Solid-Supported Reagents in Organic Synthesis

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Abstract: The current interest in solid-phase organic synthesis has led to a renewed interest in a complementary technique in which solid supported reagents are used in solution phase chemistry. This technique obviates the need for attachment of the substrate to a solid-support, and enables the chemist to monitor the reactions using familiar analytical techniques. The purpose of this review is to increase awareness of the wide range of useful transformations which can be accomplished using solid-supported reagents. Med Res Rev 19, 97–148, 1999.

Keywords: solid-supported reagents; solid-phase reagents; polymer-supported reagents; parallel synthesis; scavenger reagents; ion-exchange resins; solution-phase synthesis; combinatorial chemistry

1. INTRODUCTION

Medicinal chemists in the pharmaceutical industry now routinely utilize solid-phase organic synthesis (SPOS) to prepare libraries of small organic molecules for screening.[1] The advantages of this methodology have been well described in the recent literature: excess reagents can be used to drive reactions to completion, impurities and excess reagents can be removed by simple washing of the solid-phase, and enormous numbers of compounds can be created using the mix and split technique. Limitations to SPOS may include (a) the presence of a resin vestige in the final molecules (the point of attachment of the molecule to the solid support), (b) the need for two extra synthetic steps (attaching the starting material to the solid support, and removing the material from the solid support), (c) a potential scale limitation imposed by the loading level of the solid support, and (d) the need to re-optimize solution phase chemistry on the desired solid support. Recent reports indicate that pharmaceutical companies are now also increasing efforts toward high throughput solution phase synthesis using solid supported reagents (SSRs).[2] Polymer-supported reagents have been in use since the 1960s, and have been the subject of several review articles.[3] Synthesis using SSRs is attractive and suitable for parallel synthesis because the reactions are often very clean and high yielding, and the workup involves simple filtration and evaporation of the solvent. This review is prompted by the current rediscovery of the utility of these types of reagents, and exemplifies transformations of interest to the medicinal chemist that can be accomplished using polymer-supported reagents.

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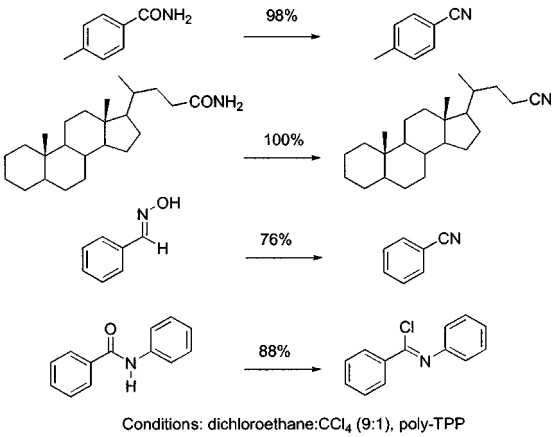
For the purpose of this review, the definition of a SSR will encompass reagents that are either covalently or ionically bound to the support. The SSR can serve a variety of purposes: stoichiometric reagents that participate in the reaction, catalysts for a reaction, protecting groups allowing for selective transformation on another portion of the molecule, or scavengers that aid in the removal of impurities (for example, excess starting material). The yields given in the schemes represent the highest yield obtained for a given transformation. The reader is encouraged to go to the primary literature for the exact conditions used to obtain a particular yield.

2. REACTIONS USING POLYMER-SUPPORTED TRIPHENYLPHOSPHINE

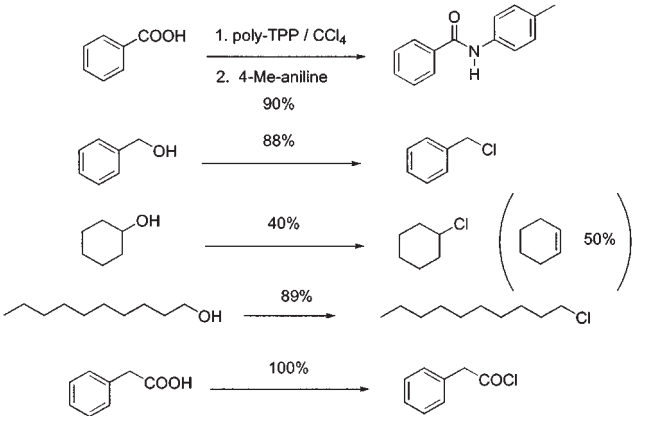
Triphenylphosphine (TPP) is a standard reagent in organic synthesis, although the by-product triphenylphosphine oxide often complicates purification of the reaction mixture. The use of polymer-supported triphenylphosphine (poly-TPP) leads to much simpler workups and product isolations. A TPP/carbon tetrachloride reagent system has many applications in organic synthesis, and a review of this reagent system has been published.[4] Many of these transformations have been carried out successfully using poly-TPP/CCl_4. As shown in Scheme 1, poly-TPP/CCl_4 can be used to convert primary carboxamides and oximes into nitriles in good yields.[5] Secondary amides can be converted into imidoyl chlorides.

The same reagent system is useful for the conversion of acids into acid chlorides and alcohols into alkyl chlorides.[6] An attractive feature of this conversion is that no HCl is evolved, so the conditions are essentially neutral. This technique can be used to generate amides by treating the carboxylic acid with poly-TPP/CCl_4 in the presence of an amine. This is exemplified by the preparation of the para-toluidide from benzoic acid in 90% yield (Scheme 2). Secondary alcohols lead to some elimination product. Carboxylic acids can also be converted into acid chlorides in excellent yields using polymer-bound triphenylphosphine dichloride (poly-$TPPCl_2$).[7] Recently, a convenient synthesis of this reagent has been described.[8]

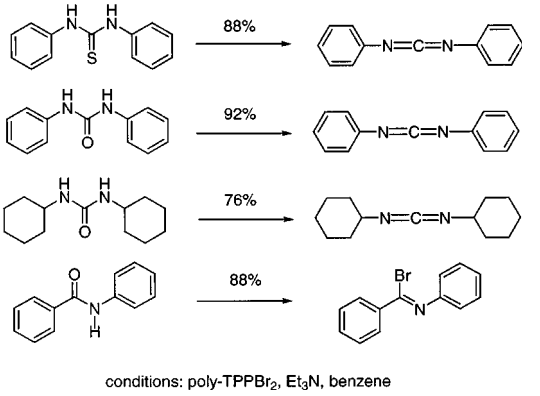
Triphenylphosphine dibromide has also been employed in organic synthesis, and has been shown to be a method of choice for the formation of unstable carbodiimides from ureas.[9] The polymer-supported derivative poly-$TPPBr_2$ has been used to convert ureas and thioureas into carbodiimides and secondary amides into imidoylbromides (Scheme 3).[10] Poly-$TPPI_2$ has been used to pre-



Scheme 1. Conversion of carboxamides and oximes into nitriles or imidoyl chlorides.



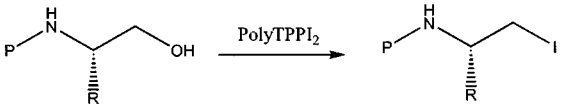
Scheme 2. Conversion of acids into acid chloride and alcohols into alkyl chlorides.



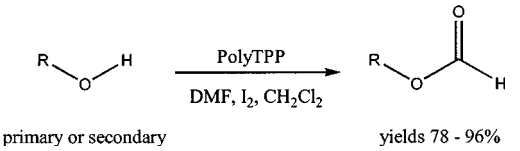
Scheme 3. Conversion of ureas and thioureas into carbodiimides, and secondary amides into imidoyl bromides.

pare *N*-protected β-amino iodides from *N*-protected β-amino alcohols.[11] The reaction proceeds without racemization and Cbz, Boc, and Fmoc protecting groups are tolerated (Scheme 4).

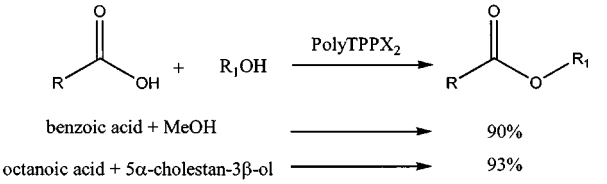
Primary and secondary alcohols can be conveniently converted to their formate esters using poly-$TPPI_2$ (generated *in situ*) and DMF (Scheme 5).[12] A range of primary and secondary alcohols were employed with yields from 78 to 96%. Under the same conditions, tertiary alcohols are converted to the corresponding iodide derivatives. Carboxylic acids can also be esterified with a variety of alcohols using poly-$TPPI_2$ (Scheme 6).[13] The alcohol component is not restricted to simple aliphatic alcohols.



Scheme 4. Iodination of N-protected β-amino alcohols.



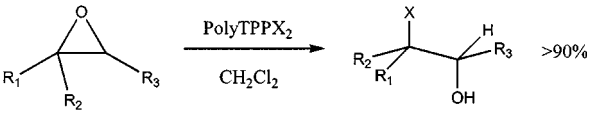
Scheme 5. Formic acid ester formation.



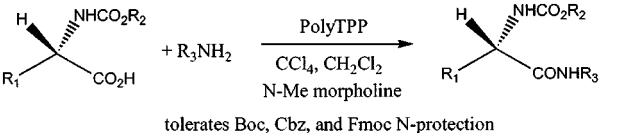
Scheme 6. Esterification of carboxylic acids with alcohols and polymer-supported triphenylphosphine dihalides.

Epoxides can be cleanly and efficiently converted to halohydrins using poly-TPP-dihalides (Scheme 7).[14] Due to the instability of some halohydrins, the nonacidic reaction conditions and facile removal of the phosphine oxide byproduct give this procedure considerable value. Yields are high and product isolation requires only filtration and evaporation of solvent.

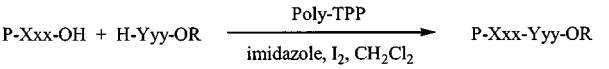
Poly-TPP is also a very useful reagent for amide bond formation, as shown in Schemes 8 and 9. The poly-TPP/CCl_4 reagent system couples *N*-protected amino acids with primary amines (including amino acid esters).[15] The chiral integrity of the amino acids employed is preserved, and the stan-



Scheme 7. Halohydrin formation from epoxides.



Scheme 8. Amide formation using poly-TPP and carbon tetrachloride.



P = Fmoc, Cbz, Boc
Xxx = L-Ala, L-Met, L-Cys(Trt), L-Leu, L-Phe, L-Val, L-Trp, L-Glu(t-Bu), L-Arg(t-Bu), L-Thr(OH)
Yyy = L-Leu, L-Ala, L-Cys(Trt), L-Phe, Gly, L-Val
R = Allyl, Methyl, t-Butyl, Benzyl, Heptyl

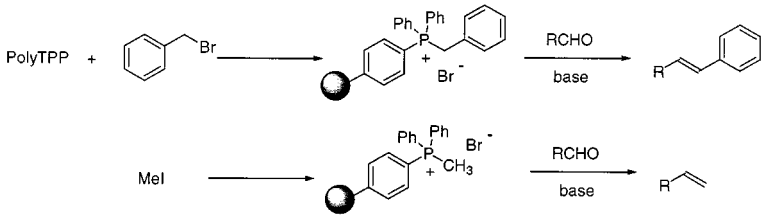
Scheme 9. Amide formation using poly-TPP, iodine, and imidazole.

dard *N*-protecting groups are not affected by the reaction conditions. Similar success is achieved with a poly-TPP and iodine reaction mixture.[16] Fmoc, Cbz, and Boc groups were utilized as *N*-protecting groups, and methyl, allyl, benzyl, and *t*-butyl esters were employed. Hindered amino acids (Fmoc-Val + Val-allyl ester) coupled well (99%) and no racemization was observed.

