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Homogeneous Catalysis

# Synthesis Strategies towards Tagged Homogeneous Catalysts To Improve Their Separation

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**Abstract:** The recycling of homogeneous catalysts while keeping them in the homogeneous matrix is an ongoing challenge many reactions face if they are to find industrial applications. While a plethora of different synthetic approaches towards better, recyclable homogeneous catalysts exist, the literature shows a gap when one searches for a concise overview of the different catalyst modifications. This Review is designed to close that gap by summarising the existing synthesis pathways towards polar, non-polar, fluorous, and molecular-weight-enlarged catalysts and by examining their respective synthesis routes with a focus on modular and late-stage approaches. Furthermore, we map out the potential for a generally applicable tag library that allows straightforward catalyst modifications to tune them for each desired recycling strategy.

## 1. Introduction

As one starts to study homogeneous (transition metal) catalysis, one will inevitably stumble upon the challenge of catalyst separation.[1] Drawing its necessity from the desire to recycle the catalysts and the need for minimal product contamination with catalyst residues,[2] several approaches to separate either the product or the catalyst from the complex reaction mixture have been developed.[3] The key point of the set-ups shown in Figure 1 is that the separated catalyst is still active and ready to be fed back (or remain) in the reactor. This allows much higher total turnover numbers (TTON) than catalysts without recycling strategy, whose turnover number (TON) is equal to their TTON.

The common ground for all these approaches lies in the generation of a second phase and the subsequent separation of that phase. One of the phases contains the catalyst, remains in the process, and is therefore recycled. Distillation and crystallization[4] (see Figure 1, left side) are only applicable for product separation from the reaction mixture due to the non-existing boiling point of most catalysts and the low catalyst content of the reaction mixture. Furthermore, distillation is limited to products of relatively high volatility and crystallization to products that easily crystallize. While these two separation techniques are based on the physical properties of the product, the majority of strategies to separate the product and catalyst rely on the modification of the physical properties of the catalyst. These modifications using building blocks (tags), which bring certain physical properties with them,[5] take place in the molecular periphery of the catalyst and therefore mostly on ligands. One way is the utilization of heterogeneous catalysis′ main advantage: The already existing second phase. In an attempt to combine favorable properties of homogeneous and heterogeneous catalysis there has been extensive research to anchor defined, homogeneous catalysts onto insoluble supports[6] (see Figure 1, right side). In theory, this approach marries the separability of heterogeneous catalysts with the possibility to tailor the steric and electronic environment of the active site. Experimental reality shows that immobilization of the homogeneous catalyst on insoluble supports usually goes hand in hand with a drop in the turnover number (TON) and turnover frequency (TOF).[7] This fact leads directly to the main dilemma of catalyst recycling: You can either have perfect catalytic performance (activity and selectivity), or perfect catalyst separation. While balancing out catalyst activity and catalyst separation leads to compromises on both sides, which then result in a better TTON, selectivity is a non-negotiable point. Especially the pharma industry relies on constant product quality to meet *Good Manufacturing Practice* (GMP) requirements.[7] Homogeneous catalysts, which are modified for separation via extraction or membrane separation (see Figure 1, green box), also face challenges regarding their performance but are free of the limitations that stem from the insoluble supports. From our point of view, the importance of GMP-compliant catalyst recycling systems, as stressed by de Vries and coworkers,[7] has not been widely considered in research until now. If the recycling of homogeneous catalysts aims to become common practice, the GMP requirements have to be a general concern in every approach.

Extraction can be achieved through either a permanently biphasic system or a switchable system, that changes from monophasic to biphasic and back again when it is triggered. The most common trigger is a temperature change, and the resulting systems are called thermomorphic multicomponent systems (TMS).[8] The extraction can be improved through the addition of solubility-inducing groups onto the catalyst, which strengthen a selective solubility in one of the two phases. Similarly, the addition of molecular weight enlargements (MWE) to catalysts increases the retention of the catalyst by organic solvent nanofiltration (OSN), i.e. membrane separation.[9]

In this review, we give a brief overview of the known functionalities that are used to tune the physical properties (namely solubility and molecular weight) as opposed to the electronic properties of homogeneous (transition metal) catalysts with a focus on the synthesis pathways used to introduce them. We identify common patterns in the syntheses to explore the possibility of a synthesis platform that allows a general approach for the introduction of moieties to tune the catalysts′ physical properties with regard to recyclability.

When thinking of the most convenient properties, a synthesis route should include mild conditions, high yield,

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and selectivity, cf. "Click" Chemistry. Although the Click Chemistry characteristic of insensitivity towards oxygen is not met when it comes to the synthesis of phosphine or phosphite ligands, the remaining criteria are important landmarks in the search for a ligand synthesis route.[10] Especially modularity and the use of readily available starting materials play relevant roles when we turn our focus from specific reactions to an overall concept of ligand modification. The latter does not only apply to the building blocks, which should be introduced into the ligand but leads to the wish for late-stage modification of commercially available ligands. A vast library of more or less commonly used ligands is available at chemical suppliers and ready for their application in catalytic reactions, but if the user searches for ligands (or catalysts) that already include a moiety for improved recycling/extraction, the library gets reduced to a small bookshelf. Hence, we see the demand for general late-stage modification strategies and/or a synthon that allows a variety of modifications for different recycling approaches.

Not all the catalysts/ligands described on the following pages have been tested in recycling. Some of them have only been modified regarding their solubility properties to enable e.g., reactions in aqueous solutions. But since the introduced functional groups are the same as those needed for biphasic recycling, these publications will be included to broaden the view on possible introduction strategies. Furthermore, some examples of syntheses of catalysts that display thermomorphic behavior will be included since they are dissolved during the reaction and their permanent solubility can be achieved by a change of the solvent. Figure 2 gives an overview of existing approaches to separate homogeneous catalysts from the reaction mixture and/or the product. Furthermore, it lists the classes of molecular tags, whose introductions into catalysts/ligands are described in this review.

The tags for fixation in polar, non-polar, and fluorous phases separate the catalyst from the product via selective solubility. Polar groups such as salts introduce strong polarity into a catalyst, which leads to improved solubility in polar media. Non-polar groups like long alkyl chains and fluorous groups like perfluorinated alkyl chains can be applied analogously. But simple solubility in the desired phase is only necessary, not sufficient for catalyst recycling. To achieve efficient recycling, the catalyst needs a distribution coefficient that is shifted to the desired phase as much as possible i.e., it needs a selective solubility in one phase. The aforementioned compromise between catalyst performance and separability leads to the use of phase mediators, phase transfer agents, or reactor systems that increase phase interface as the transport of substrate to the catalyst needs to be ensured. A notable special case of selective solubility are switchable systems, which change their polarity upon the activation of a trigger, e.g. light or $CO_2$, and force a phase switch of the catalyst. The only approach in this review that does not rely on solubility can be found in membrane separation. In this case, the tags are used to enlarge the catalyst molecule which is then held back by the membrane while the rest of the reaction mixture can pass through.

The selection of a suitable reaction system depends on the physical properties of both the substrate(s) and the product(s). Their specific requirements dictate if catalyst recycling can be performed via extraction (and which solvent is suitable) or OSN. Therefore, we have organized the following pages after the categories of different recycling approaches and the respective tags.

While this review is certainly overweight on phosphine ligands, we want to stress that as the examples of NHC, amine, and thioether ligands show, most of the presented synthesis methods are not limited to a single ligand class. Especially the modular approaches based on linker moieties can be expanded and are the focus of the analytical part of this review.

## 2. Tags for Homogeneous Catalysts

### 2.1. Polar Groups

Starting with the desire to make homogeneous catalysts applicable in polar—especially aqueous—solutions, the introduction of polar groups has been established as the most common approach for biphasic catalyst recycling. The broad variety of polar groups often mirrors the concepts and ideas of the field of surfactants (see Scheme 1). Especially the use

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*Thomas Seidensticker studied chemistry at TU Dortmund University and received his doctorate in 2016 under the supervision of Prof. Arno Behr. Since 2017, he has been working on his independent career with Prof. Dieter Vogt. His research is dedicated to sustainable process design for homogeneous catalysts, including the development of innovative recycling methods and the conversion of renewable resources. Since January 2021, he has been setting up his junior research group "renewlysis" at TU Dortmund University combining catalysis with renewable resources.*

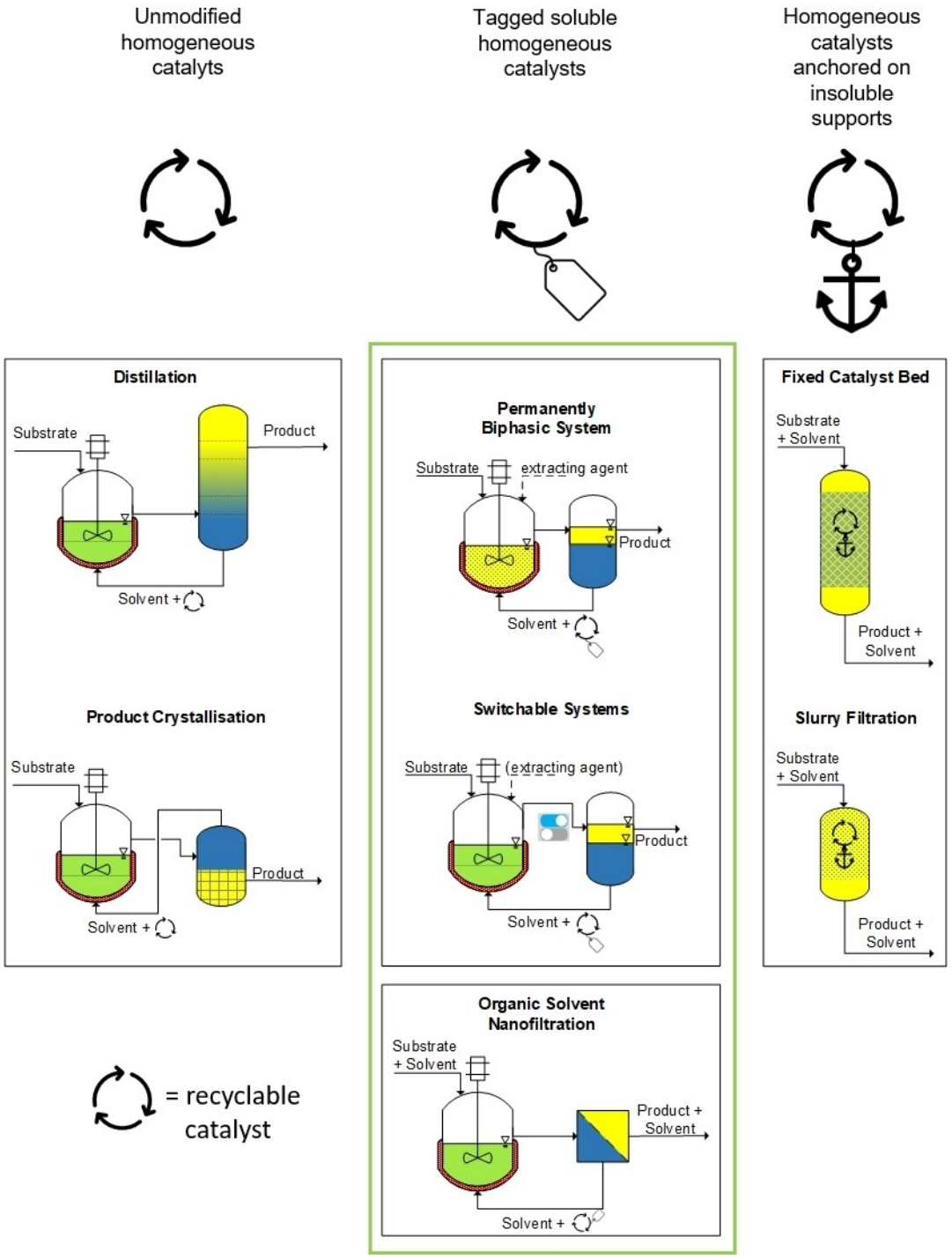



***Figure 1.*** Process set-ups for different approaches towards the recycling of homogeneous catalysts.

of sulfonate groups is highly common in both, surfactants and catalysts, which are soluble in polar solvents.

The most prominent application example of a sulfonated ligand is trisodium 3,3′,3″-phosphanetriyltri-(benzene-1-sulfonate)—commonly known as TPPTS—in the Ruhrchemie/Rhône–Poulenc process (established in 1984) where it forms a rhodium complex that catalyzes the hydroformylation of propene.[12]

We encourage the reader to see the various reviews on ligands with an affinity for polar phases that have already been published, to gain a deeper insight into different polar ligands and their applications.[13]

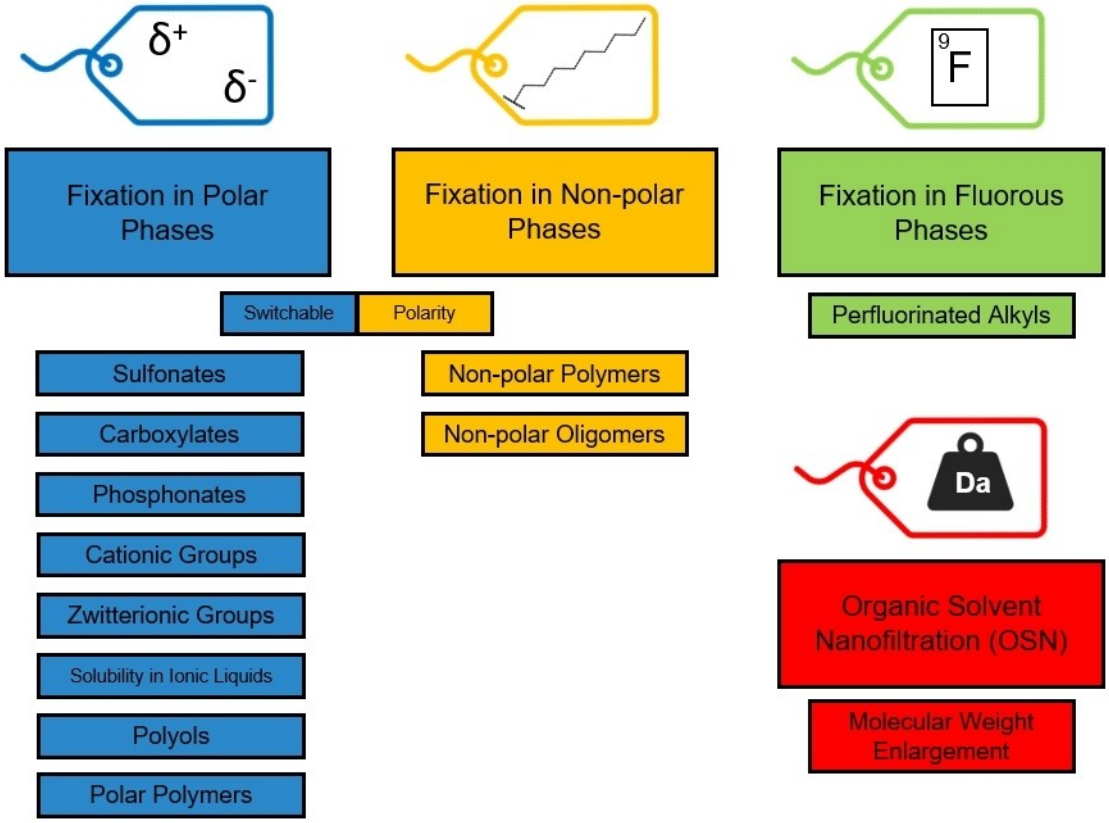
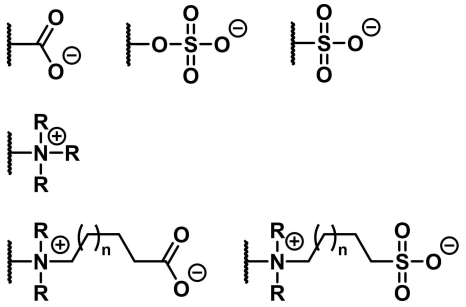



***Figure 2.*** Recycling approaches for homogeneous catalysts based on their physical properties and tags to achieve the desired separability.

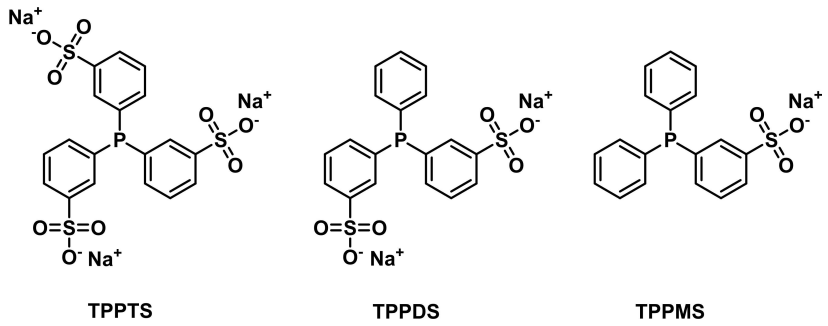


***Scheme 1.*** Ionic groups used as polar heads in surfactants.[11]

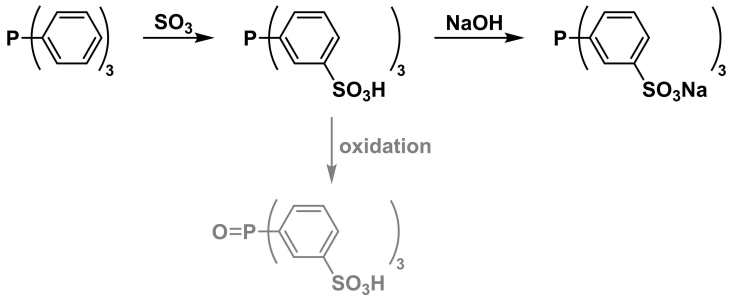
#### *2.1.1. Sulfonates*

Like the aforementioned TPPTS, many sulfonated versions of commonly used ligands exist today. While the majority of those ligands remains a purely academic endeavor, some exponents transitioned into industrial application. The mono-sulfonated Triphenylphosphine derivative TPPMS is used in the Kuraray Process which telomerizes 1,4-butadiene and water to 2,7-octadienol, an intermediate of 1-octanol production.[14]

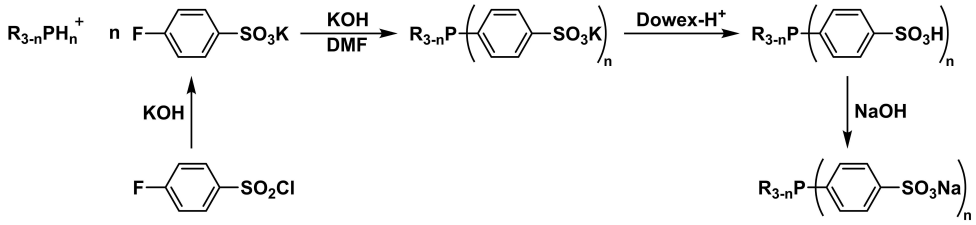
TPPMS, TPPDS, and TPPTS (see Scheme 2) are all synthesized via direct sulfonation of the existing TPP ligand with oleum and subsequent neutralization with sodium hydroxide (Scheme 3). The product distribution of the three




***Scheme 2.*** Synthesis of TPPTS and its undesired oxidation side reactions.[12]



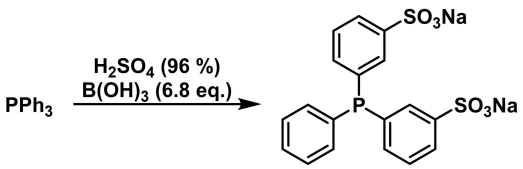

***Scheme 3.*** Tri-, di- and mono-sulfonated TPP.[12]




***Scheme 4.*** Synthesis of *para*-sulfonated TPP derivatives of varying sulfonation degrees.[15]

possible products of degrees of sulfonation depends on the reaction time and makes product separation necessary. Due to oxidizing nature of the oleum, phosphine oxide side-products are another challenge that needs to be addressed in product isolation.[12]

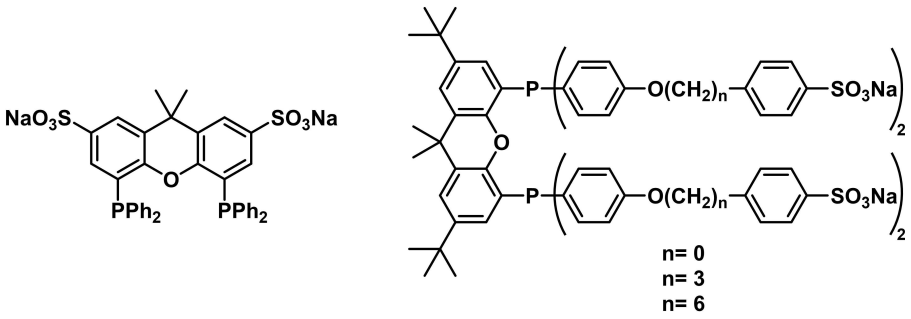
As the structures of TPPTS, TPPDS, and TPPMS show, the direct sulfonation of TPP yields *meta*-substituted products due to the directing effects of the protonated phosphine. To evade the directing effects on the substitution, pre-sulfonated building blocks can be applied to gain *para*-sulfonated TPP (Scheme 4).[15]



