazolium salt moiety may be exploited as a tag for ionic liquid if a selective detagging protocol could be devised.

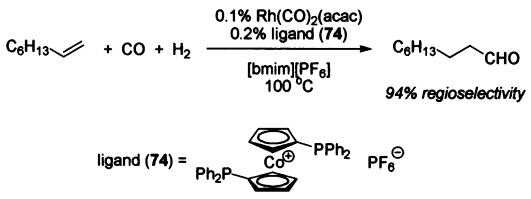
Although many transition metal catalysts dissolve in ionic liquid phase, some catalyst tags for ionic liquids have been developed. A phosphine ligand **73** having an imidazolium ionic tag was prepared and utilized for Negishi cross-coupling reactions in an ionic liquid/toluene biphasic system (Scheme 55).[163]

Scheme 55



Bisphosphine ligands **74** with ionic cobaltocenium backbone was also synthesized and applied for Rh-catalyzed hydroformylation of alkenes in ionic liquids (Scheme 56).[164] High selectivity to the *n*-product was

Scheme 56



observed, and catalyst leaching from the ionic liquid phase into the organic phase was not detected. Moreover, the recovery of catalyst was accomplished

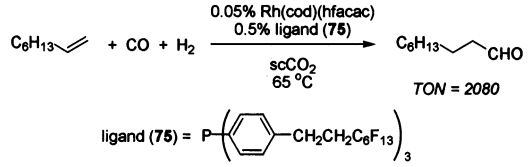
by simple decantation and the catalyst thus-recovered could be reused for the next run.

E. Tags for Supercritical Fluid Phase

Organic reactions in supercritical fluid such as supercritical CO_2 have received significant research interest from the viewpoints of high efficiency of reactions and easy separation of products, reagents, and catalysts.[165] Although many organic compounds dissolve in supercritical CO_2 ($scCO_2$), it is interesting to note that a perfluoroalkyl group is used as a CO_2-philic tag in a number of bond-forming processes.

Rh complexes tagged with perfluoroalkyl-substituted triarylphosphines or triaryl phosphites are extremely active catalysts for hydroformylation in $scCO_2$ (Scheme 57).[166] It should be noted that un-

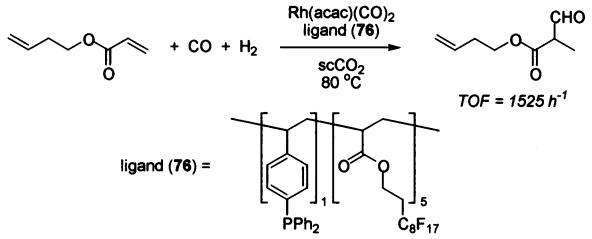
Scheme 57



tagged triarylphosphines are badly soluble in $scCO_2$ and cannot be used as ligands for the hydroformylation in $scCO_2$.

Fast and regioselective Rh-catalyzed hydroformylation of acrylates, one of the least reactive olefins, can readily be accomplished in $scCO_2$.[167] More recently, it has been found that the combined use of $Rh(acac)(CO)_2$ and fluorous polymeric phosphine ligand **76** can effect fast and chemoselective hydroformylation of acrylates in $scCO_2$ (Scheme 58).[168]

Scheme 58



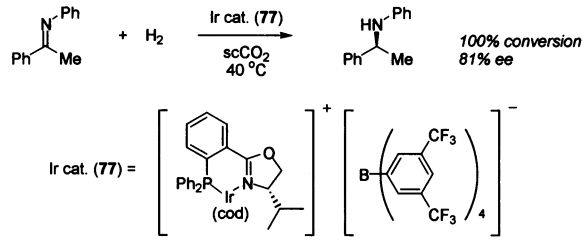
Similar fluorous polymeric phosphine Rh complexes have been prepared and tested for hydrogenation of alkenes.[169]