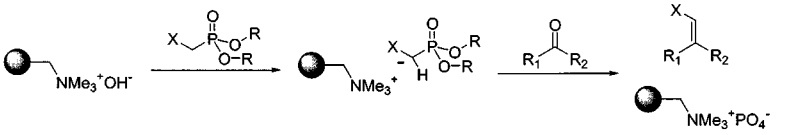
One of the most common and useful transformations employing triphenylphosphine is the Wittig reaction. A number of groups have explored this reaction using poly-TPP, and a few simple examples are outlined in Scheme 10.[17] A caveat to this transformation is that different conditions need to be employed to make the phosphonium salts from different alkylating agents, and different bases are optimal for different resins. One report describes the use of a phase transfer catalyst in the presence of the polymer-supported phosphonium salt and carbonyl compound. However, irrespective of the method of preparation, the polymer-supported Wittig reagents react with a variety of aldehdyes to give good yields of olefins. The approach was exemplified in the synthesis of ethyl retinoate.[18]

It should be noted that poly-TPP is not the only supported species that can be used to prepare olefins. Phosphonates with electron-withdrawing groups can be supported on ion-exchange resin and the supported reagent reacts with aldehydes and ketones in excellent yields (Scheme 11).[19]

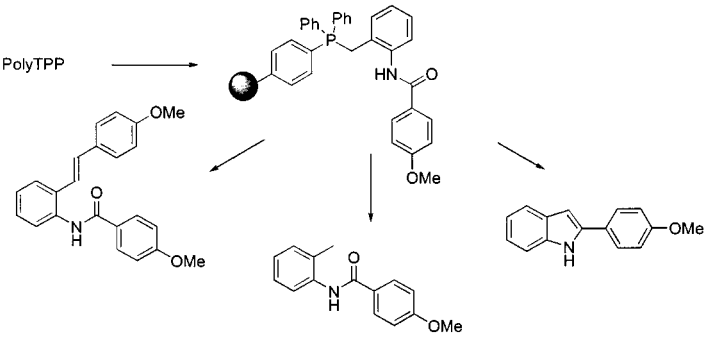
More recently, a functionalized polymer-bound phosphonium salt has been utilized to synthesize three different types of molecules, depending on the reaction conditions (Scheme 12).[20] Reaction with base and aldehyde affords the olefin, reductive cleavage affords the methyl compound, and treatment with base and heating affords the indole via an intramolecular cyclization. In these examples the poly-TPP serves as a versatile traceless linker.



Scheme 10. Wittig reactions using poly-TPP.



Scheme 11. Olefination using reagents supported on an ion-exchange resin.



Scheme 12. Poly-TPP as a traceless linker.

An additional application of poly-TPP is the synthesis of (*E*)-nitro olefins by isomerization of (*Z*)-nitro olefins.[21] The nitro olefins are prepared as a mixture of *E/Z* isomers via a nitroaldol reaction followed by dehydration of the β-nitro alcohols. Treatment of this mixture with a substoichiometric amount of poly-TPP afforded the (*E*)-nitro olefin.

3. REDUCTIONS USING POLYMER-SUPPORTED REAGENTS

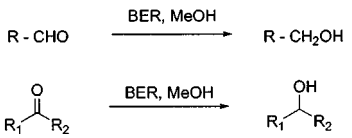
The selective reduction of functional groups is a common need in organic synthesis. Borohydride exchange resin (BER)[22] was introduced in the 1970s and has since proven to be of considerable value in the reduction of organic compounds. This reagent reduces both ketones and aldehydes readily, but can be used to reduce aldehydes in the presence of ketones as shown in Table I.[23] Interestingly, one also observes chemoselectivity between aromatic aldehydes with varying electronic characteristics in addition to between aromatic and aliphatic aldehydes.

BER can be used to reduce α,β-unsaturated carbonyl compounds into the corresponding α, β-unsaturated alcohols (Scheme 13).[24] $NaBH_4$ itself can give competitive reduction of the double bond along with reduction of the carbonyl, indicating that the polymer-supported reagent has modified reducing properties. Aldehydes react more quickly than ketones, and unhindered ketones react more rapidly than hindered ones. Not all double bonds are inert to BER, however. For example, BER cleanly reduces conjugated nitroalkenes to nitroalkanes (Scheme 14).[25] The reaction takes place at room temperature in methanol, and the desired products are isolated in high yields.

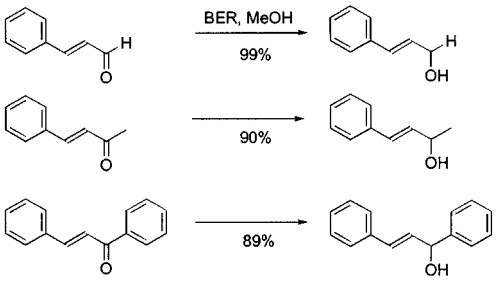
The reduction of azides to amines is a synthetically useful process. BER in MeOH reduces aryl azides and sulfonyl azides to the corresponding aryl amines and sulfonamides, respectively (Scheme 15).[26] Alkyl azides are either not reduced at all, or the reactions proceed in poor yield. The reactivity of $NaBH_4$ can be enhanced by combining it with certain transition metal salts. The same is true of BER, and a system employing BER-$Ni(OAc)_2$ reduces both alkyl and aryl azides in high yields (Scheme 16).[27] Primary, secondary, and tertiary azides are all reduced under these conditions. In addition, ketones are reduced to alcohols, and alkyl iodides are converted to the corresponding hydrocarbon.

The same BER-$Ni(OAc)_2$ system reduces aliphatic nitro groups and aryl nitro groups to amines

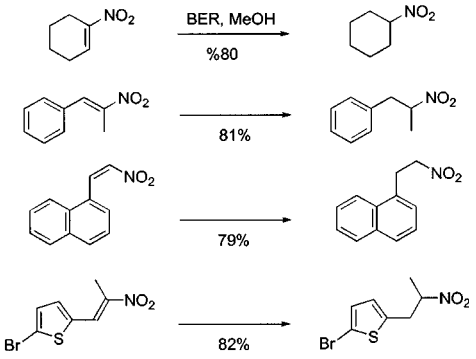
Table I. Chemoselective Reductions Using BER



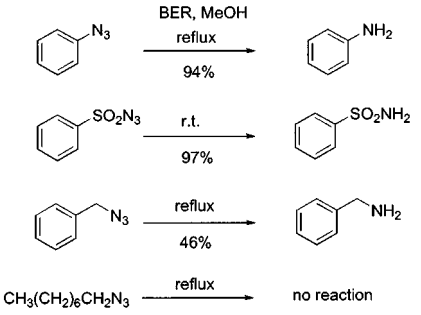
Starting Material	*Temp (°C)*	*Time (hr)*	*% Reduced*
benzaldehyde	25	5	99%
acetophenone	25	5	1%
benzaldehyde	−10	1	98.5%
hexanal	−10	1	6.5%
p-NO2 benzaldehyde	−10	1	92.3%
p-MeO benzaldehyde	−10	1	5.2%
cyclohexanone	0	9	95.1%
4-heptanone	0	9	3.9%



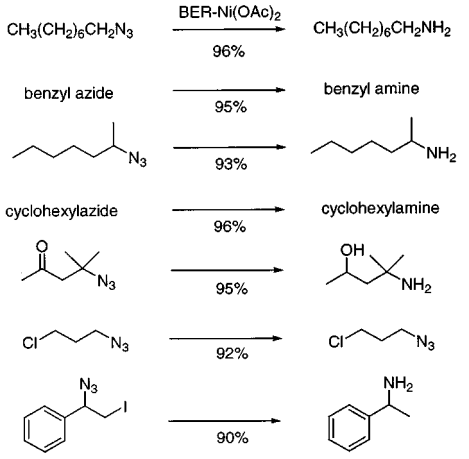
Scheme 13. Selective reduction of α,β-unsaturated carbonyl compounds.



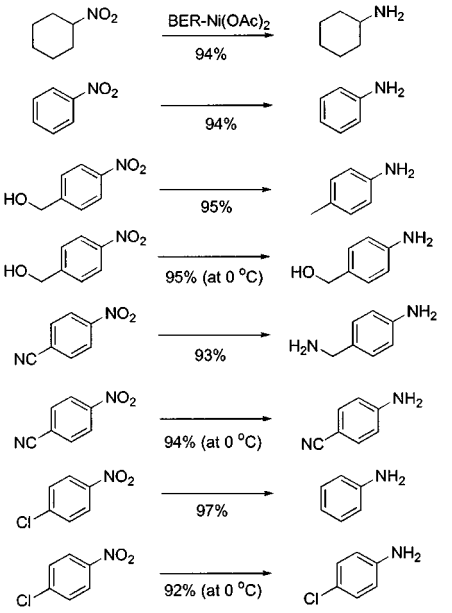
Scheme 14. Nitroalkene reduction by BER.



Scheme 15. Reduction of aryl and sulfonyl azides to amides with BER.



Scheme 16. Reduction of azides with BER-$Ni(OAc)_2$.

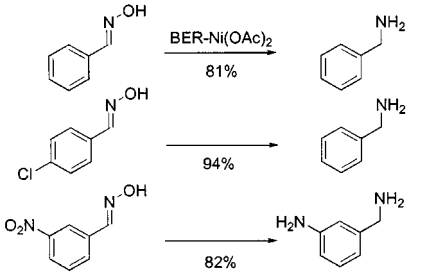


Scheme 17. Nitro reduction using BER-Ni(AcO)$_2$.

(Scheme 17).[28] At room temperature these reaction conditions convert benzyl alcohols, benzaldehydes, and benzaldehyde dimethyl acetals to the toluene derivatives, benzonitriles to benzyl amines, and aromatic chlorides to the benzene derivatives. If the reaction is carried out at 0 °C, the aromatic nitro group is still readily reduced, and these other functional groups can be preserved.

Another synthetically useful transformation carried out by BER-Ni(OAc)$_2$ is the reduction of oximes to benzylamines (Scheme 18).[29] The nature of the substituents on the ring has a significant influence on the reaction rate, but compounds with electron-donating groups can still be reduced in high yields by employing longer reaction times or elevated temperatures. These examples also show that aromatic halogens can be reduced by this system. Further examples are shown in Table II.[30]

It was mentioned in the previous examples that BER-Ni(OAc)$_2$ can be used to reduce certain aromatic halogens. This reagent also reduces a variety of alkyl halides to the hydrocarbons in good yields (Table III).[31] Primary and secondary alkyl bromides are readily reduced, although only cer-



Scheme 18. Oxime reduction with BER-Ni(OAc)$_2$.

Table II. Reduction of Aryl Halides with BER-Ni(OAc)$_2$

R-X	$\xrightarrow{\text{BER-Ni(OAc)}_2}$ R-H	
chlorobenzene	benzene	98%
bromobenzene	benzene	100%
iodobenzene	benzene	97%
2-chlorobenzoic acid	benzoic acid	81%
4-chloronitrobenzene	aniline	92%

Table III. Alkyl Reduction Using BER-Ni(OAc)$_2$

R-X	$\xrightarrow{\text{BER-Ni(OAc)}_2}$ R-H	
octyl chloride	octane	trace
octyl bromide	octane	100%
cyclohexyl bromide	cyclohexane	98%
benzyl chloride	toluene	96%
benzyl-a-bromoacetate	benzyl acetate	98%

tain chlorides can be reduced. These conditions compare favorably with the standard solution methods for reducing alkyl halides, in particular with respect to ease of workup and product isolation.