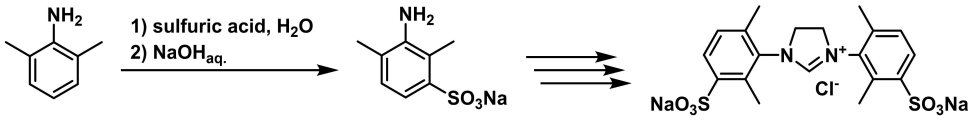

***Scheme 5.*** Selective synthesis of TPPDS via the sulfonation with sulfuric acid in the presence of boric acid.[16]

The direct sulfonation of arylphosphines comes with the disadvantage of phosphine oxide formation which can be addressed by the addition of $SO_3$ at low concentrations and short reaction times. This on the other hand leads to varying products of different sulfonation degrees. Both synthesis routes result in elaborate product separations. Herrmann et al. solved this in 1995 by adding orthoboric acid to the sulfonation (Schem 5). In combination with water-free sulfuric acid (obtained by $SO_3$-titration of the reaction mixture), TPPDS can be obtained selectively, while 30 % $SO_3$ oleum with boronic acid gives TPPTS without any oxidized species. The two reasons for this deviating behavior lie in the quaternization of the phosphines and less oxidizing sulfonating species like $[H_3SO_4]^+$.[16]

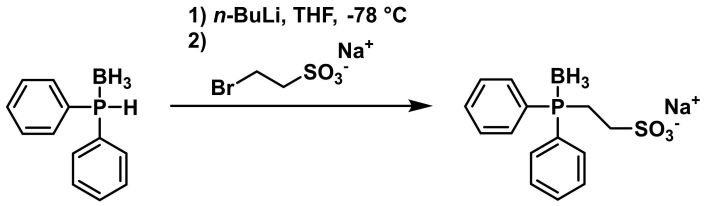
The direct sulfonation of aryl groups in ligands with the classic organic synthesis tools sulfuric acid, oleum, and chlorosulfonic acid has been utilized beyond TPP. A notable example is Sulfoxantphos (Scheme 6) which is obtained by treating Xantphos with oleum (25 % $SO_3$). Sulfonation takes place in 2 and 7 position in the ligand's backbone. The




***Scheme 6.*** Molecular structures of Sulfoxantphos (left) and a tetra-sulfonated Xantphos derivative (right).[17,18]




***Scheme 7.*** Sulfonation of a building block of an NHC ligand.[19]




***Scheme 8.*** Introduction of an ethyl sulfonate group into a monophosphine ligand.[21]

phenyl substituents of the phosphine atoms are unaffected.[17]

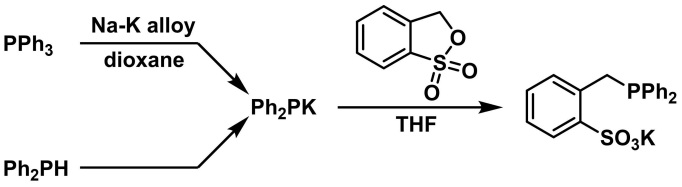
Since the direct sulfonation of Xantphos' four phenyl groups cannot be achieved, Goedheijt et al. extended the phosphine's substituents with aryl-alkyl ethers bearing a terminal phenyl group. Without the deactivating effect of a neighboring phosphine moiety, sulfonation of the terminal rings with concentrated sulfuric acid was successful. The sulfonation of 2 and 7 position was prevented by blocking them with *tert*-butyl groups (Scheme 6).[18] Therefore, a hexa-sulfonated variant of this particular ligand seems to be possible although it has not been published yet.

Another option in more complex ligand syntheses is the sulfonation of the starting material. Fleckenstein et al. have demonstrated this approach with their synthesis of sulfonate-tagged NHC ligands[19] via the glyoxal route.[20] After the sulfonation of the 2,6-dimethylaniline, the synthesis followed the same route as for the non-sulfonated ligand precursor (Scheme 7).

Apart from classic reagents for the direct sulfonation of aryl groups, different research groups have come up with less harsh reactions that introduce sulfonate groups that are already bound to carbon.

Mohr et al. deprotonated diphenylphosphine, protected as its $BH_3$ adduct, which was subsequently treated with sodium 2-bromoethane-1-sulfonate (Scheme 8). In order to obtain the final ligand, the resulting product was refluxed in morpholine to remove the borane.[21]

Paetzold et al. used a sultone to introduce a sulfonate group into a mono-phosphine. Upon reduction by alkaline metals TPP and diphenylphosphine yield potassium diphenylphosphide, which attacks the sultone's electrophilic



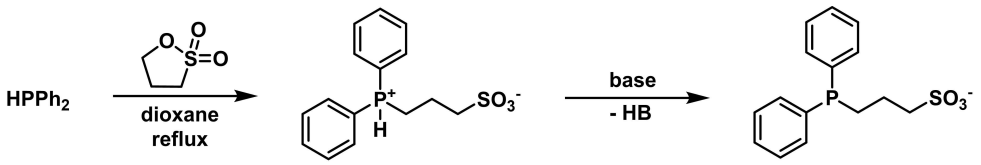

***Scheme 9.*** Synthesis of a mono-sulfonated diphenyl benzyl phosphine via a reaction with a sultone[22]

carbon atom (Scheme 9).[22] While the use of TPP as starting material implies a late-stage modification, it can be argued that this reaction does not fit into the concept since the final product is not TPP with an added polar group, but a different phosphine bearing the sulfonate group.

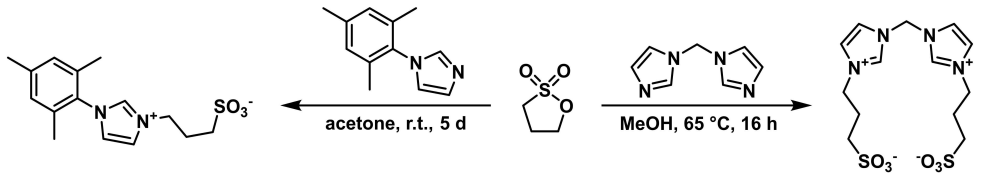
Similar to this approach, Shaughnessy et al. treated diphenyl phosphine with 1,3-propane sultone. Without the previous reduction of the phosphine, the reaction gives a bench-stable zwitterionic phosphonium salt. The free electron pair is blocked by a proton so that the active ligand is only released upon base addition in the catalytic mixture (Scheme 10).[23]

The straightforward tag approach based on 1,3-propane sultone can also be found with NHC ligands. The co-product-free reaction of the sultone with imidazoles gives zwitterionic NHC ligand precursors.[24] For a more detailed review of NHC modifications via the imidazole route, please see the review by Szczepaniak et al. (Scheme 11).[20]

Another approach to linking pre-sulfonated building blocks to phosphines has been presented by Paetzold et al. The reaction between vinyl phosphines and thiol-substituted




***Scheme 10.*** Synthesis of mono-sulfonate phosphine ligand with a sultone.[23]




***Scheme 11.*** Syntheses of sulfonate-tagged NHC ligands via imidazole alkylation with 1,3-propane sultone.[24]

building blocks gave the corresponding thioether-linked sulfo-phosphines (Scheme 12).[25]

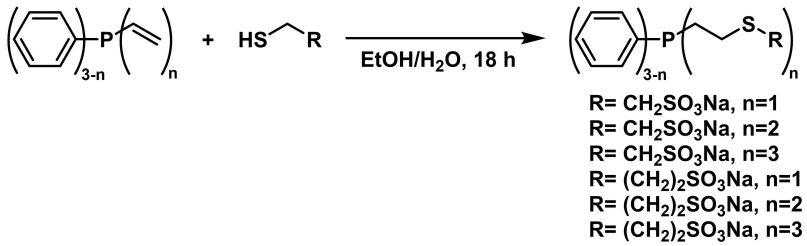
Utilizing terminal alkenes as well, Fremy et al. treated an in situ generated lithium phosphide with 2-acrylamido-2-methylpropane-1-sulfonic acid. The reaction yielded corresponding lithium sulfonate (Scheme 13).[26]

A rather exotic approach was published by Yuan et al. They oxidized a thiolato-bridged dinuclear palladium complex with oxone® and obtained a sulfonate-tagged mononuclear complex (Scheme 14).[27]

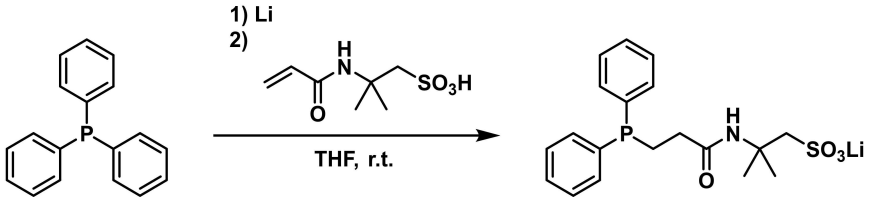
### *2.1.2. Carboxylic Acids and Carboxylates*

Closely related to the sulfonates are carboxylate-substituted ligands, both being derived from organic acids. Since the salts of carboxylic acids can be easily accessed from fatty acid esters by base hydrolysis, they have been known as soap for centuries. Therefore, their polar heads have found use in the synthesis of hydrophilic ligands.

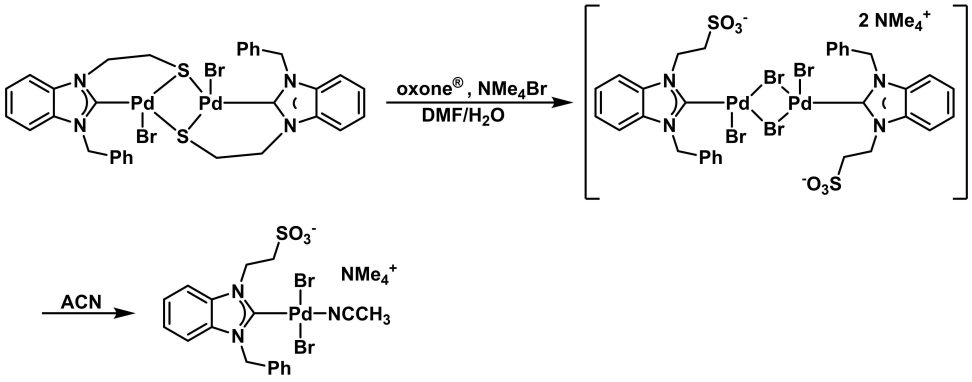
Churruca et al. utilized a carboxylic acid tag to obtain a hydrophilic CNC pincer ligand which allows catalyst separation via extraction. Ethyl 3,5-dibromo benzoate was treated




***Scheme 12.*** Synthesis of mono-phosphine ligands of varying degrees of sulfonation via the reaction of a vinyl-phosphine with a thiol-substituted sulfonate building block[25]




***Scheme 13.*** Synthesis of a lithium sulfonate ligand from TPP.[26]




***Scheme 14.*** Synthesis of a sulfonate-tagged palladium complex via the oxidation of thiolato ligands with oxone®.[27]

with an imidazole to afford the bis(imidazolium) salt (Scheme 15).[28]

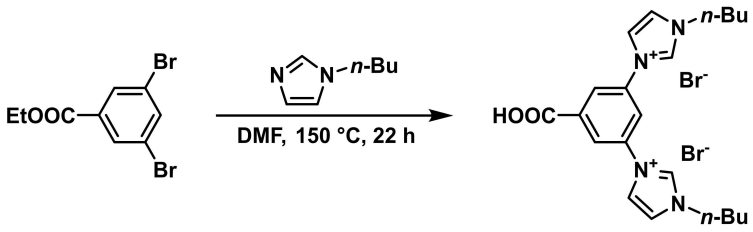
Contrary to this, Chen et al. published the salt of a carboxylic acid, a tricarboxylated derivative of TPP. It was synthesized via the aforementioned base hydrolysis. The introduction of the ester moiety proceeded through a Heck reaction. The 4,4′,4″-bromo-substituted triphenylphosphine oxide was coupled with acrylic acid butyl ester followed by reductions of the alkene and the phosphorus oxide moiety(Scheme 16).[29]

A carboxylated phosphine ligand based on TPP was published in 2002 by Amengual et al. In the first step they synthesized different tri-brominated TPP derivatives. These were then activated by a bromine-lithium exchange and the active species were quenched with a solution of $CO_2$ in THF yielding the lithium carboxylates (Scheme 17). A beneficial side effect is that due to the salt character of the product the usual LiBr waste, produced by the reaction of lithium organyls with brominated molecules, can be avoided in the second reaction.[30]

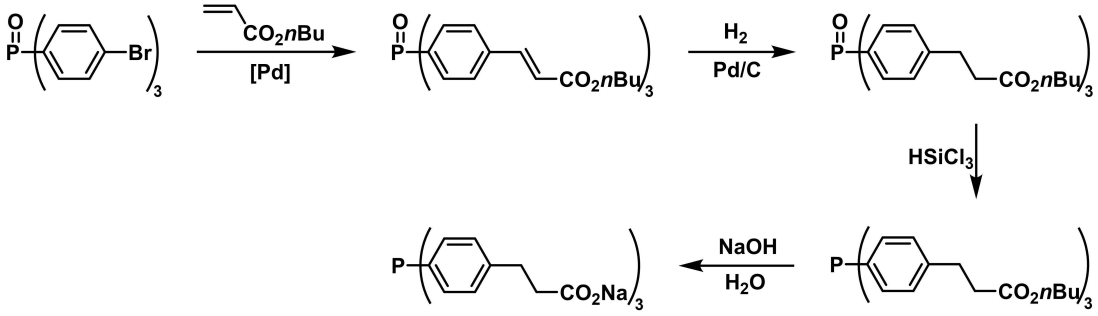
In the same manner, as they obtained a sulfonate ligand, Fremy et al. synthesized a dicarboxylated variant. Instead of a sulfonic acid, they used 2-methylene succinic acid after the reduction of TPP with lithium (Scheme 18).[26]

Moore et al. tagged an NHC ligand precursor with a carboxylate via the imidazole route. The imidazole was treated with 3-bromopropanoic acid and sodium carbonate to yield the zwitterionic ligand precursor (Scheme 19).[24a]

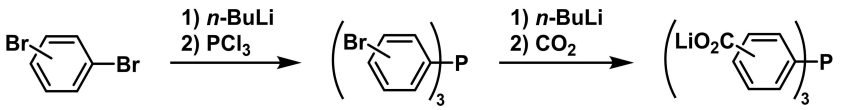
A niche approach that is limited to one specific ligand has been published by Mercier et al. Maleic acid anhydride was treated with the [4+2] dimer of 3,4-dimethyl-2*H*-phosp-



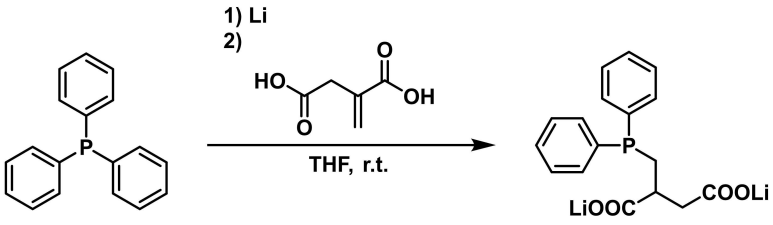

***Scheme 15.*** Synthesis of a carboxylic-acid-tagged CNC pincer ligand precursor.[28]



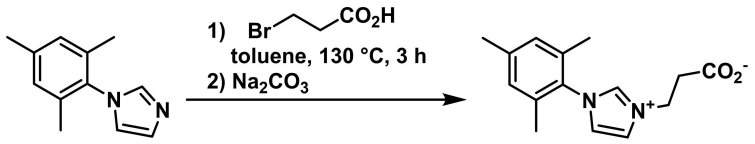

***Scheme 16.*** Synthesis of a tricarboxylated triphenyl phosphine via a Heck reaction, reduction, and base hydrolysis.[29]




***Scheme 17.*** Synthesis of tri-carboxylated triphenylphosphine by quenching lithium-aryls with $CO_2$.[30]




***Scheme 18.*** Synthesis of a dicarboxylate substituted monophosphine ligand.[26]




***Scheme 19.*** Synthesis of a carboxylate-tagged NHC ligand precursor.[24a]

hole. The resulting product was then treated with sodium hydroxide to yield the di-carboxylate ligand (Scheme 20).[31]

#### *2.1.3. Phosphonates*

A further anionic group that has been used to modify ligands towards polar solubility are phosphonates. Schull et al. introduced them over a three-step synthesis starting from (4-bromophenyl)diphenylphosphine. The phosphonate moiety is introduced in the first step. Its ethyl groups are exchanged for trimethylsilyl groups and the resulting silyl phosphonate is hydrolyzed and neutralized to the final di-sodium phosphonate (Scheme 21).[32]

#### *2.1.4. Cationic Groups*

While there is a range of different anionic groups used in polar soluble ligands, cationic groups, that induce solubility in polar media, all revolve around quaternary nitrogen.

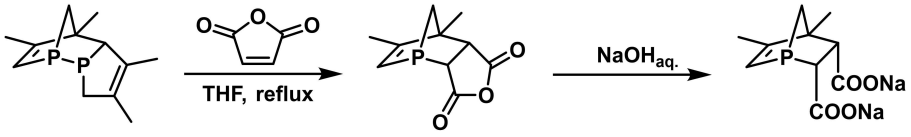
In the same way as they introduced sulfonate groups, Mohr et al. synthesized ligands that bear cationic groups. After protection of the free electron pair in dicyclohexyl phosphine with $BH_3$, it was lithiated and treated with a tertiary amine that possessed a leaving group (tosylate or chloride). The resulting tri-substituted phosphine (still bound as the $BH_3$ adduct) was then treated with methyl halides, affording the corresponding ammonium halides (Scheme 22). Treatment with morpholine under reflux yielded the final ligand.[21]

Alternatively, preformed ammonium building blocks can be introduced via the same synthesis route (Scheme 23).[21]

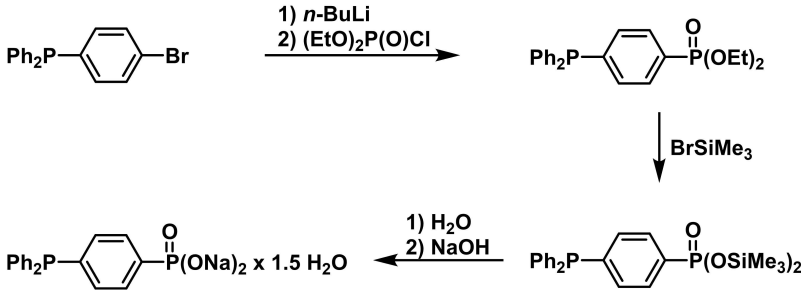
While the described syntheses of ammonium-tagged phosphine ligands use $BH_3$-adducts as protecting groups for the phosphorus during the alkylation of the tertiary amine, NHC ligands rely on another concept. Skowerski et al. avoided unwanted side reactions by applying the iodomethane to the already formed complex (Scheme 24).[33]

Dibowski et al. utilized guanidinium groups to obtain a hydrophilic ligand. Two different synthesis pathways lead to the mono-alkyl amine intermediate. The first route proceeds via the reduction of TPP with sodium in liquid ammonia and subsequent alkylation with 3-chloropropylamine. The second route starts with diphenylphosphine which reacts with acrylonitrile to give the alkyl nitrile-substituted phosphine. The cyano group is then reduced with $LiAlH_4$. The latter route can also be used for the synthesis of a dialkylamine-substituted phosphine. Both amine intermediates can be transformed into the desired guanidinium-substituted ligands by 1H-pyrazole-l-carboxamidine under basic conditions in DMF (Scheme 25).[34]

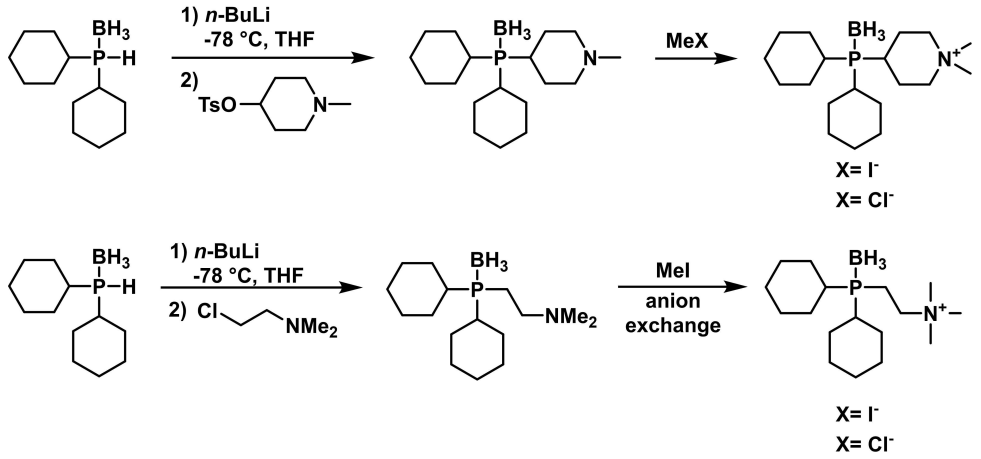
The same group applied guanidinium moieties in TPP derivatives. Mono-, di- and tri-substituted variants of the ligand were all synthesized in the same way. *m*-aminophenyl-substituted phosphines were treated with HCl and the obtained ammonium salt was treated with *N,N-dimethyl cyanamide* (Scheme 26).[35]