Fluorinated phosphine−Pd complexes have been successfully employed in Pd-catalyzed coupling reactions such as the Heck reaction,[170a,b,d] Suzuki coupling,[170a] Sonogashira coupling,[170a] and Stille coupling.[170a,b,c] Interestingly, the use of fluorinated Pd sources such as $Pd(OCOCF_3)_2$ or $Pd(hfacac)_2$ in combination with nonfluorinated phosphine ligands can give superior results in Pd-catalyzed coupling reactions in $scCO_2$.[171] The nonfluorinated $Pd(OAc)_2$/$P(t\text{-}Bu)_3$ catalyst system is also found to be highly active in promoting coupling reactions in $scCO_2$.[172] Pd complexes with trialkyl or triaryl phosphite ligands can promote the carbonylation of aryl halides in $scCO_2$.[173]

Rh-catalyzed hydroboration was successfully conducted in $scCO_2$ using a combination of fluorinated Rh source, $Rh(coe)_2(hfacac)$, and fluorinated phosphine ligand, $Cy_2PCH_2CH_2C_6F_{13}$.[174] In this reaction, significantly higher regioselectivity was obtained in $scCO_2$ relative to fluorocarbons and THF.

Cationic Ir complexes with chiral phosphinooxazolines, modified with perfluoroalkyl groups in the ligand or in the anion, were found to effect enantioselective hydrogenation of prochiral imines in $scCO_2$ (Scheme 59).[175] Separation of product from the reac-

Scheme 59



tion mixture was easily accomplished by supercritical fluid extraction, leaving the catalyst in the reactor in active form. Reuse of the catalyst was also demonstrated.

Sc complexes tagged with perfluoroalkyl groups were found to catalyze Diels−Alder and aza Diels−Alder reactions in $scCO_2$.[176] More recently, 1-dodecyloxy-4-perfluoroalkylbenzene was found to accelerate several $Sc(OTf)_3$-catalyzed reactions such as aldol reaction and Friedel−Crafts alkylation in $scCO_2$. It was suggested that perfluoroalkylbenzene works as a surfactant to form emulsions in $scCO_2$.[177]

Tagging in reagent is also feasible for the reaction in supercritical fluids. For example, radical reduction of organic halides in $scCO_2$ was successfully accomplished by using fluorous tin hydride.[178]

Not only perfluoroalkyl groups but also other groups are known to act as CO_2-philic groups. For example, perfluoropolyether moieties can also render organic compounds or metal complexes soluble in $scCO_2$.[179,180] Production of hydrogen peroxide by the sequential hydrogenation and oxidation of perfluoropolyether-tagged anthraquinones was achieved in $scCO_2$.[176] Fluoroacrylate[181] and fluoroether[182] polymers are also known to exhibit extremely high solubility in $scCO_2$ and have been used as surfactants for various purposes.

Recently, the search for nonfluorous (less expensive) CO_2-philic groups has been an active area of research. For example, Beckman has discovered that nonfluorous polymers such as propylene oxide−CO_2 copolymers exhibit very high solubility in $scCO_2$.[183] Following the same design principles as those for nonfluorous CO_2-philic tag, certain carbonylated phosphines have been prepared as CO_2-philic ligands for catalysis in $scCO_2$.[184] Nonfluorous PEG derivatives were also found to function as surfactants for catalytic Mannich and aldol reactions in $scCO_2$.[185]

VII. Conclusion

The examples shown here demonstrate that tag strategy has been widely utilized for separation and recovery of products, reagents, and catalysts. Phase tags enable separation of tagged molecules from

untagged molecules by simple macroscopic operation of phase separation. Tags can be categorized into several types based on parent component of reactions, usage, and preferable phase. It is important to note that some tags can be used in an orthogonal fashion, and one of the key issues of tag strategy will be the combination of multiple tag protocols simultaneously to achieve easy separation and recovery of all the components of reactions, such as unchanged substrate, product, catalyst, or reagent, by simple operation. With such a scheme, both high throughput synthesis in laboratories and highly economically and environmentally benign industrial production of a variety of chemicals and pharmaceuticals can be achieved. A number of phase tags based on different principles will hopefully be exploited and work together to meet demands for high-throughput organic synthesis in this decade.

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