As mentioned previously, aldehydes are easily reduced by BER to alcohols. Complete reduction of benzaldehydes to the corresponding hydrocarbons can be accomplished using BER-Ni(OAc)$_2$ (Table IV).[32] Less reactive aromatic aldehydes, such as those with two electron-donating groups, are reduced only to the benzyl alcohols.

$CuSO_4$ has also been used as an additive to increase the reactivity of BER.[33] The results of several different reductions using BER-$CuSO_4$ are depicted in Table V. Aldehydes and ketones are reduced to alcohols. Amides and esters are not reduced, and nitriles are reduced only in poor yield. Alkyl and aryl halides (not chloro) can be reduced to hydrocarbons under certain conditions. Azides and nitro compounds are cleanly reduced to give amines in high yields. Acetylenes and di- or tri-substituted olefins are reduced only very sluggishly by this reagent, but carbon-carbon double bonds conjugated with an aromatic ring or a carbonyl group are readily reduced. Pyridine *N*-oxide is cleanly reduced to pyridine in 99% yield at reflux temperature.

Zinc borohydride has been used as a selective reducing agent. It is typically prepared as an ethereal solution, and stored cold, due to instability. Zinc borohydride supported on crosslinked 4-polyvinylpyridine (XP4-Zn$(BH_4)_2$) is a white powder that is stable at room temperature for months,

Table IV. Reduction of Aromatic Aldehydes to Hydrocarbons Using BER-Ni(AcO)$_2$

ArCHO	$\xrightarrow{\text{BER-Ni(OAc)}_2}$ $ArCH_3$	
furfuraldehyde	2-Me-furan	86%
benzaldehyde	toleune	91%
4-Me-benzaldehyde	4-Me-toluene	92%
4-Cl-benzaldehyde	toluene	95%
3-NO_2-benzaldehyde	3-NH_2-toluene	97%
2-OH-benzaldehyde	2-OH-toluene	98%
3-MeO-benzaldehyde	3-MeO-toluene	93%
4-$(CH_3)_2$N-benzaldehyde	4-$(CH_3)_2$N-toluene	98%
3-MeO-4-OH-benzaldehyde	3-MeO-4-OH-benzyl alcohol	78%
2,4-di-MeO-benzaldehyde	2,4-di-MeO-benzyl alcohol	82%

Table V. Reductions Using BER-$CuSO_4$

aldehyde or ketone	BER-$CuSO_4$ → alcohol	
benzaldehyde	benzyl alcohol	99%
2-heptanone	2-heptanol	98%
D-camphor	no reaction	
acetophenone	1-phenylethanol	100%
cyclohexenone	cyclohexanol	98%
ester, amide, or nitrile	**BER-$CuSO_4$ → no or little reaction**	
ethyl benzoate	no reaction	
benzamide	no reaction	
hexanenitrile	hexylamine	35% (reflux)
benzonitrile	benzylamine	58% (reflux)
	(dibenzylamine)	(21%)
R-X	**BER-$CuSO_4$ → R-H**	
1chlorooctane	no reaction	
1-bromooctane	octane	99%
1-bromo-4-chlorobutane	1-chlorobutane	95%
benzyl chloride	toluene	83%
	(1,2-diphenylethane)	8%
chlorobenzene	no reaction	
bromobenzene	benzene	36%
bromobenzene	benzene	55%[a]
bromobenzene	benzene	100%[a,b]
iodobenzene	benzene	99%
p-bromochlorobenzene	chlorobenzene	99%[a,b]
p-bromoiodobenzene	bromobenzene	97%
$R-N_3$	**BER-$CuSO_4$ → $R-NH_2$**	
octyl azide	octylamine	97% (6 hr)
benzyl azide	benzylamine	99% (6 hr)
phenyl azide	aniline	97% (1 hr)
$R-NO_2$	**BER-$CuSO_4$ → $R-NH_2$**	
nitrocyclohexane	cyclohexylamine	98%
nitrobenzene	aniline	95%[a]
p-bromonitrobenzene	p-bromoaniline	95%[a]

[a]reflux
[b]0.5 eq $CuSO_4$ instead of 0.1 eq

and shows useful reducing properties (Table VI).[34] The utility of this reagent lies in its discrimination between aldehydes and ketones; ketones are not reduced.

A similar reagent prepared with zirconium instead of zinc (XP4-$Zr(BH_4)_4$) has enhanced reactivity (Table VII).[35] Ketones are now also reduced, although, unlike BER-$CuSO_4$, conjugated double bonds are left untouched. $Zr(BH_4)_4$ decomposes at close to room temperature, inflames in air,

Table VI. Aldehyde Reduction Using XP4-$Zn(BH_4)_2$

aldehyde	XP4-$Zn(BH_4)_2$ → alcohol		
benzaldehyde	8 h	benzyl alcohol	80%
p-Br-benzaldehyde	8 h	p-Br-benzyl alcohol	87%
p-Cl-benzaldehyde	5 h	p-Cl-benzyl alcohol	95%
p-MeO-benzaldehyde	12 h	p-MeO-benzyl alcohol	75%
p-NO_2-benzaldehyde	8 h	p-NO_2-benzyl alcohol	90%
piperonal	8 h	piperonol	65%
cinnamaldehyde	9 h	3-phenyl-1-propanol	90%

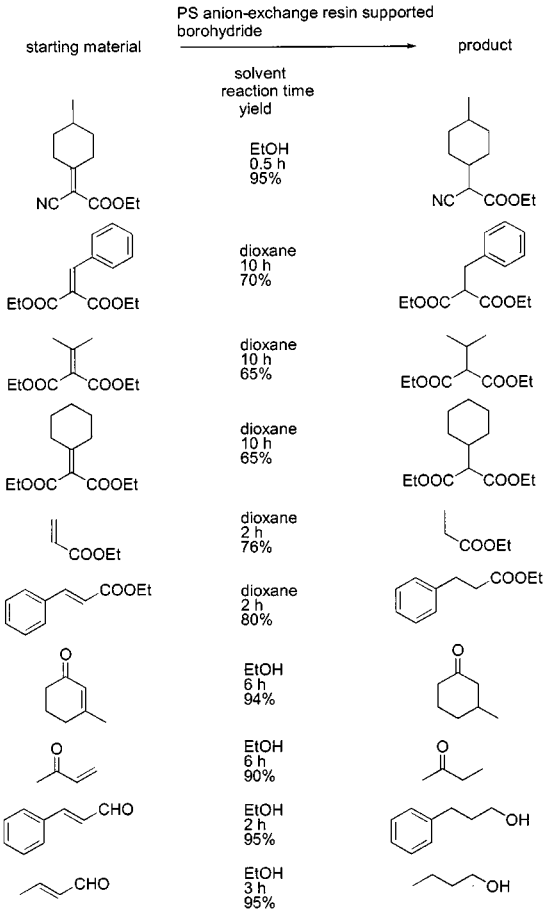
Table VII. Reduction of Aldehydes and Ketones Using XP4-$Zr(BH_4)_4$

aldehyde or ketone	XP4-$Zr(BH_4)_4$ → alcohol	
heptanal	10 h	88%
benzaldehyde	4 h	96%
p-NO2-benzaldehyde	3 h	95%
acetophenone	12 h	80%
cyclohexanone	15 h	80%
PhCH=CHCOPh	12 h	80%*

*no reduction of double bond

and hydrolyzes explosively; however, the polymer-supported version is stable. This reagent has clear advantages in terms of both safety and ease of workup and product isolation when compared to the unsupported reagent. The authors indicate that preliminary studies show reduction of acid chlorides to aldehydes, epoxides to the more substituted alcohols, and azides and nitriles to amines.

One report indicates that conjugated ethylenic linkages can be reduced by an ion-exchange resin bound borohydride (Scheme 19).[36] The double bond of α,β-unsaturated cyanoacetates, mono- and



Scheme 19. Selective reduction of conjugated ethylenic linkage using ion exchange resin bound borohydride.

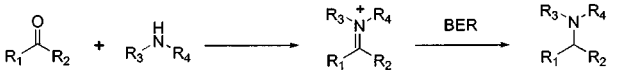
diacetates, and ketones is selectively reduced while α,β-unsaturated aldehydes are reduced to the saturated alcohols.

BER can also reduce imines, and has proven to be useful as a reducing agent in the reductive amination of aldehydes and ketones (Table VIII).[37] Aldehydes are reductively aminated cleanly with both primary and secondary amines. Ketones react well with less hindered aliphatic amines, and give lower yields with aromatic amines.

Cyanoborohydride has also been supported on an anion exchange resin, and, like its unsupported counterpart, is a useful reagent for reductive amination (Table IX).[38] The dimethylation of primary amines with formaldehyde works particularly well. An advantage of this process is that the toxic cyanide residues are retained on the polymer. Unlike the solution phase method, the Cyano-BER reaction requires mild heating to proceed, indicating a lower reactivity for the supported reagent.

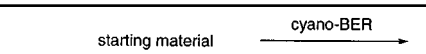
Polymer-supported reagents have been used in the reduction of ozonides formed in the ozonolysis of alkenes (Table X). Methodology using poly-TPP was developed when the scientists had dif-

Table VIII. Reductive Amination Using BER



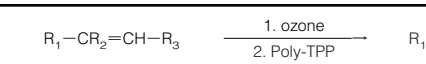
Carbonyl	*Amine*	*Yield*
hexanal	cyclohexylamine	89%
hexanal	diethylamine	86%
hexanal	piperidine	92%
benzaldehyde	cyclohexylamine	94%
benzaldehyde	aniline	88%
benzaldehyde	piperidine	90%
cyclohexanone	benzylamine	92%
cyclohexanone	NH_4OAc	59%

Table IX. Reductive Amination Using Cyano-BER



Starting material(s)	*Product*	*Yield*
PhCOMe, NH_4OAc	$PhCH(NH_2)Me$	53–66%
Cyclooctanone, NH_4OAc	cyclooctylamine	49%
$PhCH(Me)NH_2$, CH_2O	$PhCH(Me)NMe_2$	84%
Aniline, CH_2O	$PhNMe_2$	78%
4-cyano-N-(p-NO_2-benzyl)-pyridinium bromide	4-CN-N-(p-NO_2-benzyl)-1,2,5,6-tetrahydropyridine	71%

Table X. Reduction of Ozonides Using Poly-TPP

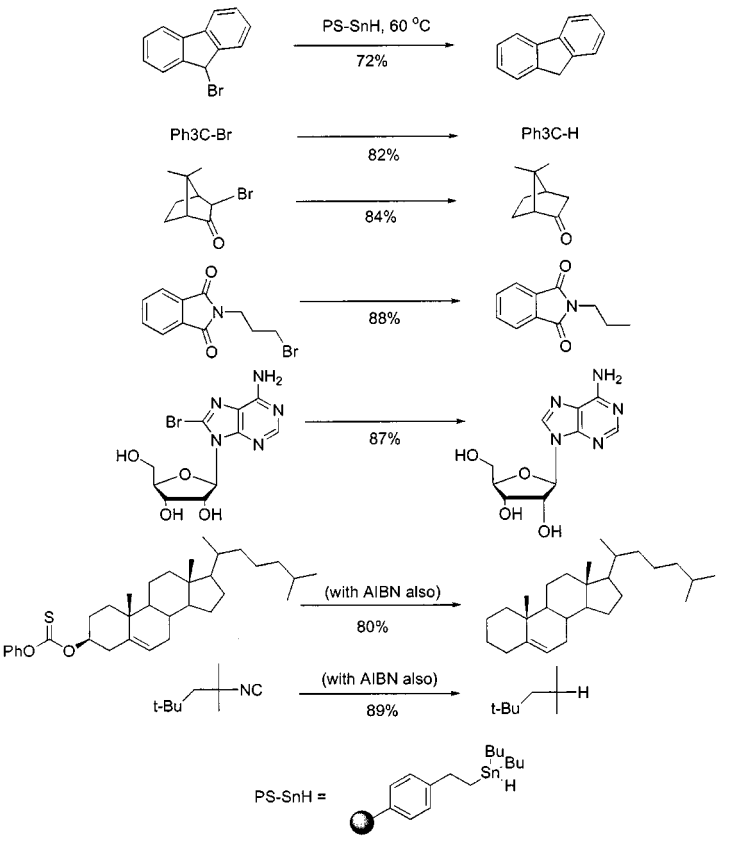


R_1=Ph, R_2=H, R_3=H	80%
R_1=C_9H_{19}, R_2=H, R_3=H	92%
R_1=C_7H_{15}, R_2=H, R_3=C_7H_{15}	91%
R_1=Ph, R_2=Me, R_3=H	86%
R_1=C_5H_{11}, R_2=Me, R_3=H	88%

ficulty removing triphenylphosphine oxide from a particular steroidal aldehyde product.[39] 3,3′ thiodipropionic acid bound to an ion-exchange resin has also been used in the reductive quenching of ozonolysis reactions.[40] The resin can be readily regenerated and, thus, provides a cost-effective reagent.