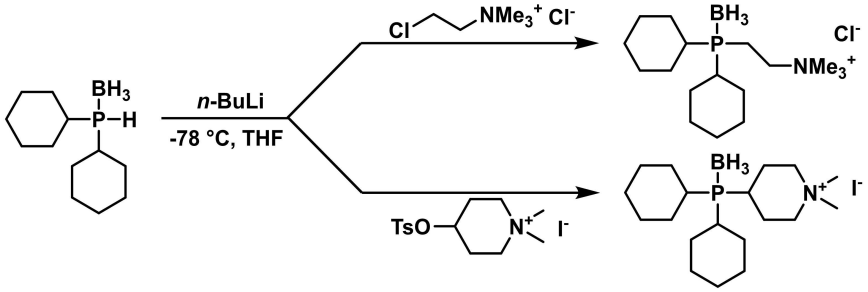

***Scheme 20.*** Synthesis of di-sodium 3,4-dimethyl-1-phospha-2-norbornene-5,6-dicarboxylate.[31]



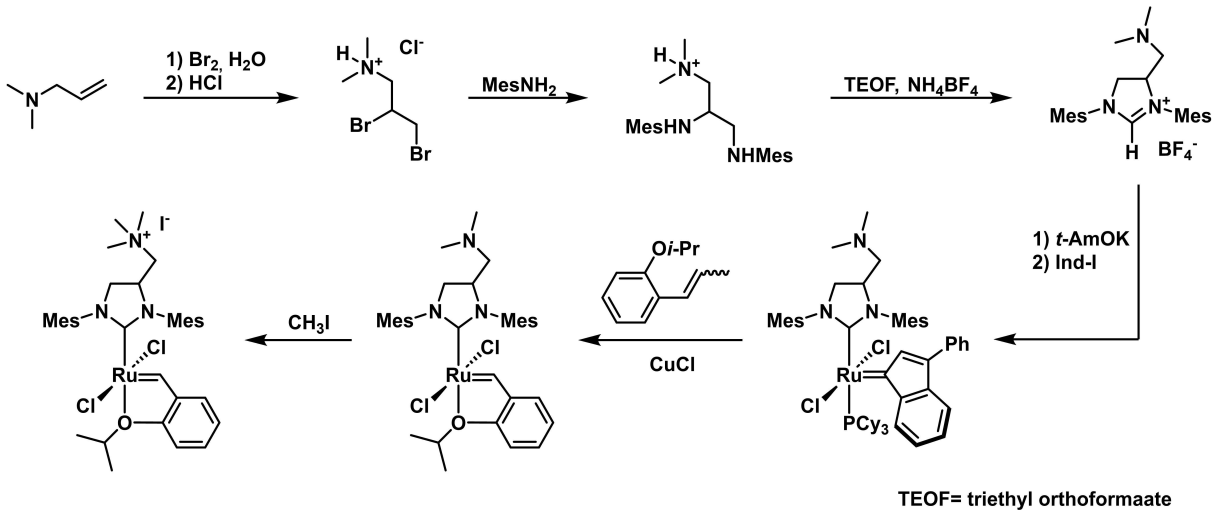

***Scheme 21.*** Mono-phosphonate substituted triphenylphosphine.[32]




***Scheme 22.*** Introduction of tertiary amines into alkyl phosphines and subsequent formation of an ammonium group.[21]



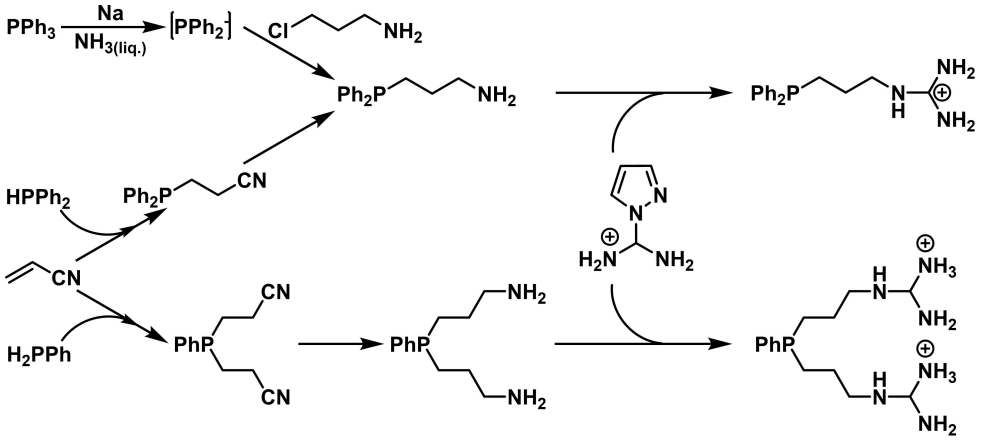

***Scheme 23.*** Introduction of preformed ammonium building blocks into alkyl phosphines.[21]



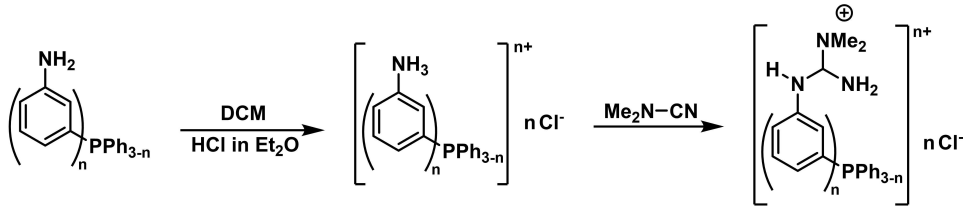

***Scheme 24.*** Synthesis of a tetraalkyl-ammonium-tagged Grubbs-Hoveyda II catalyst.[33]

Contrary to the aforementioned approaches that rely on specifically introduced amine groups for the synthesis of ammonium moieties in ligands, Ramarou et al. utilized existing amine groups in the 1,3,5-Triaza-7-phosphaadamantane (PTA) to create an even more hydrophilic ligand than PTA itself. Treating PTA with chloromethyl benzene, 1,4-bis(chloromethyl)benzene, and 1,3,5-tris(chloromethyl)benzene afforded the cationic ligands shown in Scheme 27.[36]

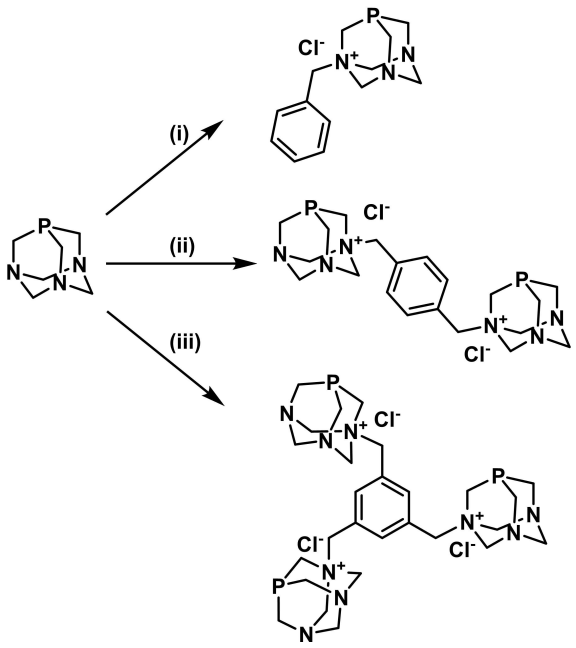
Just as NHC ligands replaced phosphines in several catalyst systems years ago,[37] they are now challenged by the class of cyclic alkyl amino carbenes (CAAC).[38] Nagyházi et al. have published a CAAC ruthenium complex, which is soluble in polar solvents. The polar tag is an *N*,*N*,*N*-



***Scheme 25.*** Syntheses of mono- and di-guanidinium-substituted phosphines.[34]



***Scheme 26.*** Synthesis of phosphine ligands bearing *m*-guanidinium phenyl moieties.[35]



***Scheme 27.*** Synthesis of alkylated cationic PTA ligands for mono, bi-, and trinuclear complexes. (i) Chloromethyl benzene, MeOH, 70 °C, 2 h; (ii) 1,4-bis(chloromethyl)benzene, acetone, 60 °C, 2 h; (iii) 1,3,5-tris(chloromethyl)benzene, acetone, 60 °C, 18 h.[36]

trimethylanilinium cation with triflate as the counter ion. Contrary to most tags, the polarity is introduced in the last synthesis step as with ammonium salt tags on NHCs. The starting material for the ligand already includes a *N*,*N*-dimethylaniline moiety but alkylation of the amine with methyl triflate only takes place after complex formation with the ruthenium precursor (Scheme 28).[39]

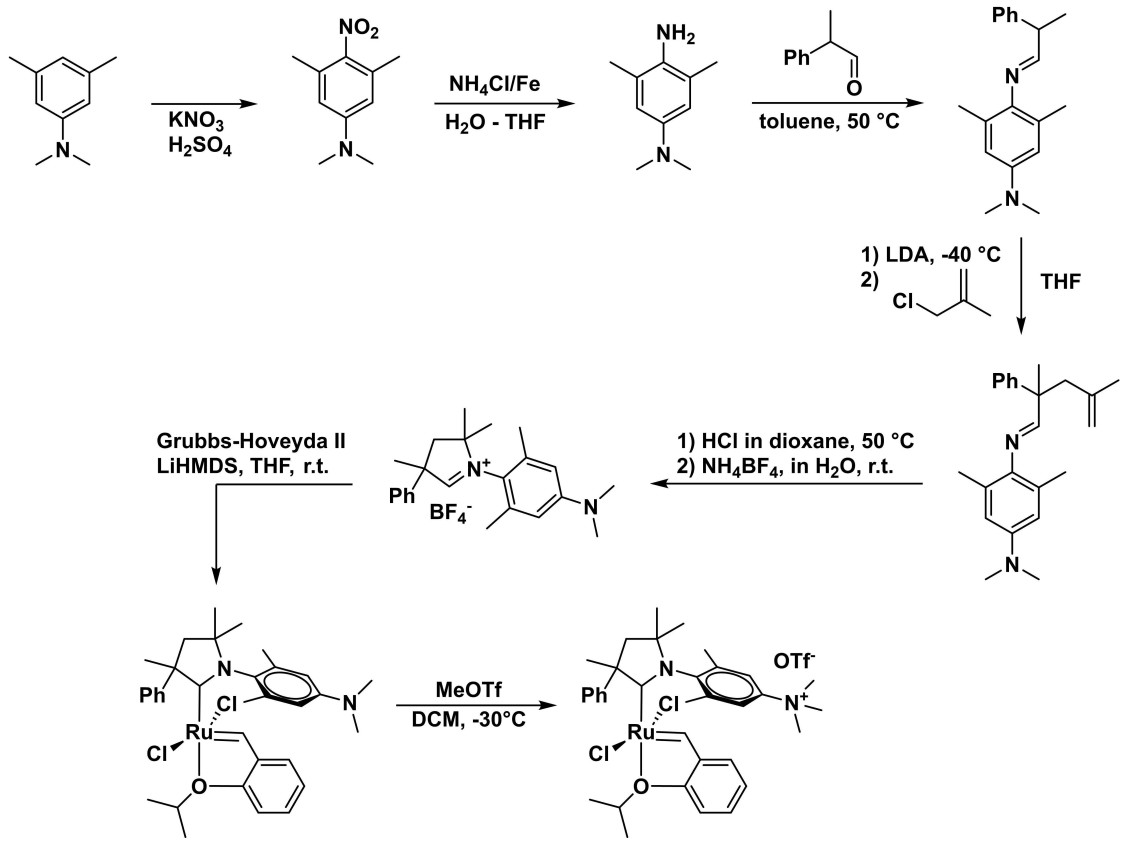
#### 2.1.5. Zwitterionic Groups

The combination of anionic and cationic ligands can be found in sulfobetaines derived from 1,3,5-triaza-7-phosphaadamantane (PTA). This zwitterionic ligand was published by Bergamini et al. in 2013.[40] Starting with the commercially available and already water-soluble PTA ligand, the addition of 1,3-propane sultone or 1,4-butane sultone gives the corresponding sulfobetaines (Scheme 29). Although Bergamini et al. described the use of three equivalents of sultone, only the mono-sulfobetaine is described as the product. A possible explanation for this could be that upon the quaternization of the first amine, the positive charge withdraws electron density from the remaining tertiary amines. Consequently, these amines are deactivated and do not undergo further reactions with sultones.

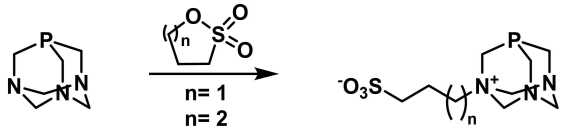
Although sulfobetaines are quite common in surfactants we are only aware of this one ligand system as an example of the use of sulfobetaines to modify catalyst solubility.

#### 2.1.6. Groups for Catalyst Fixation in Ionic Liquids

Ionic liquids are the pinnacle of liquid polar phases. In order to fixate a homogeneous catalyst in one of these it has to bear salt groups. Due to their polarity, many hydrophilic




***Scheme 28.*** Synthesis of an *N*,*N*-dimethylaniline-tagged CAAC ligand, complex formation, and subsequent alkylation of the amine to the polar soluble ammonium salt of the complex.[39]




***Scheme 29.*** Synthesis of zwitterionic sulfobetaine ligands by reaction of a tertiary amine with sultones.[40]

ligands can therefore be dissolved and fixated in ionic liquids due to the attached sulfonates, carboxylates, or ammonium groups. Nonetheless, there have been attempts to synthesize ligands exactly for application in ionic liquids. For a deeper insight into ionic tags and ionic liquids, we recommend the reviews by Lombardo and Trombini[41] as well as Šebesta.[42]

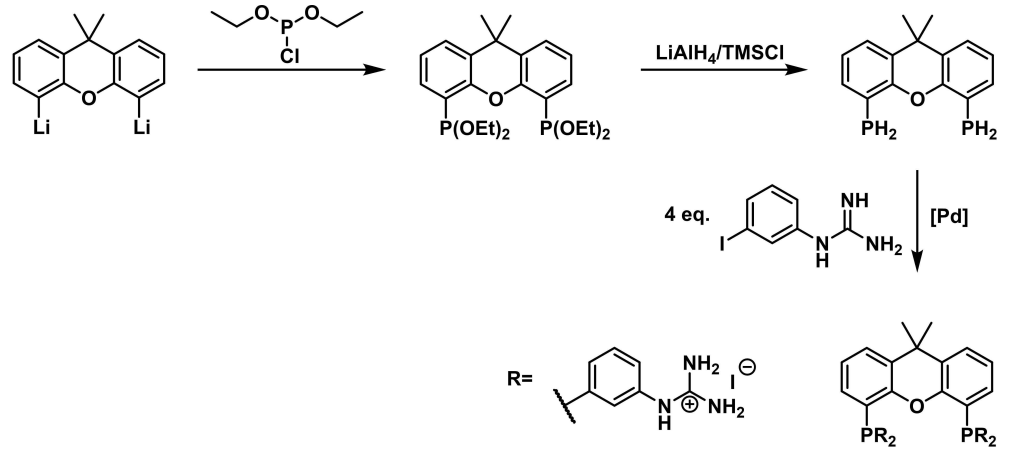
One of the groups applied in this approach is guanidinium whose introduction has already been described for different ligands in section 2.1.4. Instead of building up the desired guanidinium moiety in an already-formed phosphine ligand, Wasserscheid et al. took a modular approach that introduces a building block containing a guanidine moiety. Using the bis(primary phosphine) as a platform (synthesized according to Dierkes et al.[43]), the guanidine building block was linked to the phosphorus atoms via a palladium-catalyzed coupling reaction (Scheme 30).[44]

Kottsieper et al. utilized 1-vinyl imidazole as a building block to introduce imidazolium groups into phosphine ligands. Primary and secondary phosphines with 1-vinyl imidazole give imidazole intermediates under basic conditions. These can be either quaternised directly with HX (X = Cl, Br) or after phosphine protection with methyl iodide or triethyl oxonium hexafluorophosphate (Scheme 31).[45] Imidazolium tags are the most common modification of catalysts regarding their solubility in ionic liquids.[42]

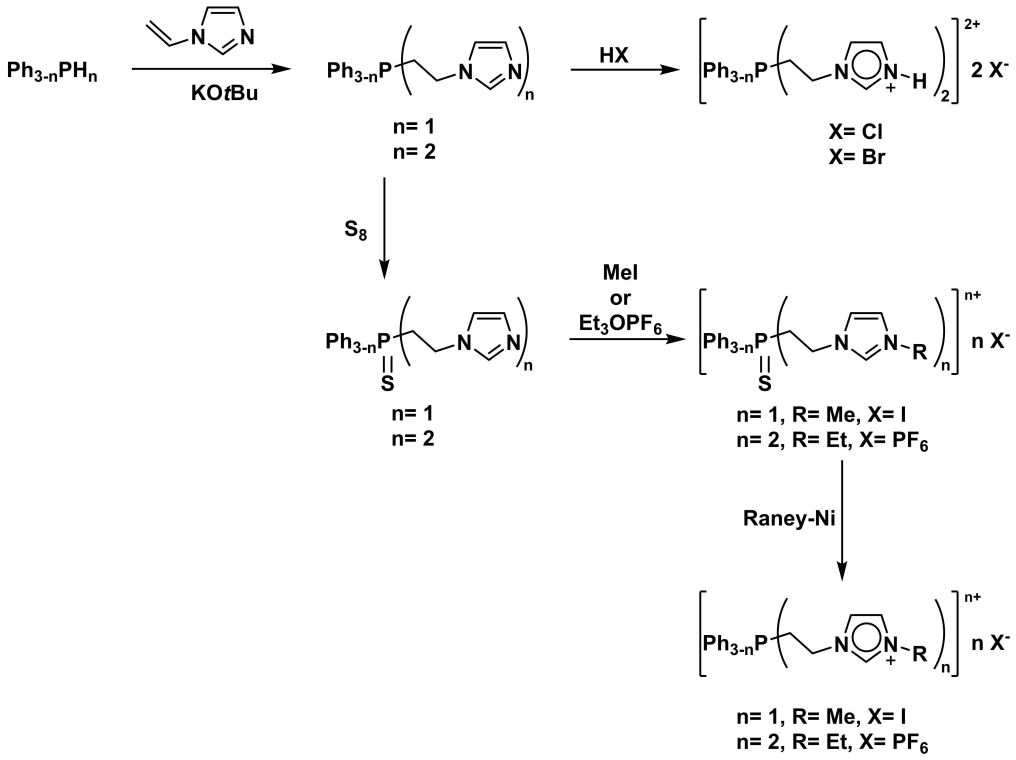
While mimicking the structural motifs of ionic liquids to fixate a catalyst in an IL is the most obvious approach, Brasse et al. took a different one. They incorporated a cobaltocenium moiety in the backbone of a diphosphine ligand and combined it with the non-coordinating anion $PF_6^-$ to create a ligand salt, which is soluble in ILs. Two closely related compounds were prepared via phosphine-substituted cyclopentadienyls and cobaltocene intermediates. The cobaltocenes were oxidized by hexachloroethane and the chloride anions were exchanged for hexafluorophosphate (Scheme 32).[46]

### 2.1.7. Carbohydrates and Other Polyols

Another class of hydrophilic groups are polyols. Their hydrophilic properties stem from the large number of




***Scheme 30.*** Introduction of a guanidinium building block into xantphos.[44]

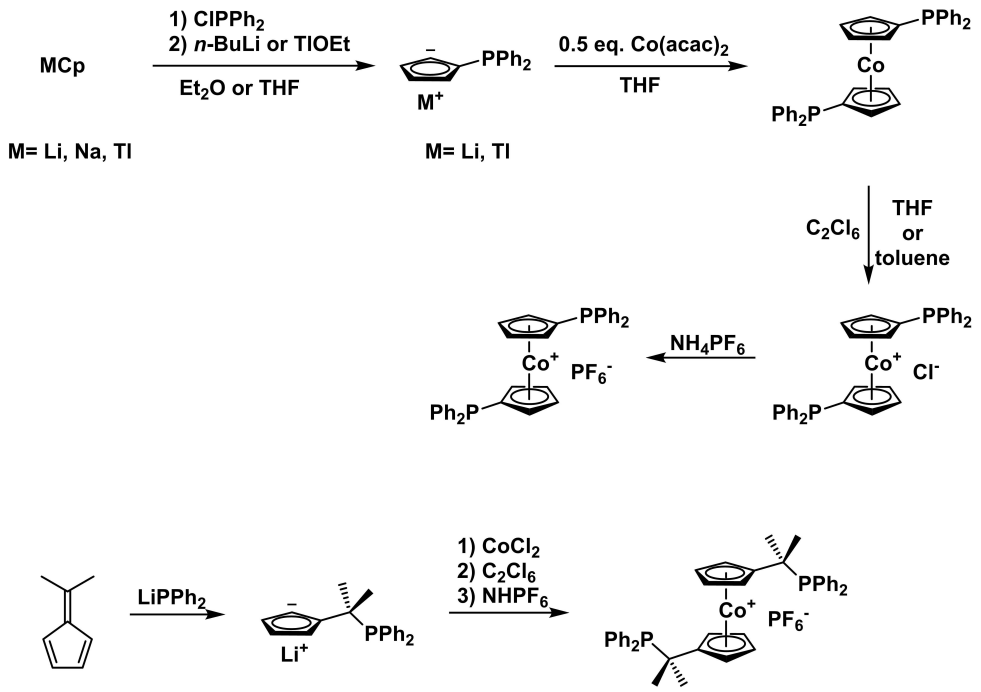



***Scheme 31.*** Synthesis of cationic phosphine ligands with 1-vinyl imidazole for application in ionic liquids.[45]

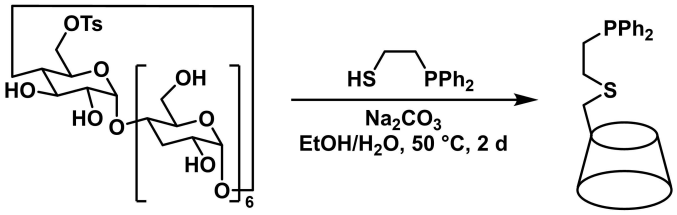
hydroxy groups they incorporate. Carbohydrates are prominent examples of the polyol class, which can be found in our everyday life. Their hydrophilicity has already been used in surfactants and can be transferred into hydrophilic ligands as well.