Tributyltin hydride is a versatile reagent useful for many transformations in organic synthesis. One drawback to this reagent is the difficulty in removing the tin byproducts from the desired compound. One way to address this problem is the incorporation of the tin reagent onto a polymer backbone. Indeed, an organotin hydride bound to crosslinked polystyrene and some of its uses have been reported (Scheme 20).[41] A variety of compounds can be dehalogenated in good yield, including molecules with significant functionality. The reagent is also useful for the second step of the Barton-type dehydroxylation of alcohols and in the conversion of isocyanides into the corresponding hydrocarbons. In order to further reduce the tin contamination further a system has been recently developed which uses "catalytic" amounts of polymer-supported tin hydride reagent generated in situ from a polymer-supported organotin halide and sodium borohydride.[42] The use of Polymer-$(CH_2)_4SnBu_2I$/$NaBH_4$ system afforded >90% yields in the reduction of 1-bromoadamantane using 0.2 equivalents of the tin halide with no tin being detectable.

A BER-NiB_2 system has also been used in radical addition of alkyl halides to alkenes.[43] Coupling of representative alkenes with a-bromo acid derivatives occurred in the presence of excess sodium iodide using BER-NiB_2 prepared *in situ* from BER-$Ni(OAc)_2$ in methanol.



Scheme 20. Transformations with polymer-supported organotin hydride.

4. OXIDATIONS USING POLYMER-SUPPORTED REAGENTS

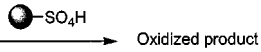
Medicinal chemists often need to perform mild and selective oxidation reactions. A variety of polymer-supported oxidizing agents have been developed which offer some advantages over more traditional oxidants. Peracids can be utilized for epoxidation reactions, oxidation of sulfides or sulfoxides to sulfones, and conversion of ketones to esters. Peracid type resins (PARs) prepared from polymer-bound carboxylic acids perform the same transformations (Table XI), and offer ease of removal of the spent reagent.[44] The PARs are quite stable, and can be easily regenerated after each use. Polymer-supported persulfonic acids have been used to carry out similar transformations in good yields (Table XII).[45]

A number of chromium derived oxidants are routinely used in organic synthesis. Removal of the by-products from the reaction can often be a problem, and with certain reagents, safety is a large issue. Frechet and colleagues developed poly(vinylpyridinium dichromate) (PVPDC) as an inexpensive, convenient to use, recyclable oxidant.[46] Table XIII lists some of the oxidations of alcohols to carbonyl compounds performed with this reagent. Primary alcohols are converted to aldehydes, and

Table XI. Oxidations With Peracid Resins

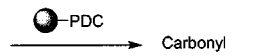
Substrate	*Solvent*	*Temp (°C)*	*Time (h)*	*Conversion (%)*	*Product*
CH_3SOCH_3	dioxane	20	0.1	98.7	sulfone
cyclohexene	dioxane	20	0.5	83.8	epoxide
CH_3SCH_3	dioxane	20	2	92.2	sulfone
2-pentene	dioxane	30	2	85.4	epoxide
cyclododecene	t-BuOH	30	2	86.0	epoxide
cyclohexanone	H_2O	40	1.5	96.0	lactone
styrene	t-BuOH	60	6	81.2	epoxide

Table XII. Oxidations Using Polymer-Supported Persulfonic Acid



acetophenone	phenyl acetate	85%
benzophenone	phenyl benzoate	81%
cyclopentanone	d-valerolactone	99%
ethyl methyl ketone	ethyl acetate	99%
cyclohexene	epoxide	80%
styrene	epoxide	80%
stilbene	epoxide	80%
chalcone	epoxide	80%

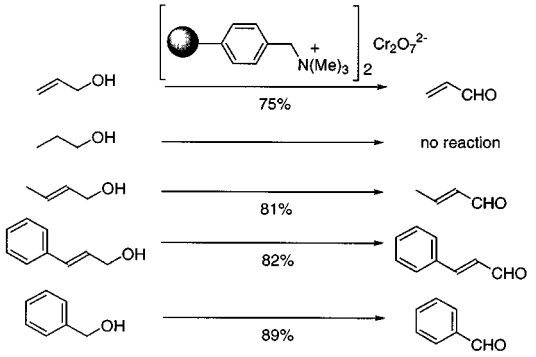
Table XIII. Oxidations of Alcohols With PVPDC



benzyl alcohol	benzaldehyde	>99%
1-phenylethanol	acetophenone	>99%
cinnamyl alcohol	cinnamaldehyde	98%
cyclopentanol	cyclopentanone	93%
cyclohexanol	cyclohexanone	93%

secondary alcohols are transformed into the corresponding ketones. Other polymer-supported chromium based oxidants have been prepared, and may be useful in certain circumstances. For example, a polymer-supported quaternary ammonium perchromate converts allylic alcohols to α,β-unsaturated aldehydes but does not oxidize saturated alcohols (Scheme 21).[47]

Several groups have reported on the utility of chromium reagents supported on silica gel. A silica gel-supported chromium trioxide reagent was recently described that is easily prepared, oxidizes alcohols cleanly in short reaction times at room temperature, uses a simple work up, and has a good shelf life.[48] A few transformations carried out by the reagent are shown in Table XIV. Silica gel supported bis(trimethylsilyl)chromate has also been appeared recently disclosed in the literature.[49] This reagent oxidizes various types of alcohols to carbonyls, reaction times are short, and over oxidation to carboxylic acids is not observed (Table XV). Oxidation of aryl substituted unsaturated alcohols (e.g., cinnamaldehyde) is not satisfactory in that partial cleavage of the double bond is observed. The reagent can also be used with cyanotrimethylsilane to convert benzaldehydes into the corresponding aroyl cyanides, useful precursors for amino alcohol synthesis.



Scheme 21. Selective oxidation of allylic alcohols.

Table XIV. Oxidations With Silica-Gel-Supported CrO_3

alcohol	SiO_2-CrO_3 → aldehyde	
octanol	octanol	85%
benzyl alcohol	benzaldehyde	80%
2-nitrobenzyl alcohol	2-nitro-benzaldehyde	46%
cinnamyl alcohol	cinnamaldehyde	67%

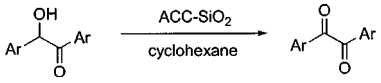
Table XV. Oxidations With Silica-Gel-Supported Bis(trimethylsilyl)chromate

alcohol	BTSC / SiO_2 → carbonyl	
o-MeO-benzyl alcohol	o-MeO-benzaldehyde	99%
p-Br-benzyl alcohol	p-Br-benzaldehyde	98%
m-NO_2-benzyl alcohol	m-NO_2-benzaldehyde	98%
1-octanol	1-octanol	94%
2-cyclohexylethanol	cyclohexylacetaldehyde	97%
phenylethanol	phenylacetaldehyde	96%
1-indanol	1-indanone	98%
menthol	menthone	98%
methyl mandelate	methyl phenylglyoxalate	93%
mandelonitrile	benzoyl cyanide	96%

Ammonium chlorochromate adsorbed on silica gel is another convenient oxidant recently reported.[50] The reagent is prepared by adding silica gel to a solution of ammonium chlorochromate in water, and evaporating to dryness. The reagent can be stored in the air at room temperature without losing activity. Benzoins are converted cleanly to benzils (Table XVI). Alcohols are converted to ketones or aldehydes, and sensitive structures such as allylic alcohols work well (Table XVII). Unlike the oxidation with BTSC on silica, cinnamyl alcohol is cleanly converted to cinnamaldehyde. Table XVIII depicts selected oxidations using $KMnO_4$ supported on kieselguhr.[51] Once again, preparation of the reagent is simple, and the oxidations are easy to perform.

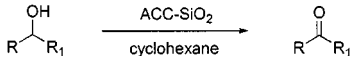
A polymer-supported perruthenate (PSP) has been developed on Amberlyst resin,[52] and was

Table XVI. Oxidations of Benzoins With Silica-Gel-Supported Ammonium Chlorochromate



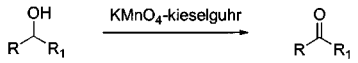
Ar	*Yield*
Ph	95%
p-Me-Ph	91%
p-MeO-Ph	90%
p-Cl-Ph	79%
2-furoyl	85%

Table XVII. Oxidations of Alcohols With Silica-Gel-Supported Ammonium Chlorochromate



R	*R_1*	*Yield*
Ph	H	91%
Ph	Me	90%
Ph	Ph	80%
$PhCH{=}CH_2$	H	81%
$PhCH_2$	H	65%
$-(CH_2)_4-$		85%
$CH_2(CH_2)_6$	H	81%

Table XVIII. Oxidations With $KMnO_4$ Supported on Kieselguhr



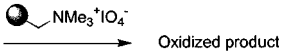
R	*R_1*	*Yield*
Et	Me	82%
Ph	Ph	97%
Ph	H	91%
PhCH=CH2	H	94%
p−MEO−Ph	H	86%

used in the oxidation of primary and secondary alcohols as a stoichiometric reagent or in catalytic amounts with a *N*-oxide co-oxidant. A further development was the use of molecular oxygen as an oxidant in conjunction with catalytic PSP.[53] This modification allows the oxidation of a range of alcohols to aldehydes and avoids the need for conventional workup procedures. This procedure affords the highest yield of cinnamaldehyde of the solid supported reagents described above (>95%).

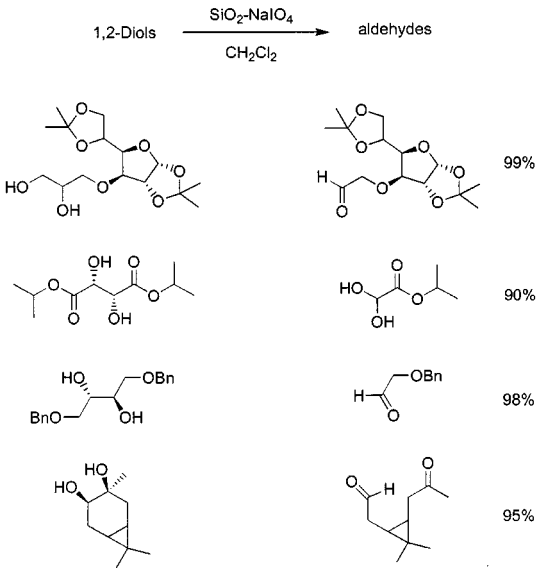
Periodates oxidize various functional groups, but due to solubility limitations, these salts are typically only utilized in hydroxylic media. Polymer-supported periodate, however, can be used in a variety of solvents, and in many cases, filtering off the resin and evaporating the solvent gives clean oxidized product. Quinols are converted to quinones, 1,2-diols are cleaved to the corresponding carbonyl compounds, sulfides are oxidized to sulfoxides, and triphenylphosphine is converted to triphenylphosphine oxide (Table XIX).[54]

A silica-gel supported metaperiodate reagent useful for the oxidative cleavage of 1,2-diols has been reported.[55] The reagent is easy to prepare, can be stored, and affords products in high yield, and pure enough for further synthetic operations (Scheme 22). The reaction can be performed in dichloromethane, and the reagent can thus be used for reactants not soluble in THF or water (typical solvents for the nonsupported reagent).

Table XIX. Oxidations Using Polymer-Supported Periodate



Substrate	Oxidized product	
quinol	p-quinone	86%
cyclohexane-trans-1,2-diol	adipaldehyde	90%
cycloheptane-trans-1,2-diol	pimelaldehyde	90%
dibenzyl sulfide	dibenzyl sulfoxide	99%
benzylmethyl sulfide	benzylmethyl sulfoxide	85%
thioanisole	phenylmethyl sulfoxide	81%
triphenylphosphine	triphenylphosphine	100%



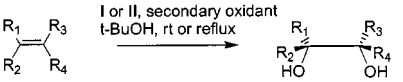
Scheme 22. Oxidative scission of glycols with silica-gel-supported sodium metaperiodate.

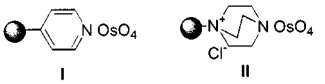
Osmium tetroxide is a useful reagent for converting alkenes to diols. This reagent has been anchored to solid supports either via an ionic interaction or more recently via microencapsulation, and can be used with co-oxidants to catalytically hydroxylate olefins (Table XX).[56] The polymer-supported reagent offers ease of workup compared to the classical method. Use of these polymers in conjunction with sodium periodate allows for cleavage of the vicinal diol formed by the hydroxylation reaction to the corresponding carbonyl compounds (Table XXI).[57]

Sulfonium salts have been anchored to solid supports, and have been used to prepare epoxides by reaction of their ylides with carbonyl compounds (Table XXII).[58] These salts are prepared by derivatization of crosslinked polystyrene. The polymeric reagent can be regenerated and reused without loss of reactivity.

Dimethyl dioxirane oxidizes alkenes to epoxides, primary amines to nitro compounds, tertiary amines to amine oxides, and sulfides to sulfoxides. This reagent is prepared at low temperature, often in situ, is unstable to heat and light, and has a short shelf life unless stored cold. The recently reported polymer-bound dioxirane overcomes these liabilities, and still affords a versatile oxidizing agent.[59] Table XXIII outlines some of the transformations using the polystyrene-supported dioxirane.

Table XX. Catalytic Hydroxylation of Olefins by Polymer-Bound Osmium Tetroxide

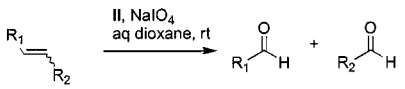




I II

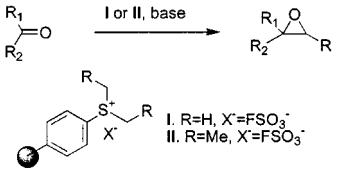
R_1	R_2	R_3	R_4	*Catalyst*	*Co-oxidant*	*Temp*	*Time*	*Yield*
H	H	H	n-C_8H_{17}	2	Me_3NO	83	0.5 h	95%
H	H	H	n-C_8H_{17}	1	Me_3NO	83	0.5 h	90%
Me	H	H	n-C_8H_{17}	2	Me_3NO	83	0.5 h	90%
	cyclooctene			2	Me_3NO	83	0.5 h	90%
Ph	H	H	Ph	2	Me_3NO	83	0.5 h	80%
Ph	H	H	CO_2Et	2	tBuOOH	r.t.	48 h	70%
CO_2Et	H	H	CO_2Et	2	tBuOOH	r.t.	60 h	95%

Table XXI. Cleavage of Olefins by Polymer-Supported Osmium Tetroxide and Sodium Periodate



R_1	R_2	*Time*	*Product*	*Yield*
H	n-C_8H_{17}	0.5 h	nonanal	77%
n-C_3H_7	n-C_3H_7	2 h	butanal	90%
CH_3	n-C_5H_{11}	2 h	hexanal	75%
Ph	Ph	1 h	benzadehyde	73%
$-(CH_2)_4-$		1 h	hexanedial	65%
Ph	CO_2Et	2 h	benzaldehyde	85%
Ph	$COCH_3$	2 h	benzaldehyde	80%

Table XXII. Conversion of Carbonyl Compounds to Epoxides via Polymer-Bound Sulfonium Ylide



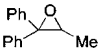
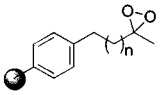
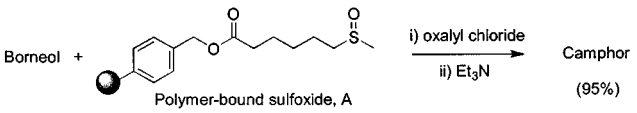
Carbonyl	*Polymer*	*Product*	*Yield*
benzaldehyde	I		97%
acetophenone	I		94%
benzophenone	I		96%
benzophenone	II		96%

Table XXIII. Oxidations Using Polystyrene-Supported Dioxirane



Substrate		PSD → Product	
aniline	43 h	nitrobenzene	83%
o-toluidine	39 h	o-nitrotoluene	85%
2-aminophenol	52 h	2-nitrophenol	80%
pyridine	35 h	pyridine N-oxide	83%
2,6-lutidine	30 h	2,6-lutidine N-oxide	85%
2-aminopyridine	50 h	2-nitropyridine	80%
styrene	40 h	styrene oxide	82%
cyclohexene	60 h	cyclohexene oxide	73%

The Swern oxidation is a particularly valuable tool in organic synthesis, often affording good yields of aldehydes and ketones under mild conditions. One downside to this reaction is the generation of the unpleasant smelling, volatile byproduct dimethyl sulfide. Linking 6-(methylsulfinyl)-hexanoic acid to crosslinked polystyrene affords a polymer-bound dimethylsulfoxide substitute that can be used in a modified Swern oxidation (Scheme 23).[60] Regeneration of this reagent by oxidation results in reduced oxidation capacity. Use of a soluble polymer, poly(ethylene) glycol (PEG), allows the preparation of a supported sulfoxide that can be regenerated without loss of activity.[61] In this case the reagent is removed from the reaction mixture by precipitation and filtration.



Scheme 23. Swern-type oxidation with a polymer-bound sulfoxide.

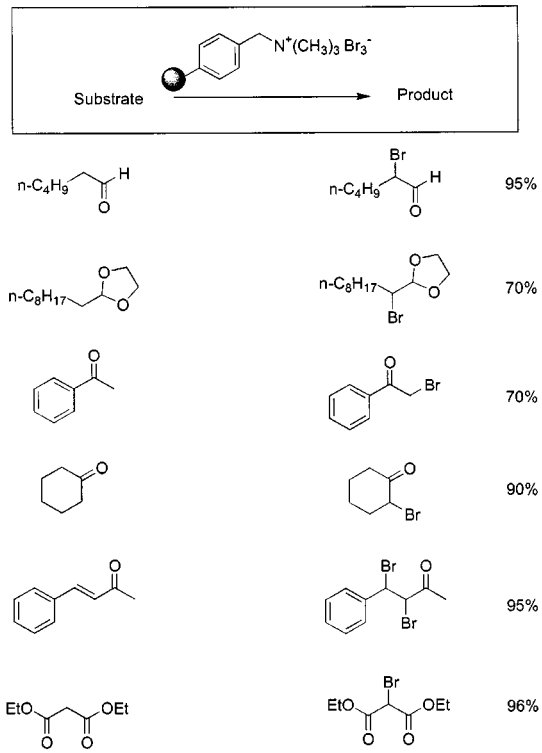
5. HALOGENATIONS USING POLYMER-SUPPORTED REAGENTS

Many methods are available for the halogenation of organic molecules and the choice of reagents often comes down to selectivity, functional group compatibility, and ease of use. Included in the arsenal are a number of polymer-supported halogenating agents. Attachment to a polymer backbone often increases the ease of handling of some of these reagents, and can serve to modulate the reactivity profile of the reagent.

Amberlyst A-26 in the perbromide form conveniently brominates a number of organic substrates in good yields (Scheme 24).[62] Saturated aldehydes are readily brominated, as are ketones. α,β-Unsaturated ketones are converted into the saturated di-bromo product in high yield. Esters are not alpha brominated, except for a doubly activated compound such as diethyl malonate.

Poly(4-methyl-5-vinylthiazolium)hydrotribromide has recently been introduced as a stable and useful brominating agent.[63] The polymer backbone is prepared by radical copolymerization of 4-methyl-5-vinylthiazole with styrene and divinylbenzene. Alkenes are readily dibrominated (Table XXIV). Acetophenone is quantitatively alpha-brominated, and diethyl malonate can be cleanly converted to the monobromo derivative.

In addition to brominations of olefins, or brominations alpha to carbonyls, side chains of aryl groups can also be brominated with polymer-supported reagents (Table XXV).[64] The bromine complex of poly(styrene-co-4-vinylpyridine) in the presence of dibenzoyl peroxide converts alkyl substituted benzene derivatives into the brominated products. The yields obtained are higher than those found preparing the compounds by other methods, and the experimental procedure used is operationally simpler.



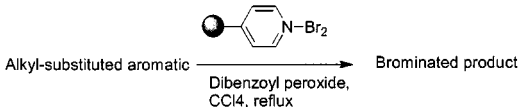
Scheme 24. Brominations with Amberlyst A-26 perbromide form.

Table XXIV. Brominations With Poly-(4-Me-5-vinyl-thiazolium)hydrotribromide

s.m.	*Product*	*Yield*
styrene	dibromide	100%
cyclohexene	dibromide	100%
trans-stilbene	dibromide	100%
acetophenone	bromo	100%
diethyl malonate	bromo	100%

PMVTHT = Poly-(4-Me-5-vinyl-thiazolium)hydrotribromide

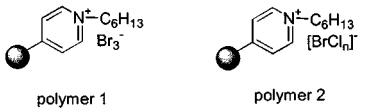
Table XXV. Side Chain Bromination Using Bromide Complex of Poly(styrene-co-vinylpyridine)



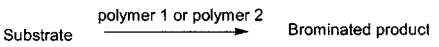
toluene	(bromomethyl)benzene	78%
1-methylnaphtalene	1-(bromomethyl)naphthalene	63%
2-methylnaphthalene	2-(bromomethyl)naphthalene	79%
ethylbenzene	1-phenyl-1-bromoethane	81%
1,2-dimethylbenzene	1,2-bis(bromomethyl)benzene	85%
2,6-dimethylpyridine	2,6-bis(bromomethyl)pyridine	66%

Bromination of aryl rings can also be accomplished using polymer-supported reagents. Table XXVI lists the bromination of a variety of aromatic molecules using derivatives of crosslinked co-polystyrene-4-vinylpyridine.[65] Polymer 1 is the milder brominating agent, and in certain cases gives better selectivity; for example, polymer 1 converts phenol to 4-bromophenol, and polymer 2 converts phenol to 2,4-dibromophenol. *N*-methyl indole, benzofuran, and benzothiophene could all be brominated, although they each gave a different type of product (see Table XXVI).