A special class of carbohydrates, cyclodextrins, are common phase transfer agents in polar/non-polar biphasic reaction systems. Due to their cyclic structure, they can imbed non-polar molecules inside themselves and bring them into the polar phase. Reetz et al. attached 6-mono-6-p-toluenesulfonyl-β-cyclodextrin to 2-(diphenylphosphanyl)ethane-1-thiol via a simple $S_N2$ reaction. The obtained product was a bidentate ligand with phosphorus and sulfur as donor atoms (Scheme 33).[47]

The reaction published by Reetz et al. has the advantage that it can be performed without the protection of the hydroxy groups and is therefore a simple one-step synthesis. Other synthesis routes need protecting groups to prevent unwanted side reactions between hydroxy groups and the active site on the carbohydrate. Beller et al. linked their phosphine ligand to the carbohydrate via the formation of an ether. 4-hydroxy triphenylphosphine was deprotonated by NaOH and then treated with the carbohydrate halide. To prevent reactions between halide and hydroxy groups, the




***Scheme 32.*** Synthesis of phosphine ligands with cobaltocenium backbones for use in ionic liquids.[46]



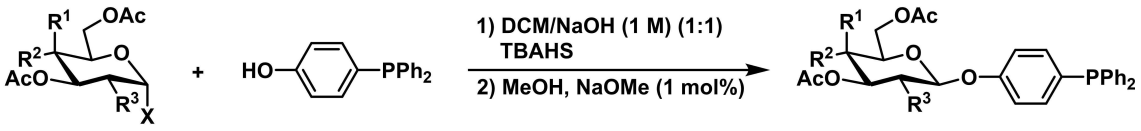

***Scheme 33.*** Synthesis of a β-cyclodextrin substituted bidentate PS ligand via an $S_N2$ reaction.[47]

latter were acetyl-protected, which were then partially removed with sodium methoxide (Scheme 34).[48]

Similarly to this, Parisot et al. used acetyl-protected glucosamine. The primary amine moiety reacts with the 3- or 4-(diphenylphosphanyl)benzoic acid and forms an amide. The deprotection of the hydroxy groups differs between the two synthesis routes Parisot et al. published. The first route proceeds via the reaction of glucosamine with the benzoic acid derivative in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC) and 1-hydroxy benzotriazole (HOBT). The product was isolated and subsequently deprotected with catalytic amounts of sodium methoxide. The second synthesis route was a one-pot reaction of the same starting materials as well as EDC, HOBT, and $NaHCO_3$ in a DMF/water mixture (Scheme 35).[49]

### 2.1.8. Polar Polymers

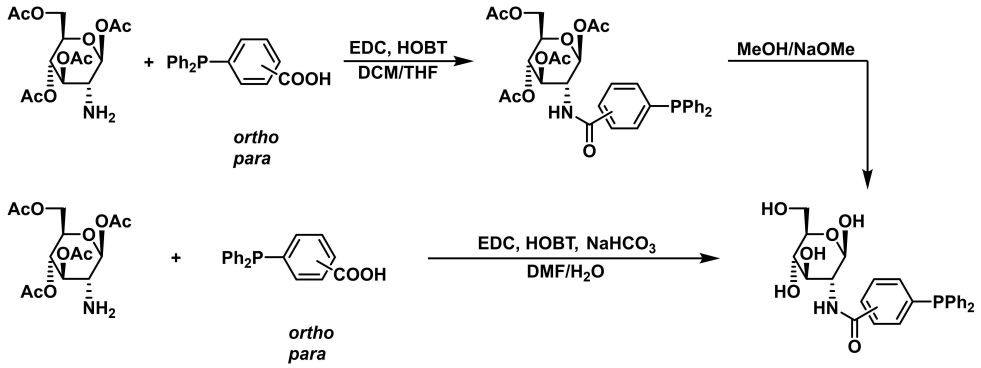
A further group of non-ionic tags, which induce polar solubility, are polar polymers. As stated in the introduction this review focuses on catalysts systems that are strictly homogeneous during the reaction. The most common soluble polymer, which is applied, is polyethylene glycol (PEG), which can be introduced in different ways.[50] Benaglia et al. tagged Me-PEG mono succinate to *trans*-4-hydroxy-L-proline, an organocatalyst, via the esterification of the acid with the proline's hydroxy group (Scheme 36).[51]



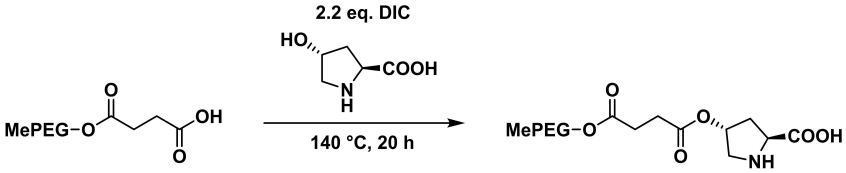

X= Cl, $R^1$= H, $R^2$= OAc, $R^3$= NHAc
X= Br, $R^1$= OAc, $R^2$= H, $R^3$= OAc
X= Br, $R^1$= H, $R^2$= OAc, $R^3$= OAc

$R^1$= H, $R^2$= OH, $R^3$= NHAc
$R^1$= OH, $R^2$= H, $R^3$= OH
$R^1$= H, $R^2$= OH, $R^3$= OH

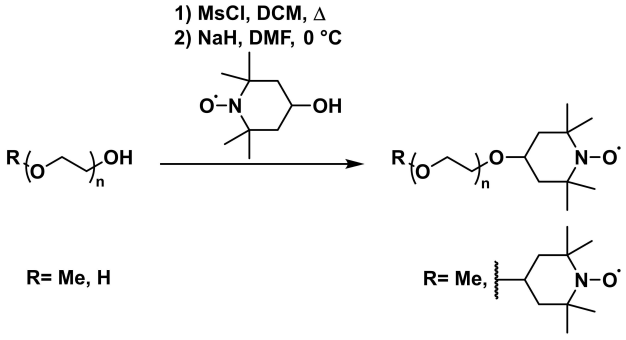
***Scheme 34.*** Synthesis of a carbohydrate-substituted triphenylphosphine.[48]




***Scheme 35.*** Linkage of glucosamine to a triarylphosphine via the formation of an amide bond.[49]




***Scheme 36.*** Synthesis of a PEG-tagged proline derivative.[51]

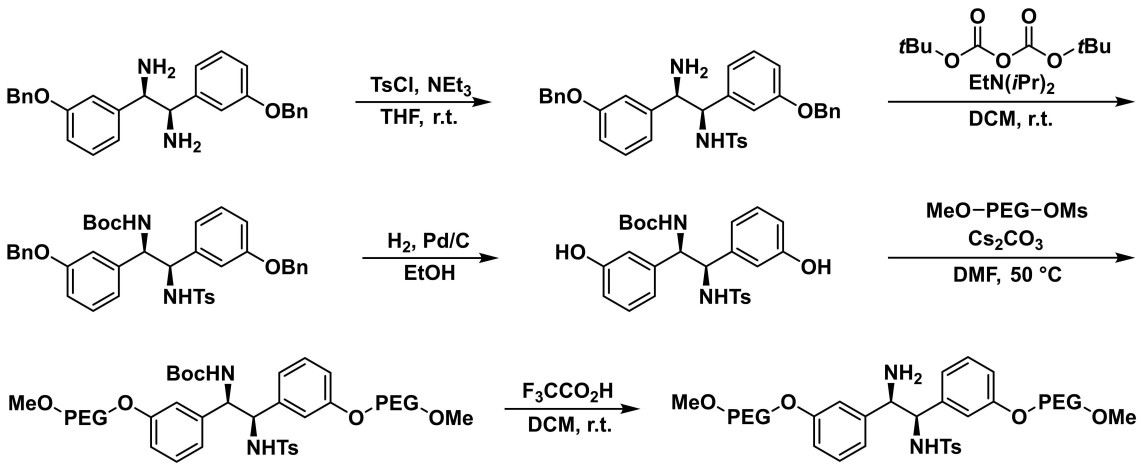



***Scheme 37.*** Synthesis of a PEG-tagged TEMPO.[52]

Another organocatalyst-PEG linkage was achieved by Ferreira et al. through the formation of the PEG-mesylate, which was then treated with the alcoholate of the 2,2,6,6-tetramethylpiperidinyloxyl (TEMPO) catalyst in a nucleophilic substitution (Scheme 37).[52]

The formation of PEG mesylates to enable the substitution of the hydroxy group is a generally useful synthesis tool, which has been applied by Li et al. in their synthesis of a diamine ligand. The PEG mesylate's affinity for nucleophiles makes a tert-butyloxycarbonyl (Boc) protecting group necessary to prevent the substitution of the PEG mesylate with the primary amine of the ligand (Scheme 38).[53]

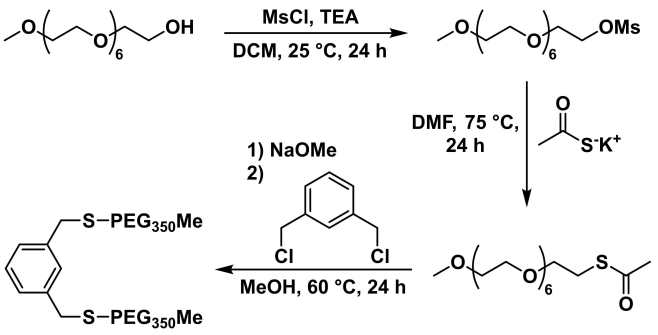
Bergbreiter et al. used PEG mesylate as well to obtain a PEG thioacetate through nucleophilic substitution. The PEG thioacetate was treated with sodium methoxide and




***Scheme 38.*** Synthesis route of a PEG-tagged chiral diamine ligand including the use of a Boc protecting group.[53]

subsequently with 1,3-bis(chloromethyl)benzene. The resulting dithioether is a precursor to a tridentate SCS ligand (Scheme 39).[54]

Wang et al. chose a pre-substituted PEG-derivative for their synthesis of PEG-tagged cinchonidine and quinine derivatives. Refluxing diacetamido-PEG2000 chloride with cinchonidine and quinine in chloroform for 100 h gave the corresponding ammonium salts through the alkylation of the tertiary amines (Scheme 40).[55]



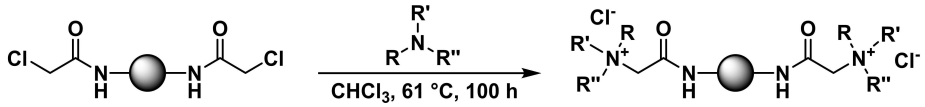

***Scheme 39.*** Synthesis of a precursor of a PEG-tagged tridentate SCS ligand.[54]

Substitution of the mesylate moiety with an azide group gives a building block capable of undergoing a Huisgen reaction with ethynylpyridines, as shown by Samanta et al. The reaction product is a PEG-tagged pyridine ligand with triazole as the linking group between ligand and tag (Scheme 41).[56]

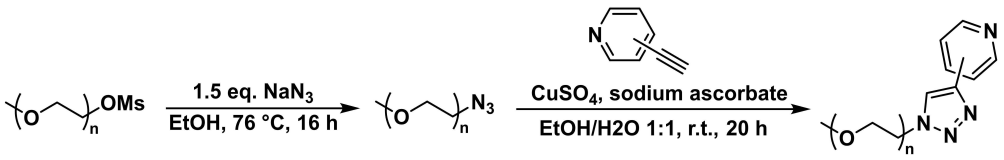
A rare example of a late-stage modification of a preformed complex instead of a ligand was published by Zarka et al. They introduced an alcohol moiety into an NHC ligand by alkylation of the imine nitrogen of 1-methyl-1*H*-imidazole, synthesized the corresponding rhodium complex, and then linked the complex to a soluble, amphiphilic block copolymer. The last step was achieved via the esterification of carboxylic acid groups on the copolymer with the hydroxy group bound to the NHC ligand (Scheme 42).[57]

### 2.2. Non-polar Groups

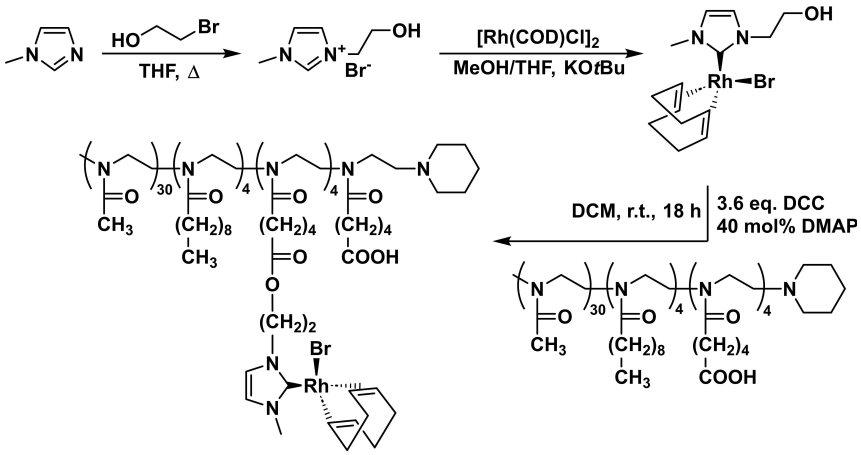
When it comes to non-polar catalysts, it is often not necessary to introduce special groups for solubility in non-polar solvents since most known ligands already contain phenyl, cyclohexyl, iso-butyl, and similar groups. Such substituted ligands are soluble in a broad range of non-polar




***Scheme 40.*** Schematic synthesis of PEG-tagged ammonium salts of cinchonidine and quinine.[55]




***Scheme 41.*** Synthesis of PEG-tagged pyridine ligand via the Huisgen reaction.[56]




***Scheme 42.*** Late-stage modification of a Rh-NHC complex through the esterification of a soluble, amphiphilic block copolymer.[57]

solvents. At the same time, a partially polar character of their corresponding complexes can lead to a residual solubility in polar solvents which makes them unsuitable for biphasic recycling strategies. In order to fixate a homogeneous catalyst in a non-polar phase the non-polar character needs to be enforced by large non-polar groups.

#### 2.2.1. Non-polar Oligomers and Polymers

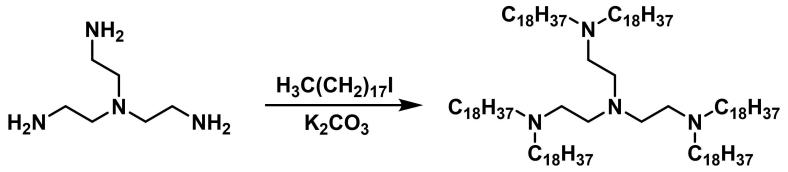
The most easily available large non-polar molecules are commonly used polymers like polyethylene, polystyrene, polyisobutylene, and their related oligomers.

Barré et al. used octadecyl groups to modify a tripodal amine ligand by a straightforward $S_N2$ reaction (Scheme 43). Although they applied it in heterogeneous recycling, utilizing its temperature-dependent solubility in dioxane, the ligand is a good example for the use of non-polar alkyl chains and could be suitable for biphasic recycling when applied in a non-polar solvent like heptane.[58]

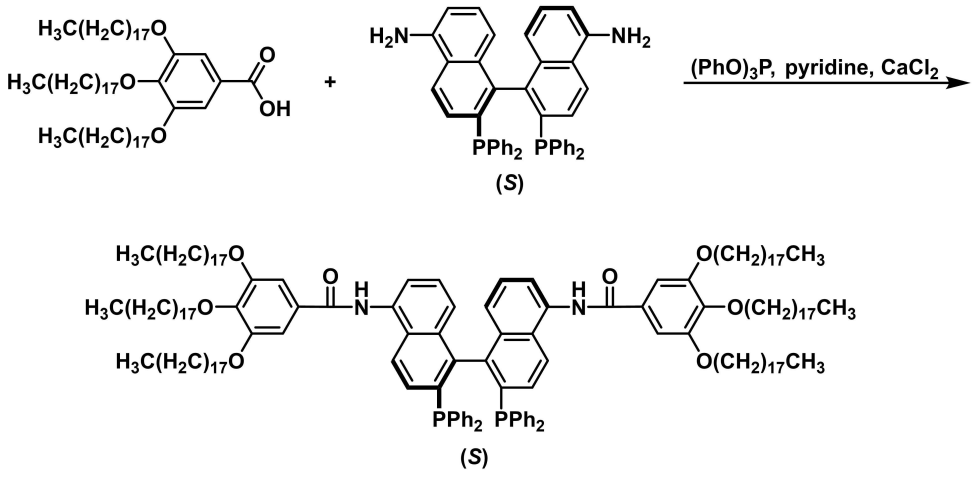
Another example of the use of octadecyl groups was published by Huang et al. The key difference to Barré's approach is the use of pre-substituted building blocks. Instead of binding the alkyl chain directly to the ligand's donor atom, two building blocks bearing three octadecyl chains were attached to the BINAP backbone. The linking moiety is an amide bond that is formed from the carboxylic acid building block and the primary amine substituent of the backbone (Scheme 44).[59] The previous introduction of the two amine moieties into the backbone is achieved via the nitration of BINAP and subsequent reduction of the nitro group (Scheme 45).[60] Like with Barré's ligand, the catalyst recycling in this publication was performed based on the thermomorphic behavior of the catalyst in a polar solvent (mixture).[59]

Bergbreiter and co-workers established various polyisobutylene oligomers in various publications as non-polar substituents, which have been used either to create thermomorphic catalysts or to fixate the catalyst in the *n*-heptane phase of liquid-liquid biphasic systems. Due to the various ligands, organocatalysts, and their multi-step synthesis routes, we compiled the routes into one overview graphic (see Scheme 46).