Table XXVI. Bromination of Aromatic Molecules



polymer 1 polymer 2



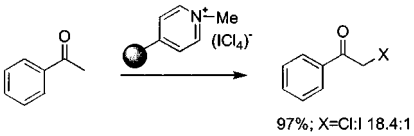
phenol	poly 1	4-Br-phenol	68%
phenol	poly 2	2,4-dibromophenol	77%
N,N-dimethylaniline	poly 1	4-Br-N,N-dimethylaniline	74%
anisole	poly 2	4-Br-methoxybenzene	77%
N-acetylaminobenzene	poly 2	1-N-acetylamino-4-bromobenzene	71%
1-methylindole	poly 1	2,3-dibromo-1-N-methylindole	72%
benzothiophene	poly 1	3-bromo-benzothiophene	79%
benzofuran	poly 1	trans-2,3-diBr-2,3-dihydrobenzofuran	76%
N-acetyltyramine	poly 2	3,5-diBr-N-acetyltyramine	84%
ortho-xylene	poly 2	4-bromo-ortho-xylene	64%

Other halogens can also be introduced with solid supported reagents. Chlorination of crosslinked styrene-4-vinyl-(*N*-methylpyridinium iodide) copolymer yields a reagent that converts acetophenone to chloroacetophenone in excellent yield (Scheme 25).[66] A similar reagent, poly[styrene-co-(4-vinylpyridinium dichloroiodate)], also smoothly chlorinates acetophenone (Scheme 26).[67] This particular reagent also iodinates the cyclic ketones indanone, 1-tetralone, and 6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one.

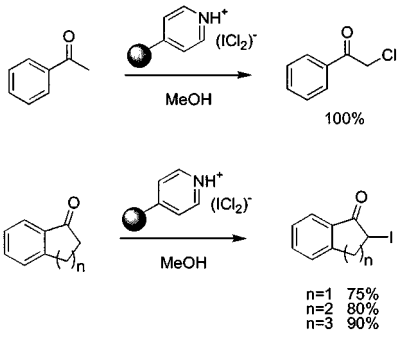
Poly[styrene-co-(4-vinylpyridinium dichloroiodate)] can also be used for regio- and stereospecific iodochlorination of alkenes and alkynes (Table XXVII).[68] This reagent gives Markovnikov type regioselectivity, and gives *trans* addition products. The solid-supported reagent gives purer products than the corresponding reaction with unsupported iodochloride.

With the increasing number of efficient metal mediated coupling reactions of aryl iodides and bromides, the simple preparation of these starting materials becomes more important. Poly[styrene-co-(4-vinylpyridinium dichloroiodate)][69] and poly[styrene(iodoso diacetate)][70] regioselectively iodinate activated aromatic and heteroaromatic molecules (Table XXVIII). Typical electrophilic iodination conditions require additional washing steps to remove impurities and iodine formed in the reaction. In some cases, multiple iodo atoms can be introduced by using more of the polymer. For example, 3-amino-2,4,6-triiodobenzoic acid is formed in 75% yield from 3-aminobenzoic acid using 2 grams of the resin for each millimole of substrate, as opposed to 0.5 g of resin for mono-iodination of 1 mmol of substrate.

Solid supported reagents that incorporate fluorine into organic molecules have also been developed. Olah and coworkers prepared poly-4-vinylpyridinium poly(hydrogen fluoride) from crosslinked poly-4-vinylpyridine and anhydrous hydrogen fluoride.[71] This material is a stable solid up to 50 °C, and needs to be stored under nitrogen. This reagent hydrofluorinates alkenes and alkynes, fluorinates secondary and tertiary alcohols, and, in the presence of N-bromosuccinimide, bromofluorinates alkenes (Table XXIX). This fluorinating agent offers the typical advantages of polymer-supported reagents.

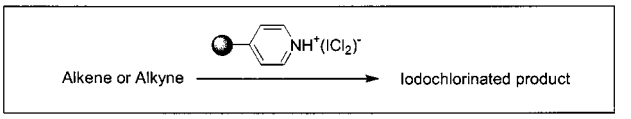


Scheme 25. Chlorination with cross-linked styrene-4-vinyl(N-methyl pyridinium iodide) copolymer.



Scheme 26. Halogenation with poly[styrene-co-(4-vinylpyridinium dichloroiodate).

Table XXVII. Iodochlorination of Alkenes and Alkynes With Poly[styrene-co-(4-vinylpyridinium dichloroiodate)



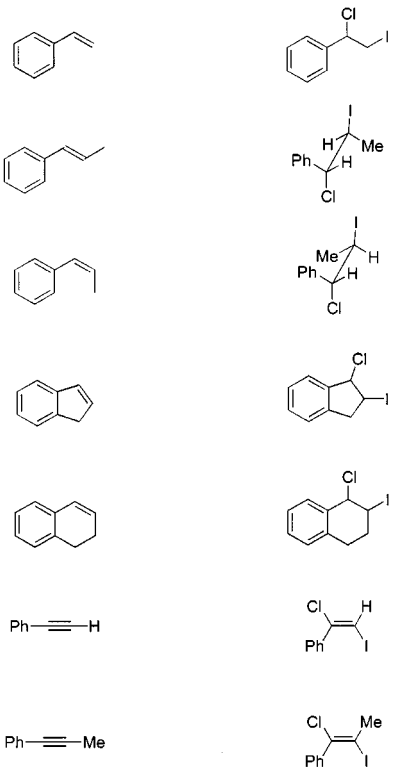
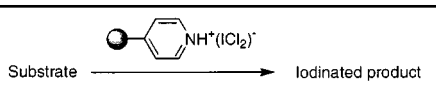


Table XXVIII. Regioselective Iodination of Aromatic and Heteroaromatic Molecules

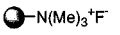


N,N-dimethylaniline	4-iodo-N,N-dimethylaniline	80%
phenol	4-iodo-phenol	60%
anisole	4-iodo-anisole	85%
1-MeO-naphthalene	4-iodo-1-MeO-naphthalene	85%
2-MeO-naphthalene	1-iodo-2-MeO-naphthalene	77%
1-naphthol	4-iodo-1-naphthol	68%
2-naphthol	1-iodo-2-naphthol	73%
1,3,5-trimethylbenzene	2-iodo-1,3,5-trimethylbenzene	76%
3-aminobenzoic acid	3-amino-2,4,6-triiodobenzoic acid	77%
1,3-dimethyluracil	5-iodo-1,3-dimethyluracil	90%
8-OH-quinoline	8-OH-5,7-diiodoquinoline	81%
4-pyridone	3,5-diiodo-4-pyridone	81%

Table XXIX. Fluorinations With Poly-4-vinylpyridinium poly(hydrogen fluoride)

Substrate	PVPHF → Fluorinated product	
cyclohexene	cyclohexyl fluoride	76%
1-methylcyclohexene	1-Me-1-F-cyclohexane	80%
norbornene	2-norbornyl fluoride	79%
cycloheptene	cycloheptyl fluoride	81%
1-hexyne	2,2-diflourohexane	56%
3-hexyne	3,3-diflourohexane	59%
1-adamantanol	1-adamantyl fluoride	94%
2-adamantanol	2-adamantyl fluoride	88%
triphenylmethanol	triphenylmethyl fluoride	77%
cycloheptanol	cycloheptyl fluoride	67%
2-norborneol	2-norbornyl fluoride	65%

Table XXX. Fluorinations With Polymer-Supported Fluoride Ion

Alkyl Halide	 → Fluorinated product
n-octyl bromide	82%
n-octyl chloride	87%
n-octyl mesylate	92%
benzyl chloride	100%
ethylbromoacetate	65%
bromoacetophenone	98%

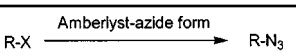
Alkyl fluorides can also be obtained from the reaction of the fluoride form of Amberlyst A-26 ion exchange resin with primary alkyl bromides, chlorides, and mesylates (Table XXX).[72] Secondary alkyl halides give mostly elimination products. Secondary mesylates afford better yields of the substitution product than do the corresponding bromides. This same reaction can be utilized for bromo to iodo, bromo to chloro, and chloro to bromo conversions simply by starting with the appropriate halide supported on the anion exchange resin. Reaction conditions are mild, and yields are generally quite high.

6. SUBSTITUTION REACTIONS USING POLYMER-SUPPORTED NUCLEOPHILES OR REAGENTS

The previous section contained an example illustrating the utility of polymer-supported halide ions in nucleophilic displacement reactions (Table XXX). In addition to halogen, a variety of nucleophiles have been supported on ion exchange resin, and these reagents often offer advantages such as easy work up, high yields, and mild reaction conditions.

Alkyl azides are useful intermediates in organic synthesis, and can be prepared using a polymeric quaternary ammonium azide. This reagent allows for the conversion of activated and nonactivated alkyl halides into azides at room temperature (Table XXXI).[73] The reaction proceeds most rapidly in polar solvents such as DMF and acetonitrile, but reasonable reaction rates are also obtained in a variety of other solvents. This reagent has also been used to open epoxides of polycyclic aromatic hydrocarbons to give azidohydrins.[74]

Table XXXI. Conversion of Alkyl Halides to Alkyl Azides Using a Polymeric Quaternary Ammonium Azide



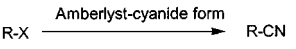
R	*X*	*Time*	*Yield*
n-C_4H_9	Br	3 h	100%
n-C_4H_9	I	1 h	100%
n-C_4H_9	OTs	24 h	100%
n-C_4H_9	Cl	>7 d	100%
$PhCH_2$	Cl	2 h	91%
$PhCH_2$	Br	1 h	100%
$PhCOCH_2$	Br	1 h	100%
EtO_2CCH_2	Cl	2 h	100%

A variety of nucleophiles have been supported on Amberlyst ion exchange resin and used for synthetic transformations. Cyanide ion supported on Amberlyst resin can be used to convert activated halides into the corresponding nitriles (Table XXXII).[75] This reagent is commercially available and can be used in a variety of solvents.

Amberlyst resin in the cyanate form converts alkyl halides into the corresponding symmetrical ureas in solvents such as benzene and pentane (Table XXXIII). Switching to ethanol as solvent gives good yields of the ethylcarbamates (Table XXXIV).[76] Thiocyanate supported on Amberlyst converts alkyl halides to thiocyanates (Table XXXV).

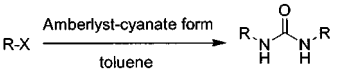
Thioacetate ion has also been supported on Amberlyst resin, and readily converts alkyl halides and tosylates into thioacetates (Table XXXVI).[77] Due to the mild reaction conditions, easy workup,

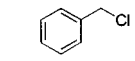
Table XXXII. Nitrile Synthesis Using Polymer-Supported Cyanide Ion



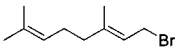
benzyl bromide	72%
p-Br-benzyl bromide	98%
p-Me-benzyl bromide	43%
m-Cl-benzyl bromide	68%

Table XXXIII. Symmetrical Urea Formation Using Polymer-Supported Cyanate Ion





90%

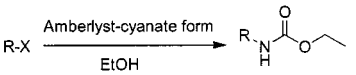


65%

n-C_8H_{17}-Br 93%

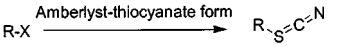
38%

Table XXXIV. Carbamate Formation Using Polymer-Supported Cyanate Ion in Ethanol



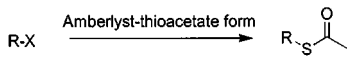
$PhCH_2Cl$	83%
$n\text{-}C_8H_{17}$	85%

Table XXXV. Thiocyanate Formation Using Polymer-Supported Thiocyanate



$n\text{-}C_8H_{17}$	90%
$EtO_2CCH_2\text{-}Br$	91%
$n\text{-}C_6H_{13}\text{-}CH(Br)CH_3$	77%

Table XXXVI. Introduction of Sulfur Using Polymer-Supported Thioacetate



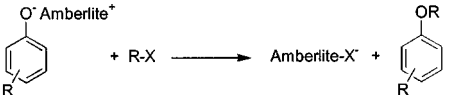
R	*X*	*Yield*
$n\text{-}C_8H_{17}$	BR	90%
$n\text{-}C_8H_{17}$	Cl	92%
$n\text{-}C_8H_{17}$	TsO	95%
$H_2C{=}CH{-}CH_2$	Br	56%
EtO_2CCH_2	Cl	85%
$PhCH_2$	Br	87%
$Ph{-}CO{-}CH_2$	Br	80%

and high yields, this reaction represents a convenient method for the introduction of sulfur into organic molecules. The thioacetate can be converted into the thiol via a palladium catalyzed methanolysis utilizing BER.[78] The formation of the thiol from an alkyl halide can be achieved in one-pot using the supported reagents in sequence.