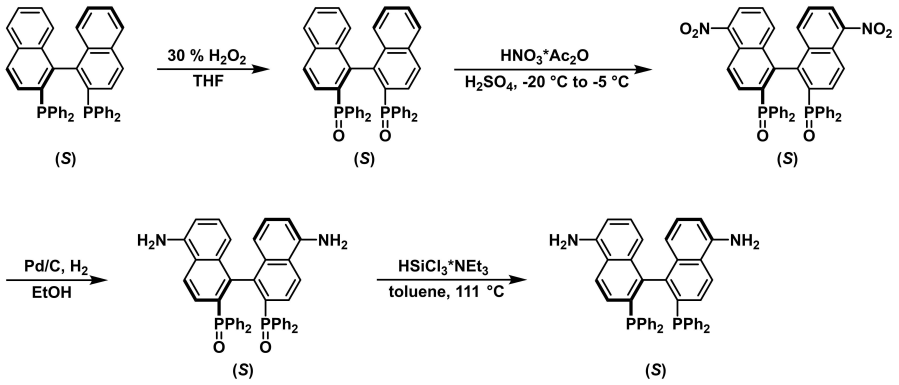
Two simple routes (1 & 2) have been established to link PIB to phenyl building blocks, which are then used to build up ligands from the alkylidene[62] (for Grubbs Hoveyda catalysts) and salen[61] (route 2) or NHC[67] (route 1) families. The reactions are either catalyzed by a Brønsted[61,62] or a Lewis acid.[67] Route 4 leads to ligands, which are tagged to PIB through a sulfone moiety. In the first step, thioacetic acid and PIB give the corresponding thioacetate which is then hydrolyzed to the thiol. The thiol is treated with 4-nitrophthalonitrile in a nucleophilic aromatic substitution reaction. The obtained thioether is oxidized to the sulfone by *meta*-chloroperoxybenzoic acid.[68] The basis for the four other synthesis routes lies in the introduction of a hydroxy group. This was achieved by the *anti*-Markovnikov addition of borane dimethylsulfide to the terminal alkene moiety of PIB. The following oxidation with aqueous NaOH and $H_2O_2$ yields the PIB with a terminal hydroxy group. The subsequent reaction with mesyl chloride in the presence of $NEt_3$ gives the corresponding mesylate.[63] Route 3 proceeds from




***Scheme 43.*** Synthesis of an octadecyl-substituted tripodal amine ligand.[58]




***Scheme 44.*** Introduction of two primary amine moieties into the backbone of BINAP.[60]




***Scheme 45.*** Synthesis of an octadecyl-substituted BINAP derivative.[59]

there with the reaction of the PIB-mesylate, 1-methyl-1*H*-imidazole, and NaI, yielding the iodide salt ligand precursor of a PIB- and methyl-substituted NHC ligand.[63] Route 5 allows for the introduction of any lithiated building block. The PIB-mesylate is refluxed with LiBr in THF to obtain the brominated PIB. In the second step, the brominated PIB reacts with the lithiated building block, e.g. lithium phosphides.[65] The brominated PIB is the starting point for synthesis route 6. Treatment with potassium phthalimide and hydrazine gives the corresponding primary amine, which can be coupled with synthons that carry a carboxylic acid moiety.[66] Another possible synthesis route (7) began again with the hydroxyl-substituted PIB, which was treated with iodine in the presence of TPP and imidazole. The obtained PIB-tagged iodide was used to form the triphenylphosphonium salt with TPP. A Wittig reaction with 4-bromobenzaldehyde and subsequent reduction of the formed alkene yielded PIB-tagged 4-bromobenzene. The last step is then a palladium-catalyzed C–N coupling reaction, that binds the PIB onto a secondary amine.[69]

Scheme 47 shows the further synthesis route from PIB-tagged 4-hydroxybenzene to a PIB-tagged alkylidene ligand for the use in Grubbs-Hoveyda catalysts. After formylation of the phenol with paraformaldehyde and ether formation from phenol and isopropyl iodide, a Wittig olefination yielded the final ligand.[62]

Apart from the use in salen ligands, where the oxygen atom serves as a donor atom, PIB-tagged phenols can be used to link PIB to a ligand via an ether group. Liang et al. deprotonated the phenol and applied it in an $S_N2$ reaction with ethyl 11-iodoundecanoate. The obtained ether-bound ester was hydrolyzed and neutralized to the carboxylic acid, a precursor for a carboxylate ligand (Scheme 48).[70]

Polyethylene (PE) and ethylene oligomers can be used as well to fixate ligands and catalysts. In principle, the same methods that have been applied for the linkage of ligands to PIB can be utilized for PE tags (see Scheme 46). Two examples of this have been presented by Hobbs et al. and Suriboot et al. Hobbs used a PE mesylate to link the non-polar chain to 1-mesityl-1*H*-imidazole (Scheme 49), a precursor of the corresponding NHC ligand.[71]

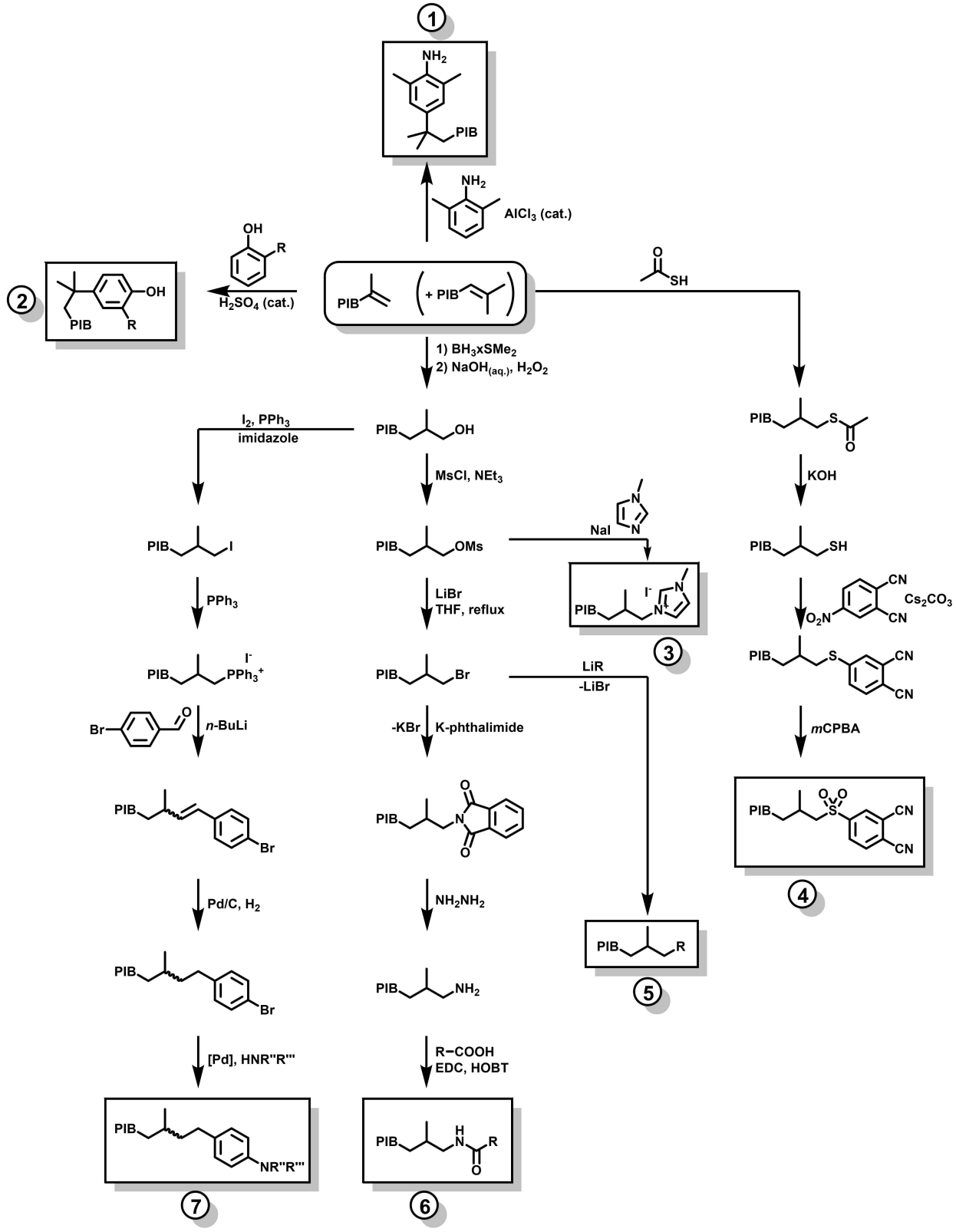
Suriboot applied a PE oligomer with a terminal hydroxy group to form the PE-tagged 4-amino-3,5-dimethylphenoxy-substituted PE. This synthesis consists of two steps due to the necessity for Boc-protection of the primary amine. The alky aryl ether is the product of a Mitsunobu reaction together with a subsequent deprotection of the aniline (Scheme 50).[72]

Furthermore, it is possible to generate PE-tagged monophosphine ligands by quenching the polymerization of ethylene with *n*-butyl lithium and reacting the lithiated oligomers with diphenylphosphine chloride (Scheme 51). The generated PE oligomers are insoluble in typical organic solvents at 25 °C, i.e. display thermomorphic behavior, when their molecular mass is greater than 1000 Da.[73] Shorter chain lengths should result in oligomers, that possess selective solubility in non-polar solvents.

While all the approaches towards polymer- or oligomer-tagged ligands and their corresponding catalysts, which have been described in the sections above, aim to tag the terminal position of a polymer/oligomer chain onto a ligand, there is also the possibility to link multiple ligands with various positions of the same polymer chain. Keller et al. used a platinum-catalyzed hydrosilylation reaction to link a vinyl-substituted diketonate ligand precursor to polysiloxane (Scheme 52).[74]

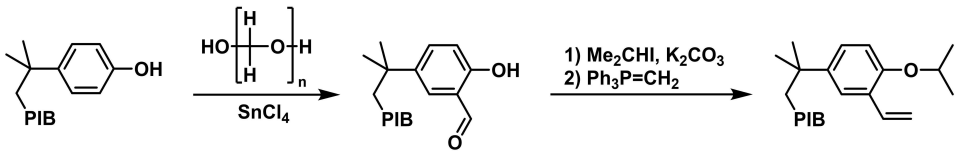
Apart from linking ligands to preformed polymers or oligomers, there is the possibility of incorporating ligand-containing building blocks into a polymer. The polymer can either contain purely ligand monomers or be a copolymer consisting of ligand building blocks and further monomers. Following this approach, Choi et al. synthesized 4-styryldiphenylphosphine via the reaction of a styryl Grignard reagent with diphenylphosphine chloride. This monomer was then used in the direct radical polymerization with styrene as well as the polymerization with styrene and 1,4-bis(4-vinylphenoxy)butane. The latter leads to the cross-linked JandaJel™ with the TPP substituent (Scheme 53).[75]

The utilization of ROMP enabled Yang et al. to build up a polymer from a bis(phosphine) monomer. Starting with the [4+2] cycloaddition of cyclopentadiene and benzoquinone they synthesized a backbone bearing a norbornene group. After the introduction of the phosphine moieties the bis(phosphine) ligand was polymerized with the Grubbs II catalyst through a ROMP (Scheme 54).[76]

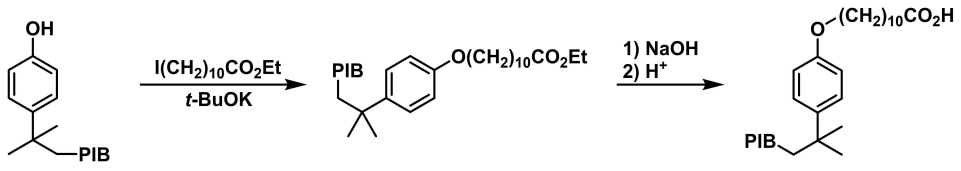



***Scheme 46.*** Functionalization of polyisobutylene (PIB) and subsequent linkage with ligands/ligand building blocks or organocatalysts.[61–69]

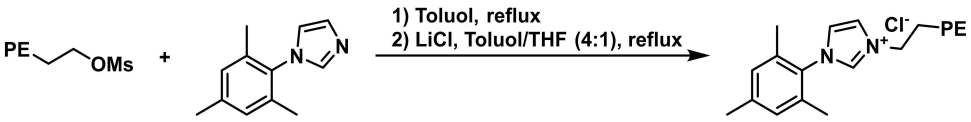
Using norbornene ROMP as well, Holbach et al. developed norbornene-tagged salen complexes of manganese and cobalt over a four-step synthesis. The polymerizable norbornene moiety was introduced in the last of the four steps via the reaction of 5-norbornene-2-carboxylic acid chloride and a hydroxyl group on the salen ligand. Instead of polymeriz-



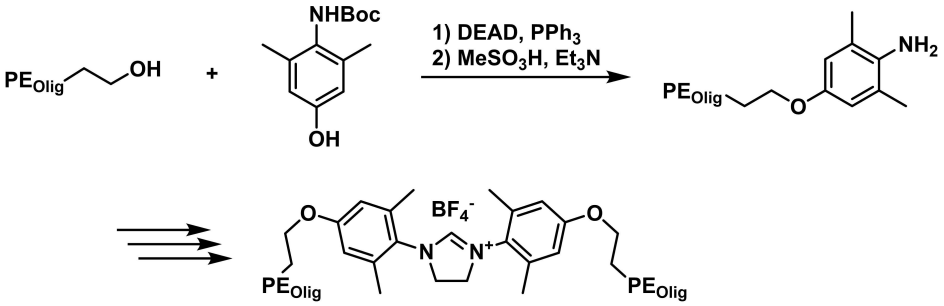

***Scheme 47.*** Synthesis of a PIB-tagged *o*-isopropoxybenzylidene ligand for Grubbs-Hoveyda catalysts.[62]



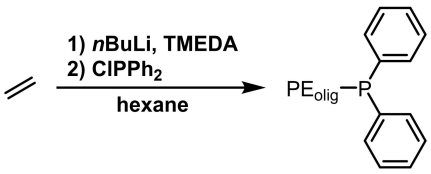

***Scheme 48.*** Synthesis of a PIB-tagged carboxylate ligand.[70]



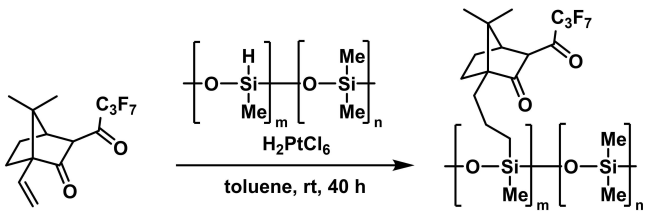

***Scheme 49.*** Synthesis of a PE substituted NHC ligand precursor.[71]




***Scheme 50.*** Synthesis of an ethylene-oligomer-substituted NHC ligand precursor.[72]




***Scheme 51.*** Synthesis of an ethylene oligomer substituted phosphine via quenching of a polymerization reaction and subsequent reaction with diphenylphosphine chloride.[73]



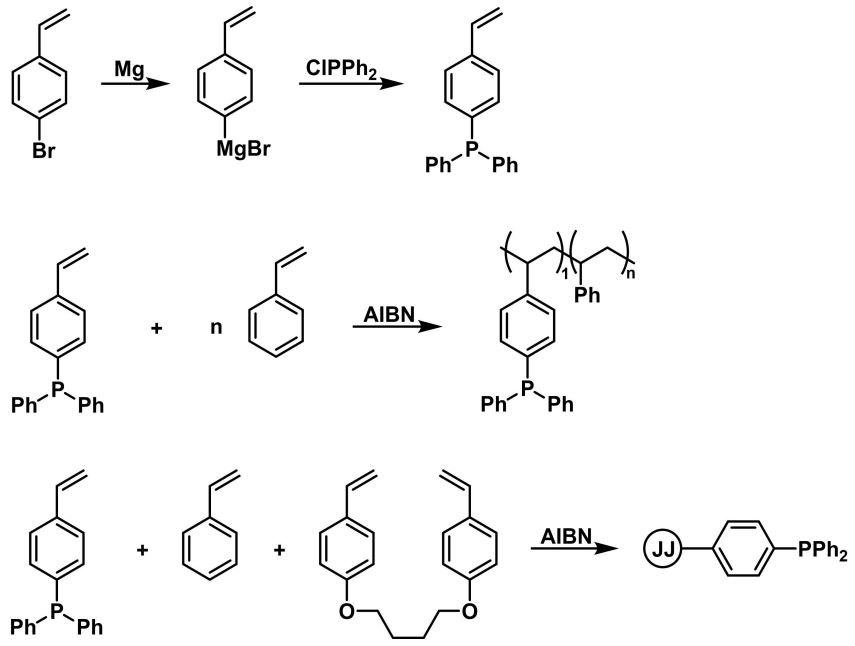

***Scheme 52.*** Linkage of a diketonate ligand precursor to polysiloxane.[74]

ing the ligand and then coordinating it to metals, Holbach et al. chose to polymerize the complexes with and without a further norbornene derivative (Scheme 55).[77]

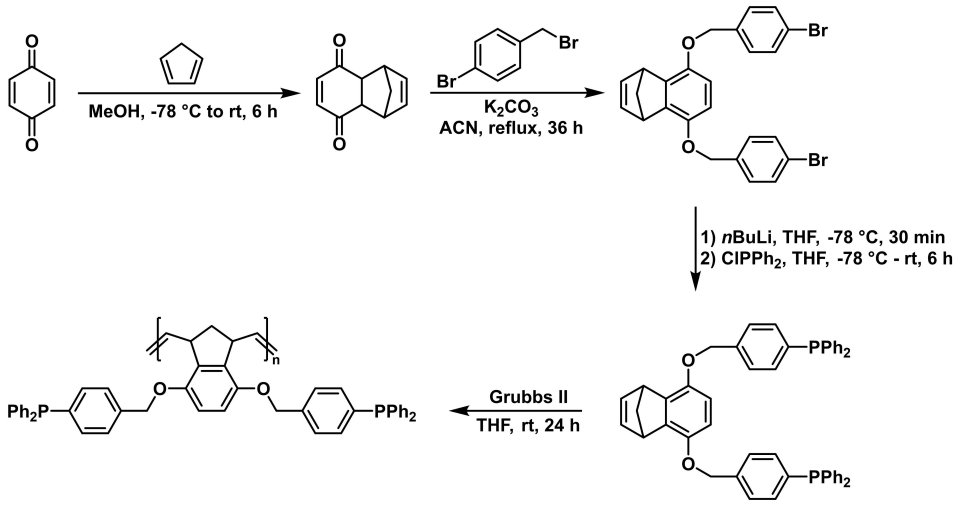
Lee et al. chose polyhedral oligomeric silsesquioxane (POSS) that is saturated with seven iso-butyl groups to increase the non-polar solubility of their PNP ligand. Starting from a POSS-tri silanol they synthesized a 3-aminopropyl-substituted POSS-cage. The reaction of this primary amine with two equivalents of $ClPPh_2$ gave the final ligand (Scheme 56).[78]

For unsymmetrically-substituted POSS-PNP ligands, they developed a similar route (Scheme 57).[78]

A notable example of POSS-substituted catalysts, although utilizing heterogenization as a recycling approach, has been published by Zheng et al. They linked Jørgensen–Hayashi's catalyst to a POSS-cage through a 1,3-cyclo-addition of 3-azidopropylheptaphenyl POSS and the alkyne-tagged catalyst (Scheme 58). The desirable properties of this reaction lie in its characterization as Click chemistry.[79]




***Scheme 53.*** Syntheses of phosphine substituted styrene monomers, non-cross-linked ligand polystyrene polymers, and cross-linked polystyrene polymers (JandaJel™).[75]



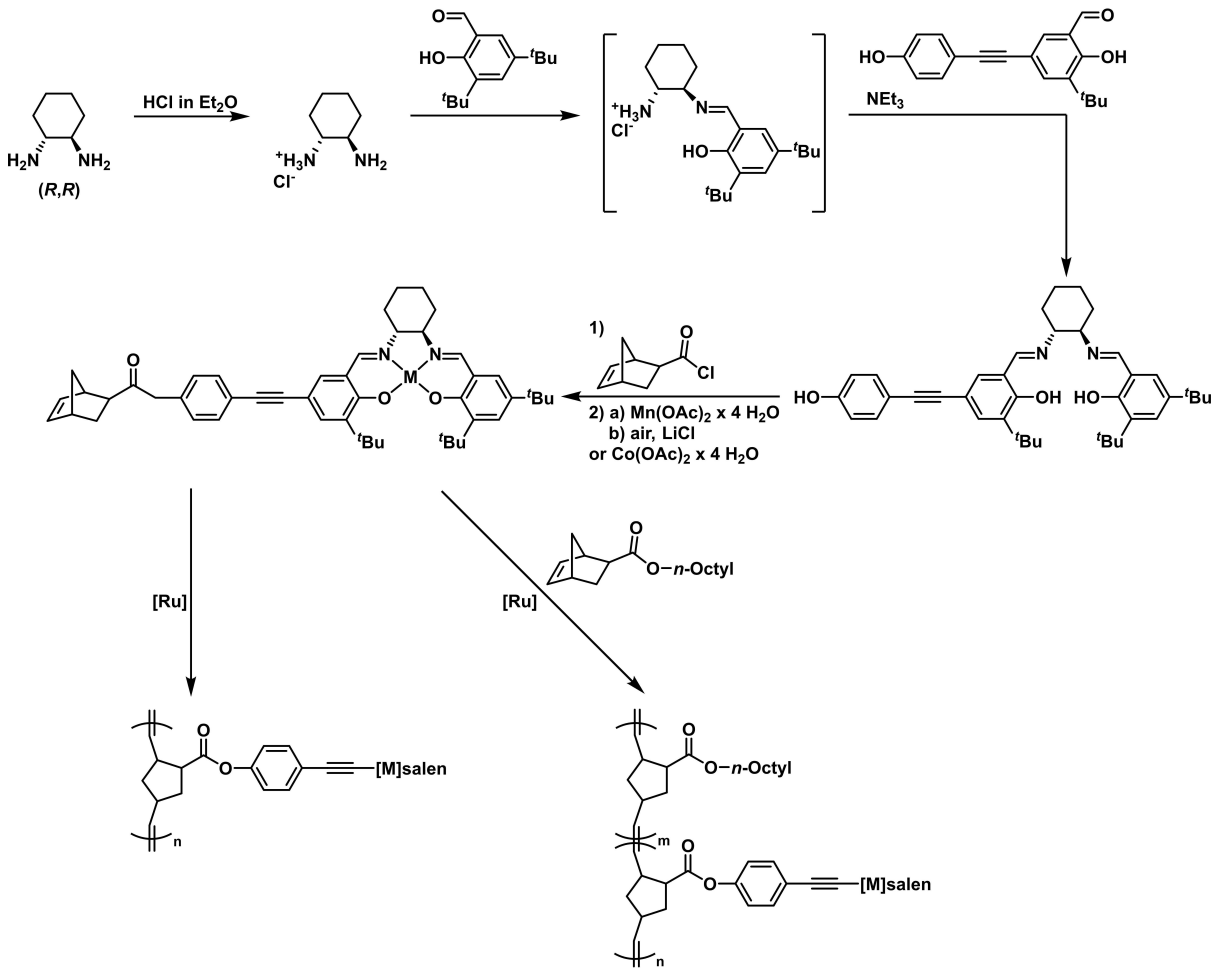

***Scheme 54.*** Polymerizing a ligand by ROMP of a norbornene-containing backbone.[76]

### *2.3. Switchable Ligands*

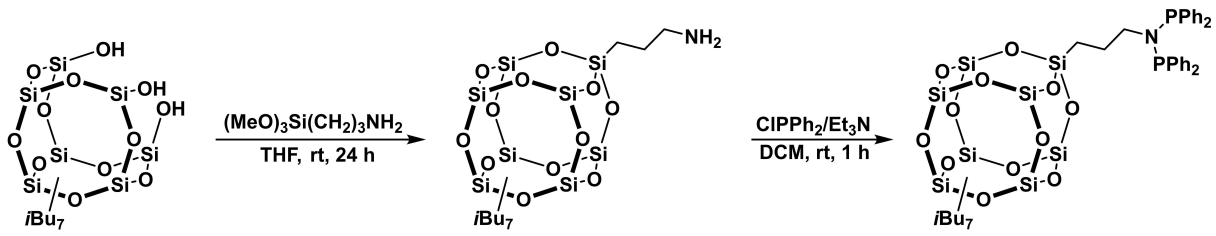
While catalyst fixation in one of two liquid phases offers a solution for recycling, it suffers from the drawback of substrate mass transport into the catalyst-containing phase. The development of ligands with switchable solubilities addresses this problem in a rather sophisticated way.

Liu et al. tagged a Grubbs-Hoveyda II catalyst with 2-(3′,3′-dimethyl-6-nitrospiro[chromene-2,2′-indolin]-1′-yl)ethan-1-ol ((*R*/*S*)-SP). This tag changes its molecular structure upon irradiation with visible light (>380 nm). Under irradiation, the molecule bears an iminium and an alcoholate ion and is therefore polar soluble, in the dark those ions transform into a tertiary amine and an ether, which leads to solubility in the non-polar phase. The introduction of the switchable tag into the complex is done by modification of the alkylidene ligand. A brominated ligand precursor is treated with *n*-BuLi and oxetane to yield the 4-aryl-butan-1-ol X, followed by reactions with the Dess–Martin reagent and $Ag_2O$. The obtained, corresponding carboxylic acid then forms an ester with the (*R*/*S*)-SP (Scheme 59).[80]

Also, $CO_2$ can be used as a trigger to switch solubilities. Desset et al. utilized a guanidine moiety to obtain a ligand that becomes polar in the presence of $CO_2$ by forming an amidinium cation and is soluble in non-polar solvents when




***Scheme 55.*** Synthesis of a polymeric catalyst via ROMP of a norbornene-tagged salen ligand.[77]



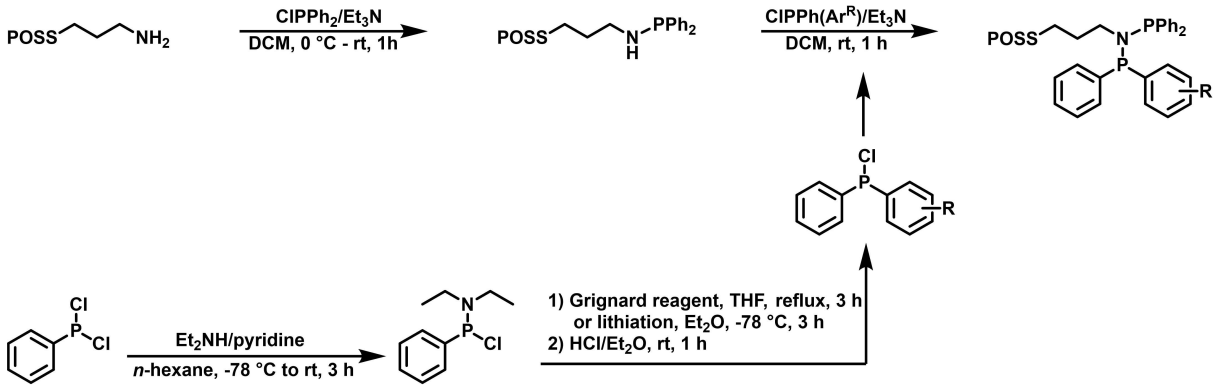

***Scheme 56.*** Synthesis of a POSS-substituted PNP ligand for enhanced solubility in non-polar solvents.[78]

$CO_2$ is removed from the solution (Scheme 60). Following a synthesis route from Hessler et al.[35] they synthesised tris(3-aminophenyl)phosphine. The product was then heated together with dimethylacetamide dimethylacetal up to 160 °C in a microwave oven yielding the final guanidine ligand (Scheme 61).[81]

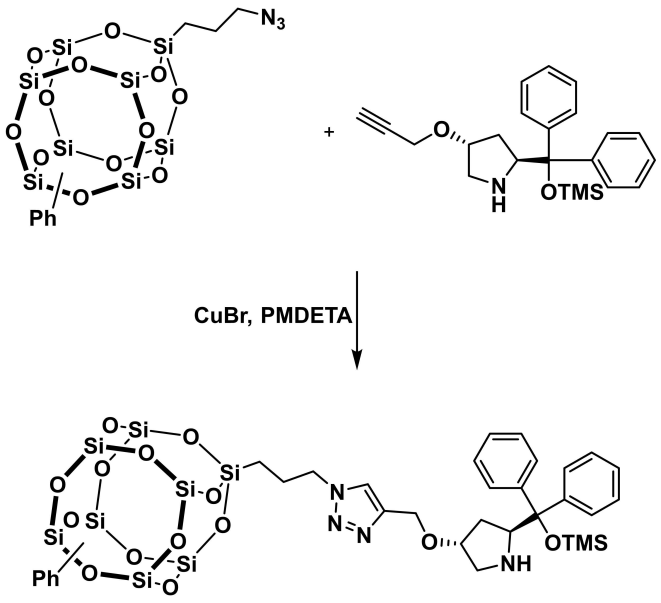
### 2.4. Fluorous Phase

While most biphasic systems rely on the classic polar/non-polar contrast, fluorous phases offer a third option. Perfluorinated solvents do not mix with water, so ligands with perfluorinated groups can be fixated in fluorous phases. Therefore, various types of perfluoro-tagged ligands have been developed.

Perfluoroalkyl-substituted phosphine, phosphite, and mixed phosphine-phosphite ligands were synthesized by Bhattacharyya et al. The phosphine ligands were obtained by the reaction of in situ generated perfluoroalkyl Grignard reagents with phosphine chlorides. Phosphites and mixed phosphine-phosphite ligands were synthesized from perfluoroalkyl alcohols and phosphine chlorides (Scheme 62). Similar ligands with phenyl groups as spacers between phosphorus and perfluoroalkyl chain were reported as well.[82]




***Scheme 57.*** Synthesis of unsymmetrical POSS-substituted PNP ligands for enhanced solubility in non-polar solvents.[78]




***Scheme 58.*** Synthesis of a POSS-tagged organocatalyst via a Huisgen reaction.[79]

An example of the use of modular synthesis strategies was published by Chen et al. They extended their approach for the synthesis of carboxylate-substituted ligands (see Scheme 16) to perfluoro-substituted phosphine ligands (Scheme 63).[29]

Bayardon et al. synthesized a chiral, perfluoro-substituted phosphine ligand through nucleophilic substitution. The two hydroxy groups on the ligand were treated with perfluoro-sulfonates under basic conditions with perfluoroethylsulfonate acting as leaving group. The previous introduction of the phenoxy group is important due to its role as a spacer between the phosphorus and the electron-withdrawing character of the fluorine atoms (Scheme 64).[83]

Another example of ligand modification via an $S_N2$ reaction with perfluoro building blocks was published by Lu et al. Fluorinated alkoxides were treated with 4,4′-bis(bromomethyl)-2,2′-bipyridine yielding the corresponding bpy ethers (Scheme 65).[84,85]

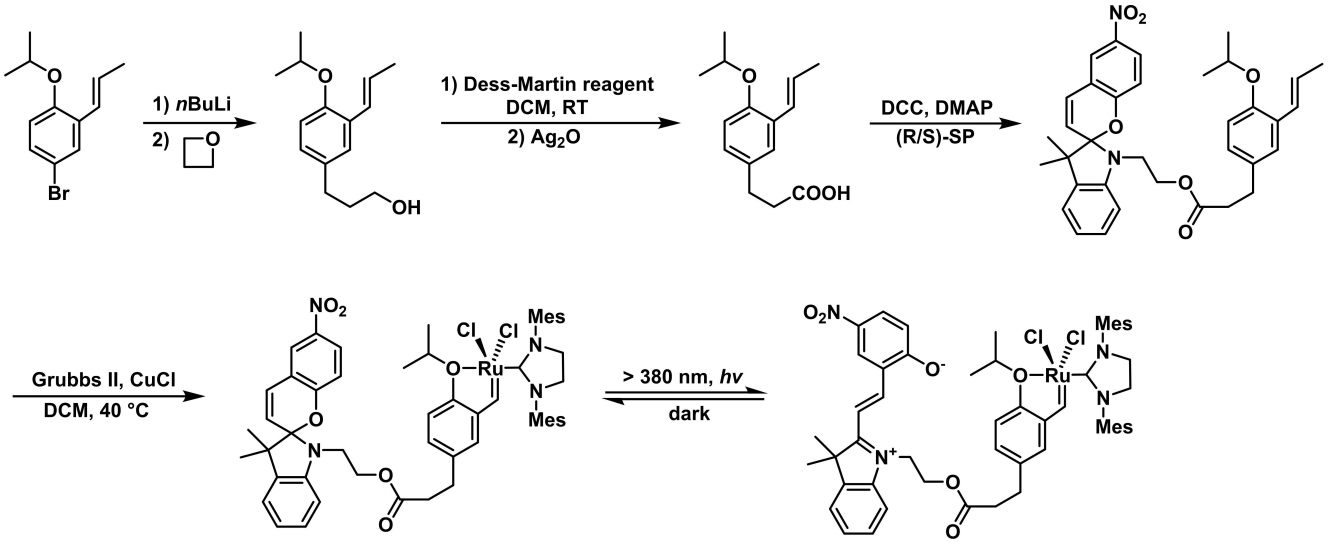
Mikami et al. synthesized the precursor for an amide ligand starting from a perfluoro-ponytail substituted sulfonyl fluoride which they treated with liquid ammonia. The resulting sulfonamide was treated again with one equivalent of the sulfonyl fluoride in triethylamine as solvent. After obtaining the ammonium salt, an ion exchange yielded the final ligand precursor (Scheme 66).[86]

### *2.5. Molecular Weight Enlargement (MWE)*

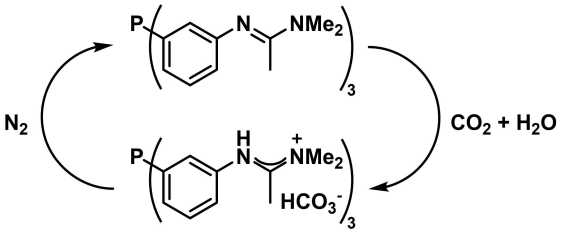
Although the fixation in certain liquid phases is the most common approach for homogeneous catalyst recycling there is another one which has been established in academic research. Instead of retaining the catalyst by different solubilities, it is possible to separate the catalyst from the homogeneous mixture by membrane filtration. The grade of the catalyst′s retention by the organic solvent nanofiltration (OSN) membrane is determined by its molecular weight. The logical consequence is to expand the molecular structure of the catalyst through the addition of large (preferably inert) building blocks. In theory, this can range from additional phenyl groups over oligomers like decyl chains to soluble polymers. Some of the ligands from previous chapters of this review are already good examples of enlarged catalysts that could work well in membrane separation, e.g. the PIB-tagged phthalocyanine.[68] In general, polymer-tagged ligands (polar, non-polar, or fluorous) should be quite useful in this recycling approach, although they have not been developed for it. Nonetheless, there have been approaches towards molecular-weight-enlarged catalysts with membrane separation as their main goal.

A rather simple approach was published by Schoeps et al. in 2009. They synthesized a SIMes-ligand derivative enlarged by four (dicyclohexylamino)methyl groups. In order to introduce the desired building blocks, they chose a drop-in strategy in which they substituted the primary amine in the standard synthesis for symmetric NHCs with a pre-tagged version (Scheme 67).[87]

Shahane et al. did also follow the glyoxal route to a molecular weight-enlarged NHC ligand. They chose an




***Scheme 59.*** Synthesis of an (*R*/*S*)-SP-tagged ruthenium carbene complex with the ability to change its polarity upon irradiation with visible light.[80]

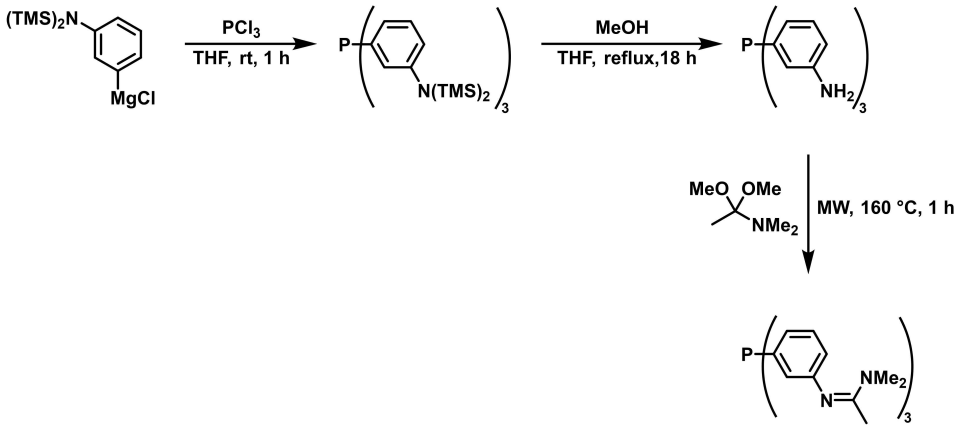



***Scheme 60.*** Synthesis route of triguanidine-substituted TPP.[81]

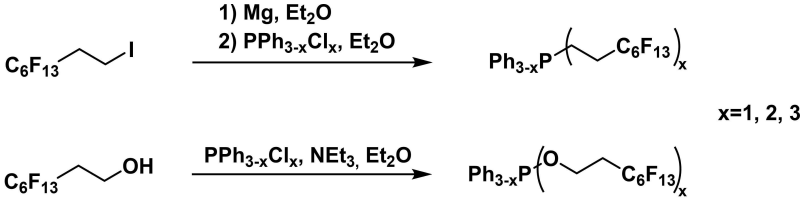
adamantyl tag which they introduced via an $S_N2$ reaction (Scheme 68).[88]

Another example of a molecular weight enlarged ligand has been published by Keraani et al. Their approach used a catalytic coupling of aryl bromides with pinacolborane (Scheme 69).[89]

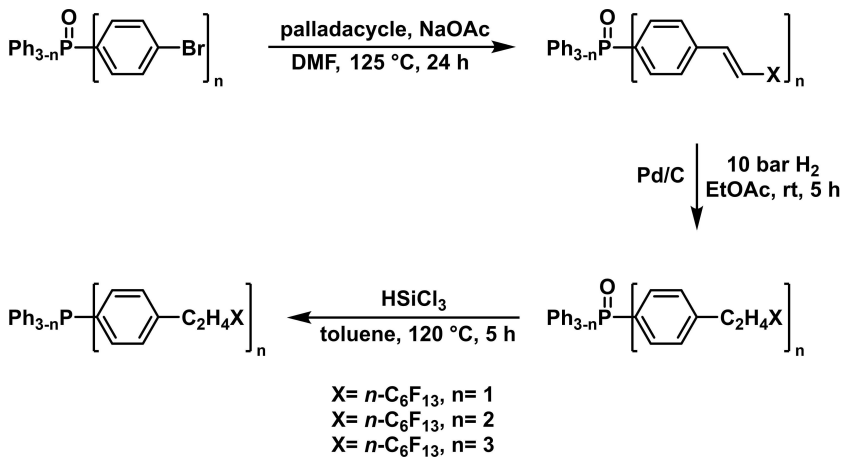
Following the approach of modified ligand precursors, Janssen et al. synthesized a (4-bromophenethyl)-substituted polyhedral oligomeric silsesquioxane (POSS) by so-called



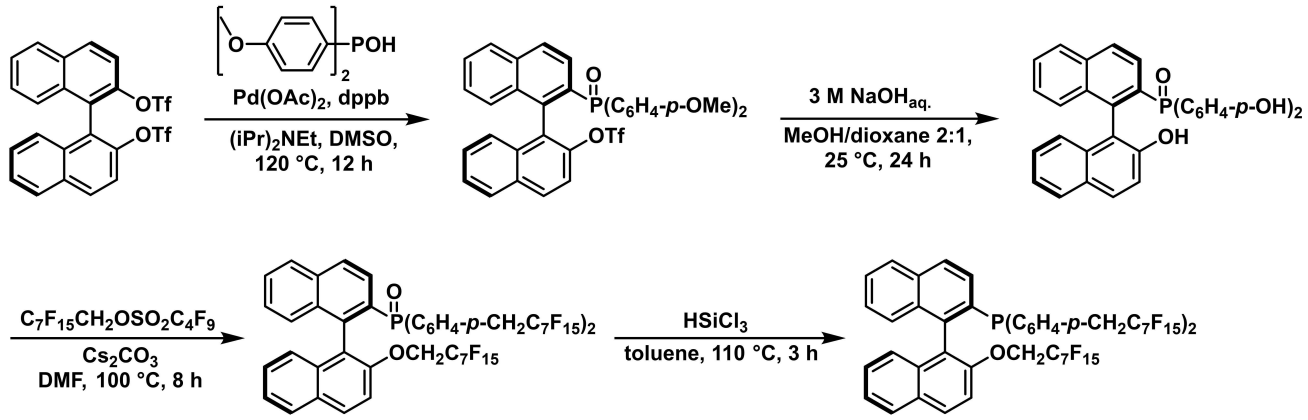

***Scheme 61.*** A guanidine-substituted phosphine ligand that allows $CO_2$-induced switchability of the solubility.[81]



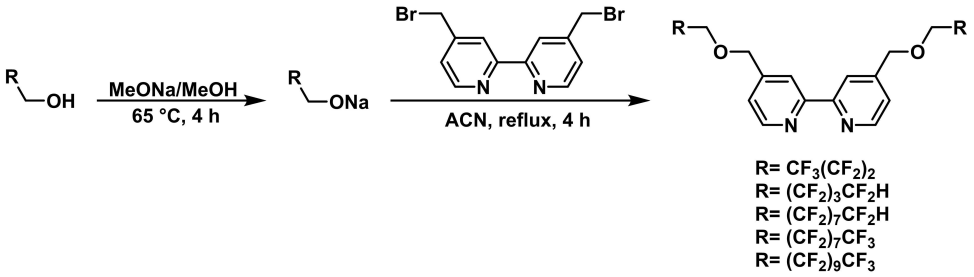

***Scheme 62.*** Synthesis of perfluoro-substituted phosphines and phosphites.[82]




***Scheme 63.*** Synthesis of perfluoro-substituted TPP ligands.[29]




***Scheme 64.*** Synthesis of a perfluoro-substituted phosphine ligand based on binaphthyl backbone[83]

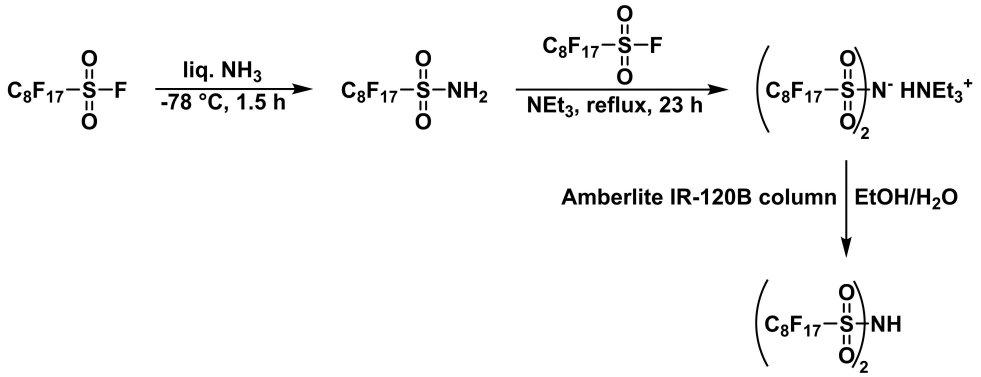



***Scheme 65.*** Synthesis of a diperfluoro substituted bpy ligand.[84,85]

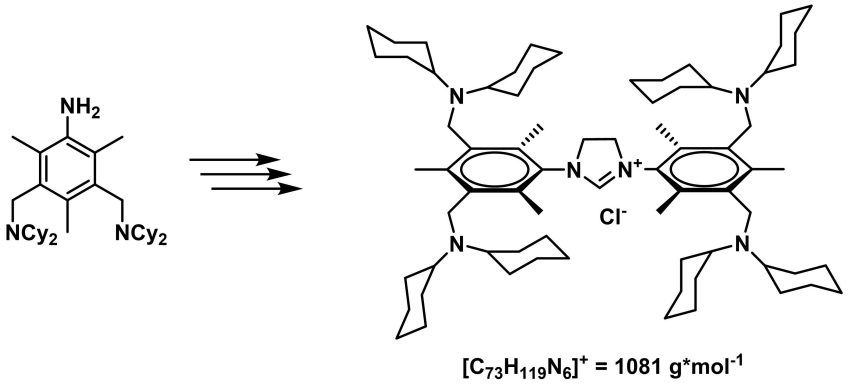
corner capping the POSS-trisilanol with (4-bromophenethyl)trichlorosilane. This precursor was then used in the standard synthesis for symmetrical TPP derivatives with *n*-BuLi and $PCl_3$ (Scheme 70).[90]

Falk et al. transferred this concept to the synthesis of a POSS-substituted NHC ligand, but instead of modifying a ligand precursor they took a ligand and linked it to the POSS cage (Scheme 71).[91] Furthermore, they combined the POSS-NHC with a POSS-tagged alkylidene ligand developed by Kajetanowicz et al. (Scheme 72)[92] in a di-POSS-substituted Grubbs-Hoveyda II catalyst (Scheme 73). The alkylidene ligand was linked to the POSS building block by the reaction of its hydroxy group with the POSS-isocyanate, which formed a urethane moiety in the presence of catalytic amounts of dibutyltin dilaurate.