Phenoxides can be supported on resin, and this serves as a useful method for carrying out O-alkylation when reacted with alkyl halides. Table XXXVII illustrates the reaction of phenoxides bound to a strongly basic Amberlite resin.[79] Primary halides give higher yields than secondary halides, and bromides give higher yields than chlorides. This methodology was recently expanded on, and used to make a library of aryl and heteroaryl ethers.[80]

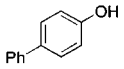
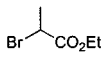
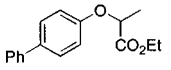
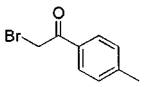
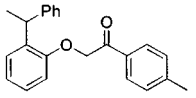
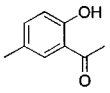
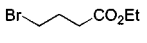
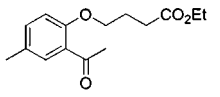
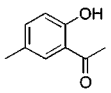
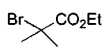
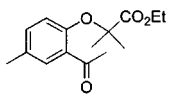
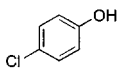
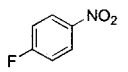
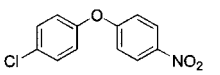
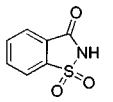
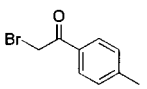
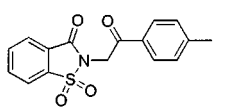
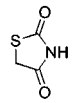
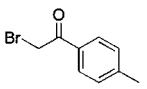
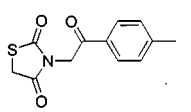
Polymer-supported 1,5,7-triazabicyclo[4.4.0]dec-5-ene (PTBD) can also be used to deprotonate and support a variety of phenols, which can then be O-alkylated with a good variety of alkyl halides (Table XXXVIII).[81] Of note is the ability to use tertiary halides and phenols with electron-donating or withdrawing groups. A wide range of aryl alkyl ethers was obtained using this methodology in good yields and high purity after filtration and solvent evaporation. A phenol supported in this manner could also be used in nucleophilic aromatic substitution reactions to give aryl ether products. As a further extension of this work, it was demonstrated that other acidic functionality, such as the nitrogen of saccharin or 2,4-thazolidinedione, could also be alkylated in the same straightforward manner.

Table XXXVII. Ether Formation Using Phenoxides Supported on Amberlite Resin



Anion	*R-X*	*Yield*
phenoxide	MeI	95%
phenoxide	allyl bromide	100%
phenoxide	benzyl chloride	100%
phenoxide	n-butyl iodide	100%
phenoxide	n-butyl chloride	15%
2-naphthoxide	MeI	60%
4-NO_2-phenoxide	MeI	95%
2,4-dinitrophenoxide	MeI	10%

Table XXXVIII. Alkylations Using the Polymer-Supported Bicyclic Guanidine Base, PTBD

Phenol	*Halide*	*Product*	*Yield*	*Purity*
			79%	91%
			98%	98%
			65%	94%
			32%	95%
			73%	99%
			39%	39%
			65%	65%

In addition to this polymer-supported bicyclic guanidine base (PTBD), a new synthesis of polystyrene supported biguanides has also been recently reported.[82] Biguanides are significantly more basic than the bicyclic guanidines, and have been used in base-catalyzed transesterification reactions. Reaction of guanidines with a polymer-bound carbodiimide yields supported biguanides which are more reactive and more stable than previously reported polymer-supported guanidines.

Polymer-supported carbonate ion has been utilized for the conversion of β-iodoamines into aziridines in high yield (Table XXXIX).[83] The reactions are performed in methanol, and pure product is obtained after filtration of the resin and evaporation of the solvent. Polymer-supported acetate ion transforms the same substrates into the amino alcohol (Table XL). Utilizing the resin-bound acetate for this transformation meant an aqueous work up was avoided, which turned out to be particularly important for these water-soluble compounds.

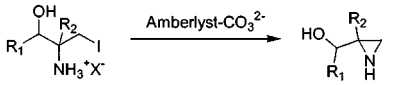
The same group used polymer-supported carbonate ion and iodine to transform allylic amines into 5-(iodomethyl)oxazolidin-2-ones in excellent yields (Scheme 27).[84] To emphasize the utility of this methodology, this research group synthesized the β-adrenoceptor antagonist propanolol in 6 steps (Scheme 28). Three of the steps involved solid-supported reagents.

The Mitsunobu reaction is a widely used reaction for the replacement of hydroxy groups by oxygen, nitrogen, and carbon nucleophiles. In certain examples, a major limitation is the purification of the crude reaction products. In addition to the use of polymer-supported phosphines,[85] a polymer-supported alkyl azodicarboxylate reagents has been prepared on polystyrene.[86] The immobilized reagent functioned effectively in Mitsunobu reactions, giving comparable yields to the corresponding soluble reagents. The resin was shown to have no tendency to explode or ignite and could be recycled at least five times.

A phthalimide containing resin has also been used in the conversion of a hydroxyl group to the corresponding amine under Mitsunobu conditions.[87] Reaction of N6-benzyladenosine with the resin in the presence of diethylazodicarboxylate and triphenylphosphine yielded a resin bound intermediate which was readily isolated. Subsequent treatment with hydrazine and evaporation gave a pure sample of the 5′-amine nucleoside as shown in Scheme 29.

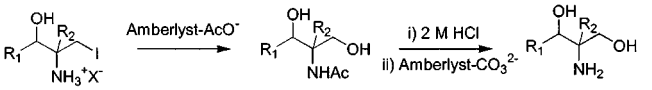
A polymer-bound tosyl azide has also been developed and used in the synthesis of diazoketones.[88] The diazo transfer reagent was synthesized on Amberlite XE 305 in two steps. The resin-bound reagent has one distinct advantage over tosyl azide in that it is not shock sensitive.

Table XXXIX. Aziridine Formation Using Polymer-Supported Carbonate Ion

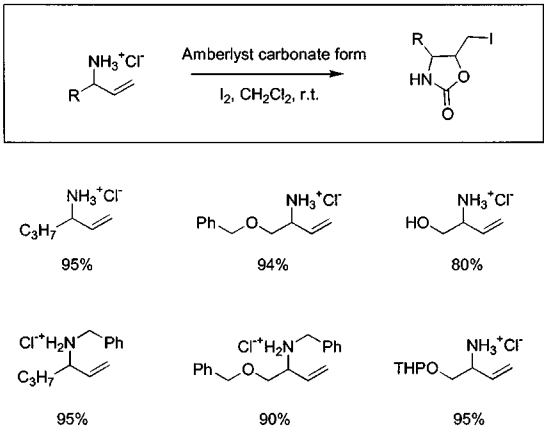


R_1=H, R_2=Me	96%
R_1=C_5H_{11}, R_2=H	95%
R_1=CH(Me)$_2$, R_2=H	95%

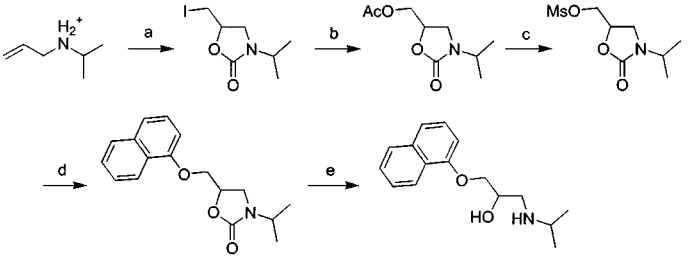
Table XL. Amino Alcohol Formation From β-Iodo-Amines Using Solid-Supported Reagents



R_1=H, R_2=Me	92%
R_1=C_5H_{11}, R_2=H	92%
R_1=CH(Me)$_2$, R_2=H	94%

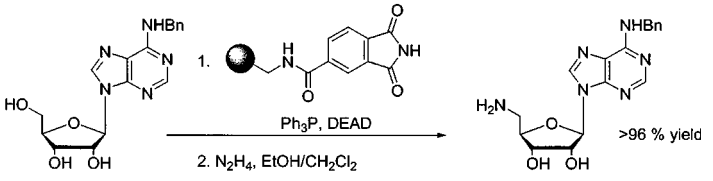


Scheme 27. Synthesis of 5-(Iodomethyl)oxazolidin-2-ones.



a. Amberlyst-CO_3^{2-} form/ I_2 b. Amberlyst-AcO^- form c. K_2CO_3in EtOH/ MsCl, Et_3N, CH_2Cl_2
d. Amberlyst-1-napthoate form e. 4 N KOH

Scheme 28. Propanolol synthesis.



Scheme 29. Phthalimide resin reagent for use in the Mitsunobu reaction.

7. PROTECTION AND DEPROTECTION USING POLYMER-SUPPORTED REAGENTS

The protection and subsequent deprotection of sensitive functionality in organic molecules is a common task in the synthesis of complex molecules. Considerable effort has gone into the development of simple, mild, and high-yielding protection and deprotection reactions. Due to some of the inherent advantages of solid-supported reagents, it is not surprising that they can play a role in these sorts of transformations.

Table XXXVII described the alkylation of polymer-supported phenoxides with various alkyl halides to give ethers. The methyl ether is a common protecting group for phenols, and can be conveniently introduced by the action of dimethyl sulfate on resin-bound phenoxides (Table XLI).[89] The

Table XLI. Protection of Polymer-Supported Phenoxides as Methyl Ethers

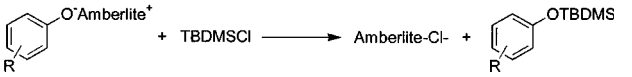
Anion	*Yield*
phenoxide	92%
o-Me-phenoxide	96%
m-Me-phenoxide	92%
p-Me-phenoxide	95%
1-naphthoxide	98%
2-naphthoxide	95%
p-Br-phenoxide	98%
2,6-diisopropylphenoxide	75%

authors found dimethyl sulfate more effective than methyl iodide in this transformation. Supported phenoxide ions can also be protected with the more readily removed t-butyldimethylsilyl (TBDMS) group (Table XLII).[90]

The tetrahydropyranyl moiety is a very useful protecting group for alcohols and phenols. It can be introduced conveniently by using the hydrochloride salt of poly(4-vinylpyridine) resin as a catalyst.[91] The reaction can be carried out on dihydropyran as solvent, and a range of alcohols are protected in high yields following filtration and evaporation of the excess DHP (Table XLIII). Sulfuric acid absorbed on silica gel has also been used as the catalyst for this transformation with great success.[92] This method also offers the advantages of no aqueous workup, mild reaction conditions, short reaction times, and high yields.