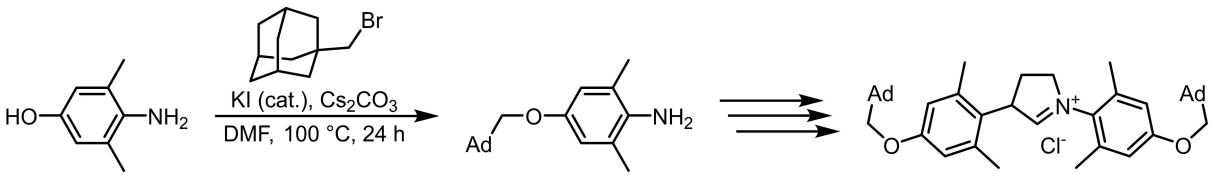
Previous to these attempts, focused on membrane separation, van der Vlugt et al. already synthesized phosphite ligands with POSS substituents via the reaction of phosphine chlorides or phosphorochloridite with a thallium silsesquioxide or POSS-disilanols (Scheme 74, Scheme 75 and Scheme 76). Although they did not perform recycling




***Scheme 66.*** Synthesis of perfluorooctyl-substituted amide ligand precursors.[86]




***Scheme 67.*** Molecular weight enlarged NHC ligand[87]




***Scheme 68.*** Synthesis of an adamantyl-tagged NHC ligand precursor.[88]

experiments, they anticipated the use of POSS ligands in recycling strategies.[93]

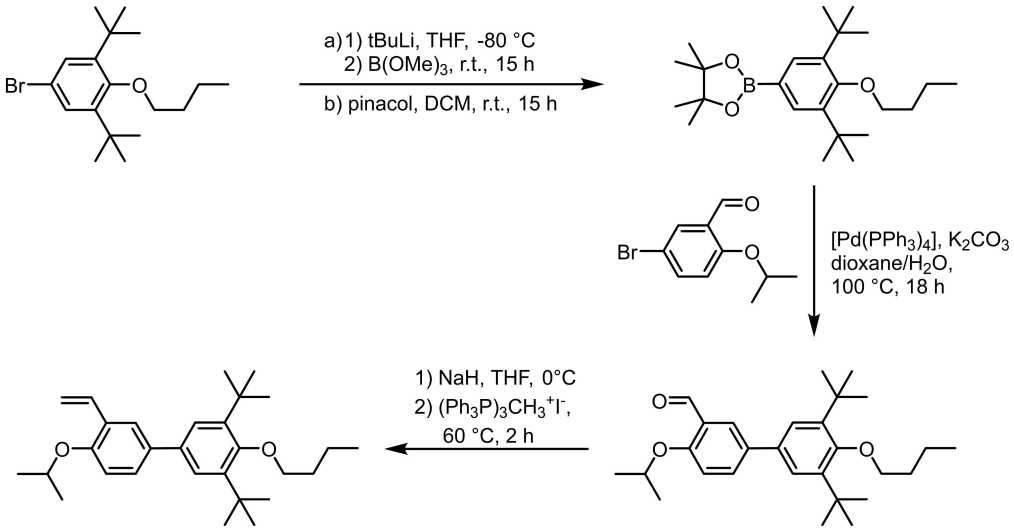
Pescarmona et al. synthesized a POSS-tagged osmium catalyst by linking an acid chloride to an amine-substituted POSS cage which was subsequently treated with an osmium source (Scheme 77).[94]

## 3. Patterns and Concepts of Ligand Modification

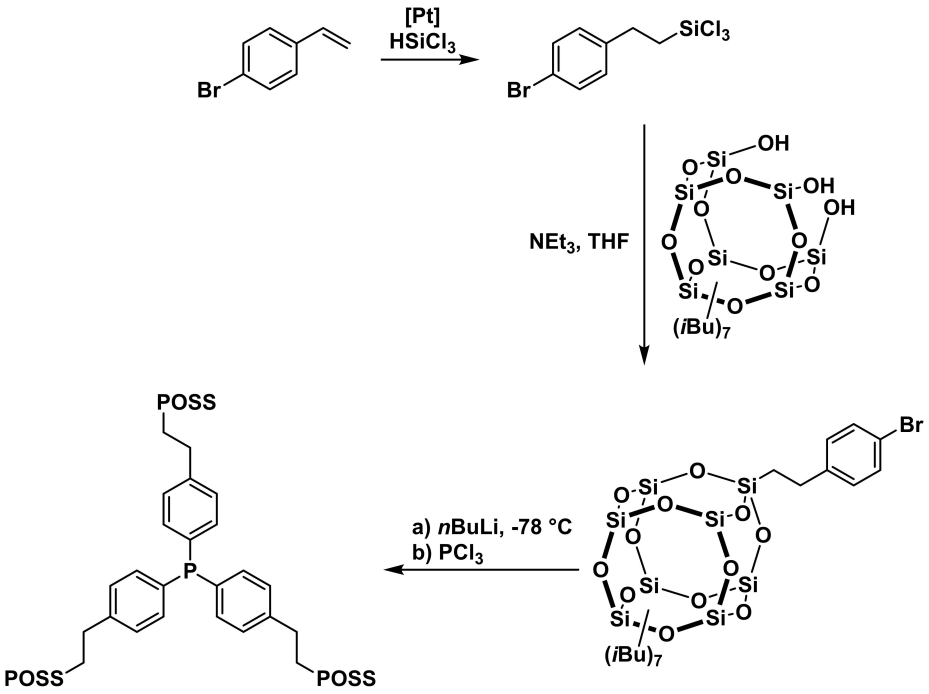
While the existing reviews for hydrophilic ligands, fluorous phase biphasic recycling, membrane separation of catalysts, etc. try to give a complete overview of their respective research field, we want to take a different approach. From our point of view, there is a gap regarding a concise summary of the possible syntheses to introduce a specific building block into a catalyst or ligand, when it comes to synthesis planning and recycling strategies. Therefore, we limited the literature to one example of each synthesis route. On the following pages, we want to examine the aforementioned syntheses regarding general applicability, late-stage modifications, and simplicity.

### 3.1. Tag Positioning

Before the evaluation of the best tagging strategies, one question needs to be asked: Where should one aim to add the tag? As simple ligands like chloride and carbon monoxide cannot be tagged, this leaves only more complex organic structures as a possible tag position. Some catalysts bear more than one organic structure, which could be modified. In these cases, it is important to take the catalytic cycle of the desired reaction into account. A tag can only be exploited if it stays with the rest of the catalyst. Therefore, ligands that stay coordinated during the whole catalytic cycle should be




***Scheme 69.*** Synthesis of a molecular weight enlarged benzylidene ligand precursor.[89]



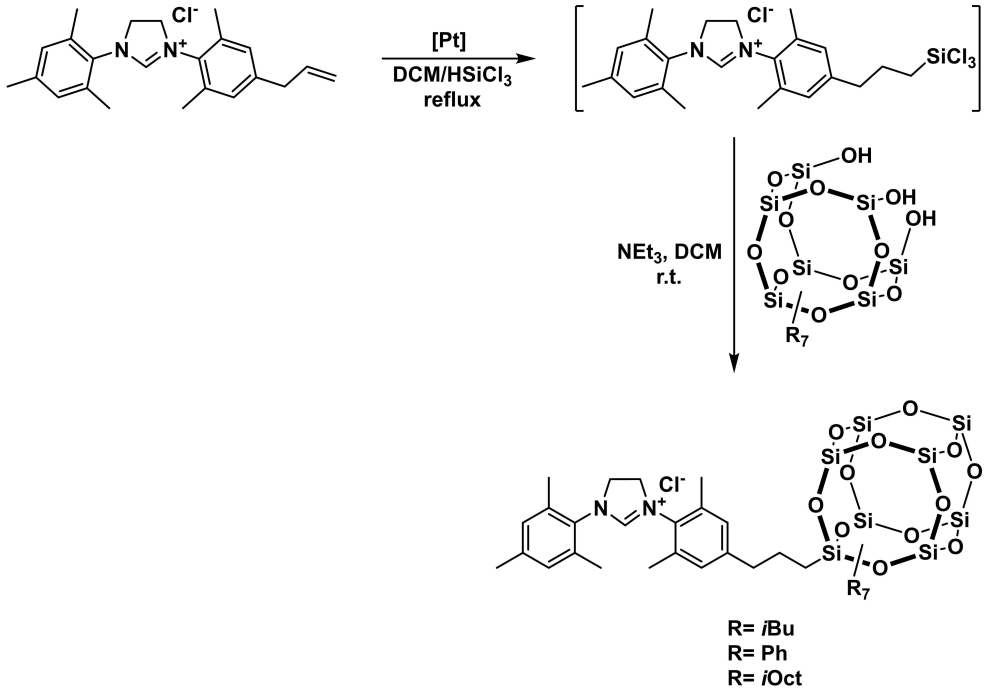

***Scheme 70.*** Synthesis of tri-POSS-substituted TPP.[90]

preferred positions for tags. The problem of dissociating ligands has been of interest in the field of metathesis catalysts, as there are several examples of Grubbs Hoveyda II catalysts, which are tagged on the dissociating alkylidene ligand.[62,80,89,92] While the boomerang mechanism has proven the return of the alkylidene ligand onto the ruthenium,[95] it remains questionable to tag the alkylidene when analog strategies exist for the NHC ligands, which do not dissociate during the reaction.

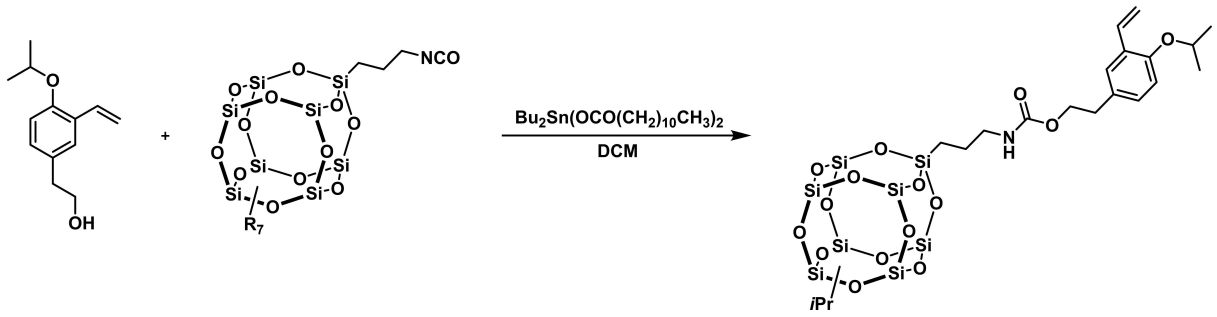
In order to have as little influence on the catalytic performance as possible, it is necessary to add the tags preferably in positions that avoid steric hindrance and a change in the electronic properties of the donor atoms. Therefore, the tags should be ideally introduced in terminal positions that do not allow inductive effects or other resonances than the original ligand.

### 3.2. Late-Stage Modifications

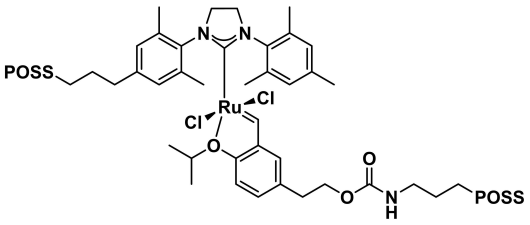
Since most homogeneous catalyst systems (metal complexes and organocatalysts) are initially developed without regard for their recycling but with a focus on the electronic properties of their active sites, it is favorable to apply synthesis




***Scheme 71.*** Synthesis of a POSS-substituted NHC ligand for a Grubbs-Hoveyda II catalyst.[91]



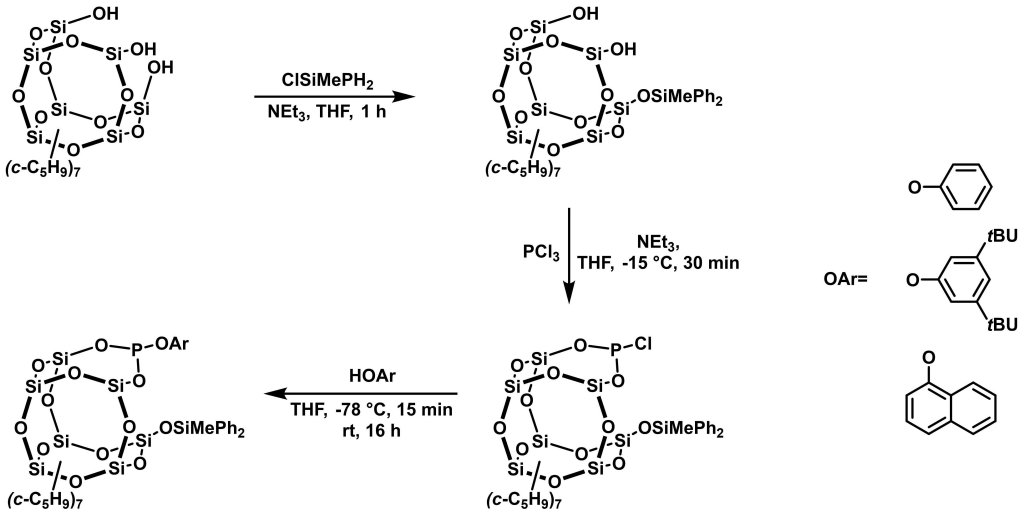

***Scheme 72.*** Synthesis of a POSS-substituted alkylidene ligand for a Grubbs-Hoveyda II catalyst.[92]



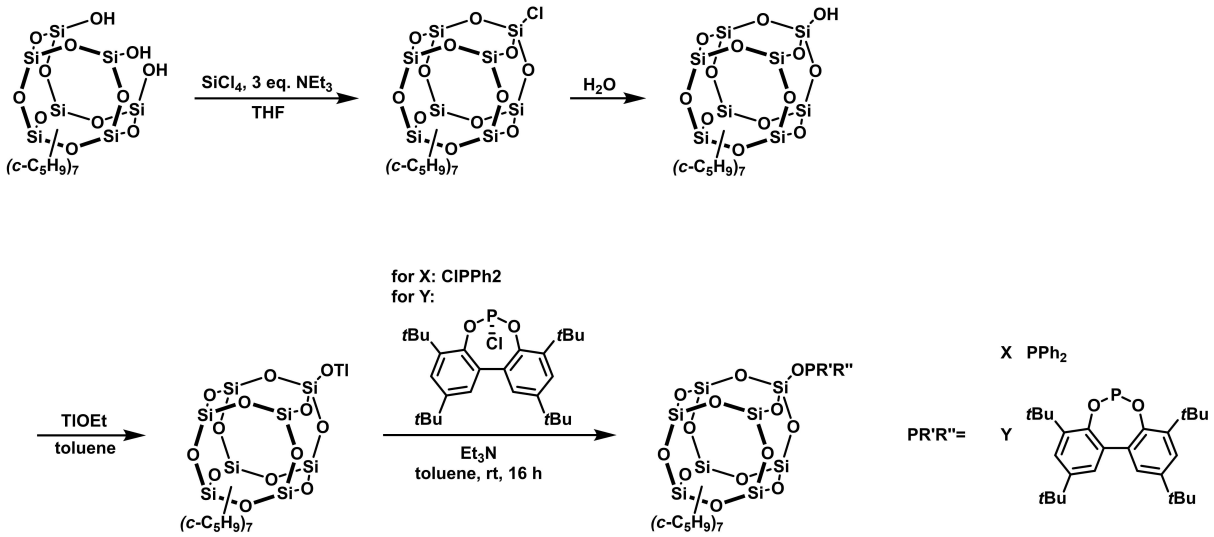

***Scheme 73.*** Structure of the Grubbs-Hoveyda II catalyst bearing two POSS-tagged ligands, which was developed by Falk et al.[91]

strategies that can modify the existing ligand/organocatalyst i.e., late-stage modifications.

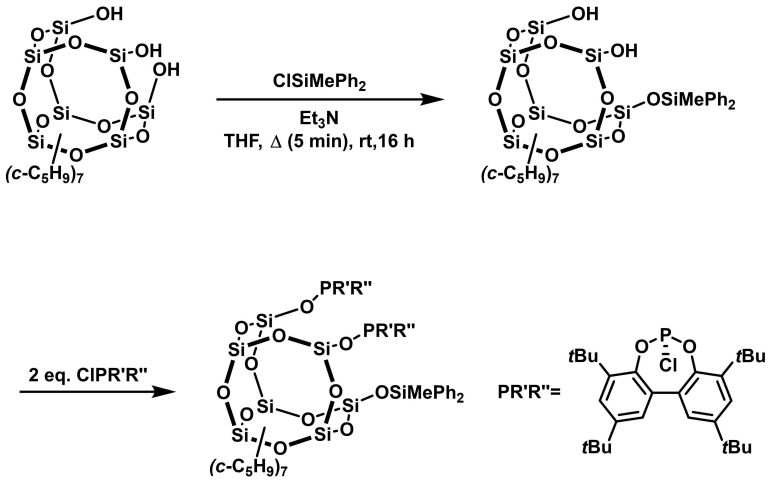
The prime example of this is TPPTS which is directly derived from TPP. Both molecules are common ligands in the hydroformylation with rhodium. The direct sulfonation of aryl groups with sulfuric acid and oleum presents the most common approach towards catalyst recycling in a liquid-liquid biphasic system. The vast majority of available ligands for homogeneous catalysis contains aryl groups, particularly phenyl groups. It is thus not surprising that direct sulfonation is a widespread method to obtain hydrophilic ligands. The drawback of the method is the oxidative nature of the used reagents ($H_2SO_4$, $SO_3$). Phosphines and phosphites are prone to oxidation and consequently need to be protected if tedious product separation is to be avoided. Herrmann et al. circumvented oxidation through the addition of orthoboric acid. TPP is the simplest phenyl group bearing phosphine and all three phenyl groups share the same chemical properties, but when it comes to more complex phosphine ligands it is not always possible to sulfonate every desired aryl group. The sulfonation of Xantphos does not occur on the four phenyl groups but instead on the xanthene backbone.[17] This is a good example of how the molecular structure limits direct sulfonation. A possible solution can be an extension of the phenyl groups with aryl groups that can be directly sulfonated, as Goedheijt et al. showed.[18] Nonetheless, the highly acidic and oxidative reaction conditions are problem-



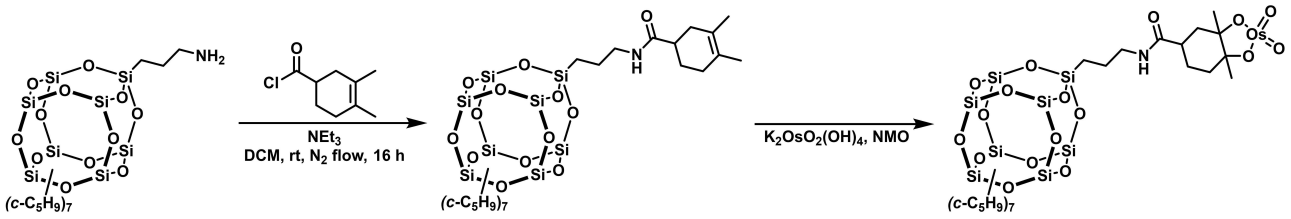

***Scheme 74.*** Synthesis of POSSphite ligands.[93b]




***Scheme 75.*** Synthesis of POSS-tagged phosphite ligands.[93a]




***Scheme 76.*** Synthesis of a POSS-tagged diphosphate ligand.[93a]



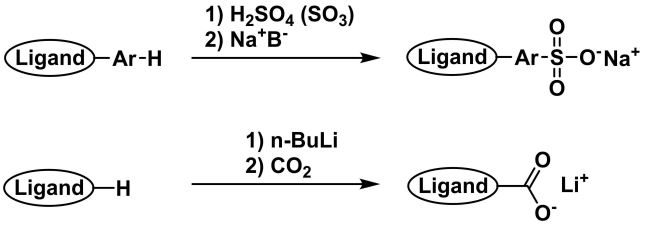

***Scheme 77.*** Synthesis of a POSS-tagged osmium catalyst.[94]

atic when it comes to more sensitive ligands or organocatalysts. Modular approaches on the other hand would allow the introduction of pre-sulfonated building blocks under milder conditions at defined positions in the molecule.

The introduction of carboxylate moieties into ligands proves to be more complicated than direct sulfonation. Apart from modular approaches, which will be discussed later on, the only late-stage modification towards carboxylate substituted ligands proceeds via lithiation of a ligand and subsequent quenching with a solution of $CO_2$ in THF. Usually, reactions that include lithiated intermediates suffer from the drawback of lithium halide salt waste, but in the case of carboxylate synthesis, this can be avoided due to the product being a lithium salt itself. The cited example relies on a metal-halogen exchange, which does not fit the definition of a late-stage modification, since the halide is not a standard part of the ligand.[30] But this general concept of carboxylate synthesis can still be used for late-stage modifications if it switches from halides to acidic protons (Scheme 78). The exchange of an acidic proton for a carboxylate does not require the previous introduction of halide moieties but is completely dependent on the given acidity of protons in the existing ligand.

An ideal example of late-stage ligand alteration was presented by Bergamini et al. with their reaction of tertiary amines and sultones.[40] A straightforward one-step synthesis with no by-product is highly desirable, but the number of ligands with non-coordinating tertiary amine groups is limited. Nonetheless, sultones are interesting reagents for the synthesis of sulfonates, either in sulfobetaines or simple anionic groups.

A challenge in the synthesis of phosphorus ligands is the protection of the phosphorus. Its proclivity towards oxidation and nucleophilic attacks on electron-poor moieties makes it sometimes necessary to keep the free electron pair occupied. The most common approach is the protection by a $BH_3$ adduct,[21] another way of protection against unwanted reactions on the phosphorus is the intentional oxidation or use of oxidized precursors.[29] Both ways need subsequent deprotection and therefore make synthesis routes more laborious.




***Scheme 78.*** Late-stage introduction of sulfonate and carboxylate groups into ligands.

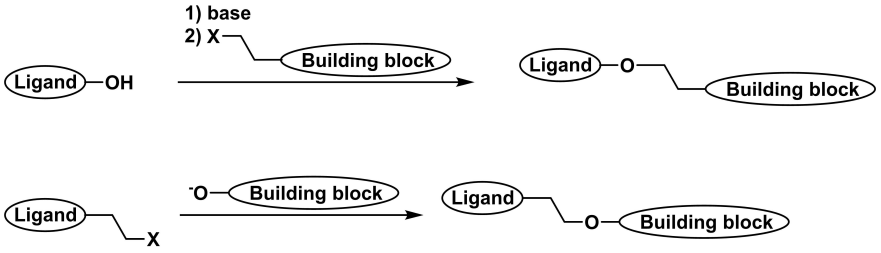
### *3.3. Linking Moieties to Connect Ligand and Tag*

If one wants to link a group, which alters the physical properties, the linking moiety plays a crucial role. Therefore, we want to list the linking moieties, found in the cited papers, and examine their feasibility for further applications. The major concern for the feasibility is the durability of the link. The group must withstand the reaction conditions in the catalytic process it is designed for. At the same time, the group should not interfere with the catalytic properties of the catalyst. While electronic effects on the metal cannot be excluded as the original ligand molecule needs new substituents in some positions, steric effects and changes in the coordination sphere of the metal (in the case of complexes) should be avoided. The latter is especially of concern when the linking moieties contain heteroatoms that can coordinate to the metal center. Placing 1,4-substituted phenyl groups as spacers between the desired donor atoms and possible further donor atoms from linking moieties can be the solution to this problem.

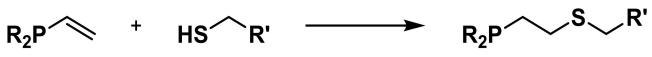
Certainly, one of the most used moieties that allow the introduction of building blocks is the ether group. The synthesis proceeds either through the nucleophilic attack of an alcoholate on an alkyl halide[48,70,84,85] or utilizes the Mitsunobu reaction.[72] The easy and straightforward synthesis route via the $S_N2$ reaction (Scheme 79) and the stability of the ether group make it a desirable reaction. Nonetheless, it requires an alkyl halide or hydroxy group in the ligand, which needs protection during the classic ligand syntheses with lithium organyls or Grignard reagents.

Thioethers are closely related to ethers and can be found as linking moieties as well. Starting with thiols, they can be synthesized in the same way but need less strong bases to generate the thiolate for the $S_N2$ reaction.[47,68] Another approach has been presented by Paetzold et al. as they used the uncatalyzed Michael reaction between a vinyl phosphine and a thiol (Scheme 80).[25]

While Reetz et al. used the ability of the thioether to coordinate a metal in a P,S bidentate ligand,[47] thioether coordination can be prevented through oxidation to the




***Scheme 79.*** General synthesis of ether functionalized ligands via an $S_N2$ reaction.




***Scheme 80.*** General synthesis of thioether functionalized ligands via a Michael reaction of a vinyl phosphine with a thiol.

sulfone as shown by Chao et al.[68] They used *m*-CPBA to oxidize the thioether.

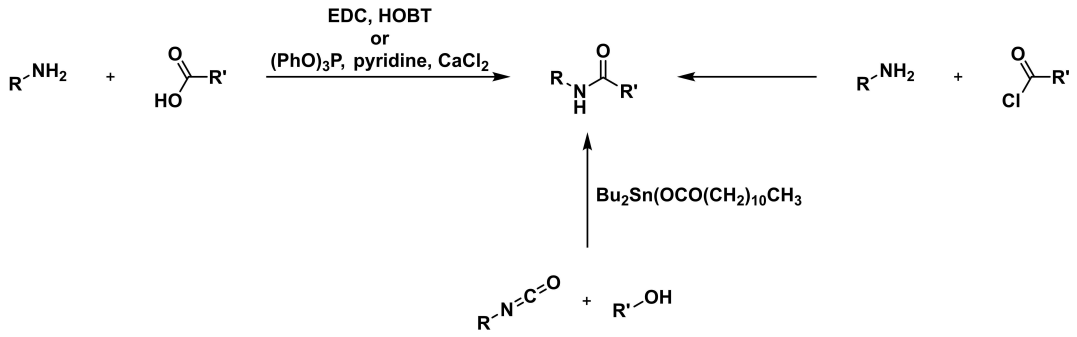
A further commonly used group for the linkage of ligands and building blocks is the amide moiety.[49,59,66,92,94] Due to their stability and inability to coordinate metals, amides are predestined for use as a linking moiety. Their drawback is the more complicated synthesis that needs special reagents (Scheme 81). If the starting materials for the reaction are a primary amine and a carboxylic acid the linkage can be done with EDC and HOBT[49,66] or can be catalyzed with calcium and triphenyl phosphite.[59] Further options are the reaction of an isocyanate with an alcohol catalyzed by dibutyltin dilaurate[92] or the reaction of a primary amine with an acid chloride.[94]

Esters are not a preferred linker, although principally easy to form, due to their proclivity towards hydrolysis and possible reduction during the catalytic process. Another problem can be transesterification especially when alcohols like methanol, ethanol, and isopropyl alcohol are used as solvents. Nonetheless, they can be found as linkers in some cases. Liu et al. tagged their light-triggered polarity switch to the alkylidene ligand by performing a Steglich esterification with DCC and DMAP.[80]

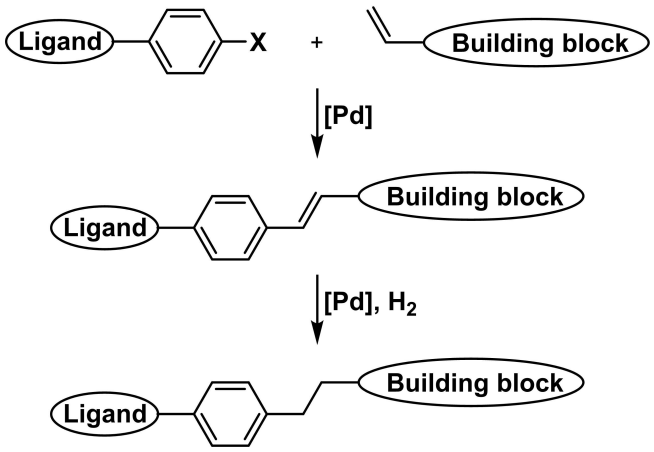
Another easily accessible group is the 1,2,3-triazole which forms during the copper-catalyzed 1,3-cycloaddition of alkynes and azides, known as the Huisgen reaction. Zheng et al. used this to link the Jørgensen–Hayashi catalyst with a POSS-cage.[79] The stability of 1,2,3-triazoles in catalytic processes has to undergo further research, as the cited example only includes reaction temperatures up to 25 °C which is far lower than most processes.

All the approaches mentioned above rely on heteroatoms to link ligand and building block. While this comes with more or less easy reactions, heteroatomic bonds are easier to cleave than C–C bonds due to their polarised character. Therefore, C–C-linked ligands and building blocks are of high interest. Catalysis itself has provided us with new possibilities for C–C bond formation over the past decades and one has been utilized to modify ligands as well. Chen et al. reported the use of a Heck Coupling to attach carboxylates and perfluorinated ponytails to a ligand.[29] The reason that only the Heck reaction out of the several known coupling reactions has been used to modify ligands can be found in the simplicity of its substrates. Terminal alkenes and aryl halides (Scheme 82) are more common and stable as opposed to Grignard reagents, tin organyls, and boronic acids. A Sonogashira coupling would also work with similar substrates (aryl halide and terminal alkyne) but needs a further substance due to the second catalytic cycle and in the end more hydrogen to reduce the intermediate to the alkyl-linked product.

A classic reaction for C–C bond formation which is not yet included in the toolbox for single ligand modification until now is (cross-)metathesis, most likely due to the difficulties in controlling the product distribution. Nonetheless, metathesis has been utilized in the formation of ligand polymers via ROMP.[76,77] Furthermore, platinum-catalyzed hydrosilylation has been used to bind catalysts to polysiloxane.[74]




***Scheme 81.*** General synthesis pathways towards amide-linked ligands.




***Scheme 82.*** General reaction Scheme of linking building blocks to ligands via a Heck reaction and subsequent reduction.

### 3.4. Click Chemistry Reactions

As mentioned in the introduction, listing the desirable properties for a synthesis led to the concept of Click chemistry. Traditional ligand syntheses, especially of phosphorus-containing ligands, fail to fit the concept quite obviously due to the regular use of organo-lithium compounds and Grignard reagents. Nevertheless, the late-stage modification of the same ligands can be tuned towards more favorable synthesis routes.

Taking a closer look at Paetzold's approach[25] we can see that although its reaction time is too long to be considered Click chemistry, the remaining features of the reaction fit the desired profile. Furthermore, the addition of a photoinitiator (PI) and UV irradiation to this synthesis route transforms it into the Thiol-ene reaction, which is classified as Click chemistry. Both variants of this reaction have their perks regarding application in ligand synthesis. While the thiol-ene reaction is faster, the reaction as published by Paetzold makes the workup easier due to the lack of PI in the reaction mixture.

A real Click reaction is the formation of a 1,2,3-triazole through a 1,3-cycloaddition of an alkyne and an azide, better known as the Huisgen reaction. It is catalyzed by $Cu^+$ compounds and provides the user with a fast and selective way to bind a building block to a ligand or organocatalyst.[79]

### 3.5. Modularity

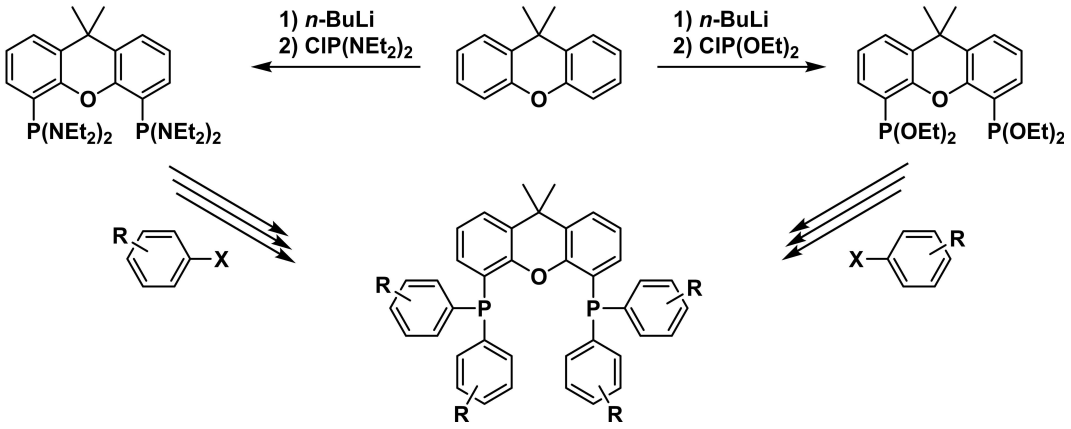
While modularity is a necessary condition in Click reactions, it can be found as well in other synthesis routes. The easiest examples for this in our scope are symmetric TPP derivatives. Substituted aryl halides can be modified and then treated with $PCl_3$ or $PBr_3$. This allows many different modifications but its simplicity is limited to symmetrically substituted phosphorus. The extension of this approach requires the use of partially protected phosphanes to obtain unsymmetrical phosphine ligands (see Scheme 83). While the need for protecting groups makes the synthesis route more laborious, the general appeal of the modular approach stays.

Further, all the approaches mentioned in section 3.2 can be summarised under the caption "modular".

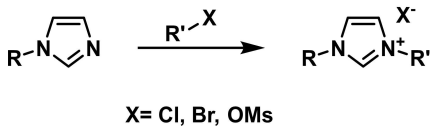
Leaving behind the field of phosphine ligands, NHC ligands can be found in many tagged variants. Szczepaniak et al. have put together a concise overview of the possibilities that arise from the different synthesis routes of NHCs. The most notable route with regard to the aspect of modularity is the imidazolium route (Scheme 84). While it only is suitable for unsymmetrically-substituted NHC ligands, it possesses a wide range of possible tags, which only rely on halides as the reactive site.[20]

### 3.6. Synthesis Costs

Apart from the chemical considerations, financial aspects play a major role, when the aim is to implement tagged catalysts into industrial applications. The cost reduction, which can be achieved through the retention and recycling of a catalyst, may be significant, especially in the case of expensive transition metal catalysts but can lose their appeal

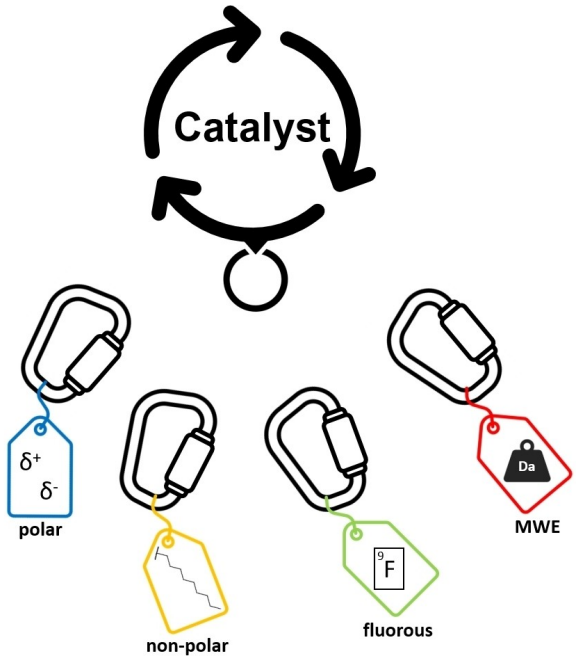



***Scheme 83.*** Modular synthesis of unsymmetrically-substituted phosphine ligands with modified aryl substituents on the example of Xantphos.[44]




***Scheme 84.*** Modular synthesis of mono-tagged NHC ligand precursors via the imidazolium route.[20]

if the tag introduction's costs exceed the savings realized in recycling. While the manifold of different catalysts and ligands in this paper prevents a detailed discussion at this point, the inclusion of a cost analysis should be a priority in any publication of a tagged catalyst that aims for industrial use. A good example of the incorporation of a cost discussion for organocatalysts can be found in a review by Antenucci et al.[96] In general, the late-stage modification of existing ligands and catalysts with simple reagents like sulfuric acid or sultones are favorable for cost-efficient tagging. Furthermore, modular approaches could prove to be beneficial, when tag strategies for catalysts can be standardized. A fixed set of standard tags and ligands fitted with the same linker could bring down the costs through scale-up effects.




***Scheme 85.*** Concept for a tag library, that allows to tailor the ligand for the desired recycling approach.

## 4. Conclusion and Perspectives

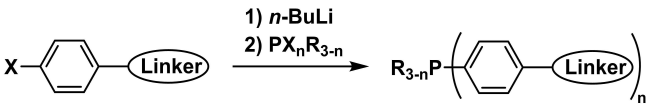
In summary, while a plethora of synthesis strategies that modify ligands and catalysts towards better recyclable properties have been reported, a general approach remains elusive. The late-stage approaches we found, especially the direct sulfonation, are the most practical syntheses in use but suffer from harsh conditions and positional modification limitations.

Consequently, we suggest a universal advance towards recyclable homogeneous catalysts. Since the manifold of synthetic challenges obstructs a "one fits all" solution, we propose the development of a tag library, which allows tailoring the recycling for each reaction. While in theory every possible building block, that brings the desired physical properties with it, could be tagged onto a ligand or organocatalyst, it seems rational to develop a standardized set of solubility-inducing building blocks (SIBBs), which covers polar, non-polar, and fluorous solubility (Scheme 85).

From our point of view, there are three major steps on the way to the tag library. The first is to choose a suitable reaction—preferably a Click reaction—that allows the linkage between the ligand and building blocks (SIBB or MWE). Apart from speed and selectivity, simplicity regarding the reaction workup is highly desirable and a stable linking moiety is necessary. Step two—as a direct consequence of the first one—is to find a feasible way to introduce a linker, which is capable to undergo the Click reaction, into the ligand. Taking into account the conclusions we have drawn in the previous sections of this paper it seems reasonable to choose a rigid structure like a 1,4-substituted phenyl ring as a spacer between the donor atoms and the modifying groups to avoid changes in the ligand's hapticity. Since many ligands that are in use today bear at least one phenyl phosphine group, we deem it best—in conclusion of the aforementioned chapters—to use substituted phenyl phosphines of the general form described in Scheme 86. 4-substituted aryl halides are readily available from commercial suppliers in a large variety and therefore allow a broad range of follow-up reactions.

The third and last step is the selection and/or synthesis of suitable SIBBs and MWEs. A suitable MWE can be found among the POSS cages as described in the MWE section of this paper. Building blocks to induce solubility in the fluorous phase will most likely consist of the perfluoro-ponytails known to literature for this purpose. A broader spectrum of different building blocks is to be expected in the fields of polar and non-polar phase catalyst fixation. While non-polar groups like alkyl chains can be extended *ad libitum* to decrease the catalyst's solubility in polar solvents, the ionic moieties of the most polar modifications usually follow the concept of one polar group per linkage. Since not all ligands offer several positions that can be modified and more polar groups increase the retention in the polar phase, it seems desirable to develop building blocks that carry more than one sulfonate, ammonium group, etc. However, it is important to keep in mind that every polar SIBB needs to be coupled to a less polar catalyst/ligand, which can lead to limitations in the choice of a proper solvent.

Naturally, a general tagging strategy that aims to increase the sustainability of catalytic processes should adhere to




***Scheme 86.*** General introduction of linkers into phosphine ligands including a 1,4-substituted phenyl spacer.

green chemistry principles itself. In practice, this means that non-toxic synthons and simple synthesis routes with minimal amounts of by-products are highly favored. Nonetheless, the effects of non-sustainable syntheses of tagged catalysts have to be assessed while keeping in mind their positive effects on the processes they are applied in. Toxic reagents (azides, sultones, etc.) and multi-step reactions with large amounts of salt waste in catalyst synthesis are certainly not ideal when the synthesis is evaluated on its own. However, a reduction of catalyst amount and product purification can justify less sustainable tagging strategies, when the process is assessed as a whole.

Succinctly, we see great potential to push for more and better catalyst separation (and recycling) through the development of a standardized set of SIBBs and MWEs in combination with generally applicable introduction strategies.

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## Conflict of Interest

The authors declare no conflict of interest.

**Keywords:** Biphasic Recycling · Carbene Ligands · Catalyst Recycling · Homogeneous Catalysis · P Ligands

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