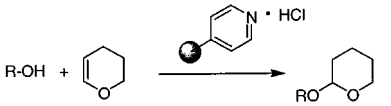
Carbonyl groups are often protected as acetals during the course of a multistep synthesis. Polymer-bound triphenylphosphine diiodide has been successfully employed to convert a range of carbonyl compounds into acetals, cyclic acetals, dithioacetals, and oxathioacetals.[93] Some of their results are highlighted in Table XLIV. The reaction is carried out in anhydrous acetonitrile at room temperature, and the reaction by-product, polymer-supported triphenylphosphine oxide, is removed by filtration. This by-product can be recycled by reduction to the starting phosphine form with trichlorosilane.[94] Polymer-supported boron trifluoride, formed by reaction of crosslinked polystyrene-4-vinyl pyridine resin with boron trifluoride in chloroform, can also catalyze the acetalization of certain carbonyl compounds.[95] This reagent can also be used to esterify carboxylic acids.

Table XLII. Protection of Polymer-Supported Phenoxides as TBDMS Ethers



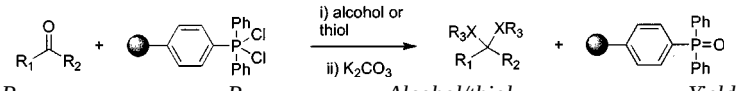
Anion	*Yield*
phenoxide	85%
4-nitrophenoxide	82%
2-nitrophenoxide	91%
2-naphthoxide	72%
2-formyl-phenoxide	96%
4-methylphenoxide	90%
2-methylphenoxide	65%

Table XLIII. Protection of Alcohols as Tetrahydropyranyl Ethers



Alcohol	*Yield*
2-pyridine propanol	94%
3-pyridine methanol	93%
cyclohexanol	98%
benzyl alcohol	97%
phenol	91%
menthol	96%
4-mehtoxyphenol	90%
cholesterol	94%
2-phenyl-2-propanol	84%

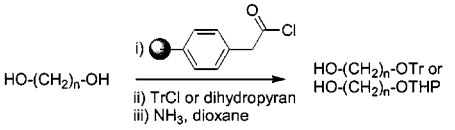
Table XLIV. Acetalization of Carbonyl Compounds Mediated by Poly-TPP-I_2



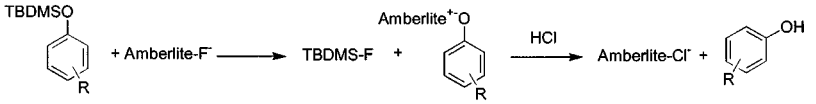
R_1	R_2	*Alcohol/thiol*	*Yield*
Ph	Me	HO—$(CH_2)_2$—OH	87%
Ph	Me	HS—$(CH_2)_2$—SH	98%
Ph	Me	HO—$(CH_2)_2$—SH	92%
Ph	Ph	HS—$(CH_2)_2$—SH	86%
Ph	H	HS—$(CH_2)_2$—SH	98%
—$(CH_2)_4CH(CH_3)$—		HO—$(CH_2)_2$—OH	90%
N—C_7H_{15}	H	HO—$(CH_2)_2$—OH	84%

In addition to the preceding examples, which mostly illustrate solid-supported reagents as catalysts for the introduction of protecting groups, the polymer itself can be used as the protecting group. This allows for selective transformations on another reactive site of the molecule, and is the basis for solid phase organic synthesis (SPOS). Leznoff and coworkers published several seminal articles in this area in the early 1970s, helping pave the way for the current explosion in small molecule SPOS.[96] Highlighted in Scheme 30 is an illustration of the selective protection of diols, and their subsequent conversion into monoethers.[97]

Table XLIV contains examples of protection of phenoxides as TBDMS ethers. Deprotection of these compounds can be accomplished using fluoride ions supported on Amberlite resin (Scheme 31).[98]



Scheme 30. Synthesis of monoethers from symmetrical diols using polymer supports.



Scheme 31. Deprotection of TBDMS ethers using fluoride ion supported on Amberlite resin.

The deprotection takes place over 24 to 36 h at room temperature, or in 6 to 12 h with heating at 50 to 60 °C. This transformation leads to resin-bound phenoxides, which are removed from the resin using 0.1 N hydrochloric acid.

Another common protecting group for alcohols and phenols is the acetate group. In addition to the numerous transformations outlined in Section 3, borohydride exchange resin (BER) cleanly removes acetyl groups from phenols, yet does not deacylate alkyl acetates (Table XLV).[99] Pure compounds are obtained after filtration to remove the resin and evaporation of the filtrate.

Protection of amine moieties can be achieved in a number of ways using polymer-supported reagents. A variety of amines can be protected as carbamate derivative (Boc, Cbz, and FMOC) using a polymer-bound 1-hydroxybenzotriazole (Scheme 32)[100] Fmoc and Cbz derivatives of primary and secondary amines were obtained in fair to excellent yields. The Boc derivatives and carbamates of aromatic amines were obtained in poor yields.

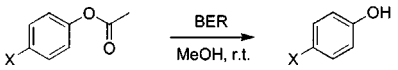
Trifluoroacetylation of amines and amino acids has been reported using a polymer-bound S-benzyl trifluorothioacetate or benzyl trifluoroacetate.[101] The reagents are prepared by reaction of trifluoroacetic anhydride with the polymer-bound benzyl thioalcohol or benzyl alcohol, respectively. Reaction with amines or amino acids results in the trifluoroacetate in high yields with no racemization of the chiral centers.

The simultaneous deprotection and purification of Boc amines has recently appeared.[102] Treatment of the protected amine with Amberlyst 15 removes the Boc group and leaves the amine ionically bound to the resin. After washing the resin to remove unreacted starting material, the amine is released upon treatment with methanolic ammonia (Scheme 33).

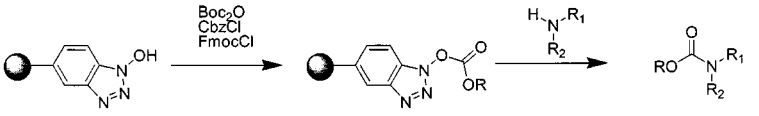
Ytterbium triflate supported on silica has been shown to be a highly selective reagent for the deprotection of BOC protected carboxamides.[103] Other acid sensitive protecting groups N-Cbz or N-Boc amino groups and acetonide were left intact by the procedure (Scheme 34).

The phthalimide group is a robust protecting group for amines, and it has found widespread use in carbohydrate chemistry. A number of deprotection methods are available, but for particularly complex or sensitive molecules, the typical methods are not always appropriate. Recently, alkyldiamines immobilized on polystyrene resin have been utilized for the removal of both N-phthalimido and N-tetrachlorophthalimido groups (Scheme 35).[104]

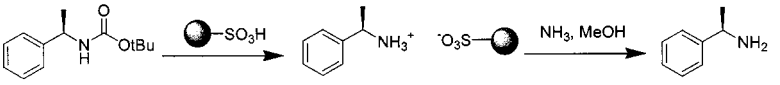
Table XLV. Deacylation of Aryl Acetates Using BER



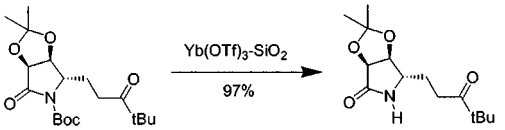
X	*Yield*
H	95%
NO_2	92%
Cl	95%
Me	94%



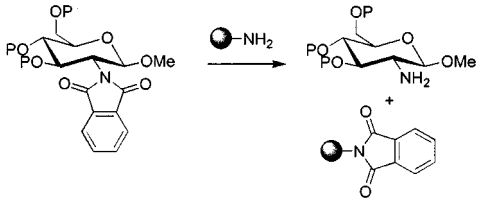
Scheme 32. Amine protection using polymer-supported HOBT.



Scheme 33. Deprotection of Boc-protected amines using a sulfonic acid resin.



Scheme 34. Deprotection of Boc-protected carboxamides with $Yb(OTf)_3$ supported on silica gel.



Scheme 35. Solid-supported alkyldiamines for the removal of N-phthalimido protecting groups.

8. POLYMER-SUPPORTED CATALYSTS AND METALS

In addition to the polymer-supported reagents and polymer-supported substrates described above, there is also an interest in polymer-supported catalysts, and metals. In many cases, these types of polymer-supported reagents can improve low reactivity, simplify work up procedures, and should be useful in large scale synthesis.

Polymer-supported quaternary ammonium cyanides have been used as catalysts for the benzoin condensation.[105] The catalyst is prepared from Merrifield resin. The yields of the benzoin are moderate (around 60%), but product isolation is simplified. A chiral resin was also used as the catalyst, and produced a benzoin with an ee of 23%.

A more successful application of a polymer-bound catalyst to an asymmetric transformation is found in the asymmetric dihydroxylation of alkenes.[106] Bolm and colleagues derivatized silica with alkaloids and used the resulting catalysts to hydroxylate various olefins. High enantioselectivities ($^{>}$98%) were achieved with both styrene and stilbene. Dec-1-ene was dihydroxylated with an ee of 84%. These catalysts were recovered quantitatively after the reactions by filtration, and the catalysts could be reused in subsequent reactions.

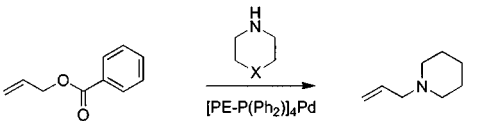
Approaches to a heterogeneous Sharpless-type epoxidation catalyst have been reported. The use of a branched/crosslinked poly(tartrate ester) for the complexation of $Ti(OiPr)_4$ is the most successful, with high isolated yields and enantiomeric excess comparable to the homogeneous catalyst.[107]

A number of research groups have explored the utility of polymer-supported palladium catalysts in organic synthesis. A diphenylphosphine-terminated ethylene oligomer has been used as a ligand for palladium (0) and palladium (II).[108] This polymer is soluble at 100°C in toluene, and successfully catalyzed reactions typically catalyzed by $(Ph_3P)_4Pd$ and $(Ph_3P)_2Pd(OAc)_2$. For example, allylic esters could be cleanly displaced by secondary amines, to give the tertiary amine product (Table XLVI). The catalyst could be removed by filtration at room temperature.

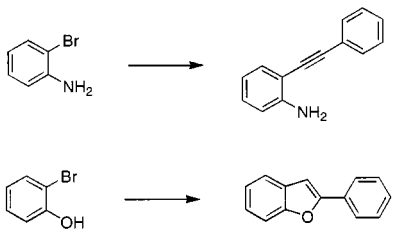
Another report describes the use of a polymer-bound $PdCl_2$ catalyst and CuI to synthesize functionalized acetylenes and benzofurans.[109] 2-Bromoaniline cleanly couples with phenylacetylene, and 2-bromophenol couples and then spontaneously cyclizes to give 2-phenyl benzofuran (Scheme 36). The palladium catalyst is made by treating polymer-supported triphenylphosphine with palladium chloride in DMF.

The Heck reaction, palladium mediated arylation of olefins, is very useful for the construction of carbon–carbon bonds. The utility of polymer-supported palladium catalysts in this reaction has been explored.[110] 2-Arylethylamines, an important moiety in many pharmacologically active molecules, can be synthesized via Heck reactions of acrylamide with iodobenzenes using a polymer-bound palladium catalyst (Scheme 37).[111] The particular catalyst used for this example is obtained from poly(styryl)phenanthroline and palladium acetate. Aryl iodides containing both electron-withdrawing and electron-releasing substituents work well in the coupling step. Reduction of the double bond of the cinnamide, followed by Hoffman reaction converts the Heck coupling product into the phenethylamine derivatives.

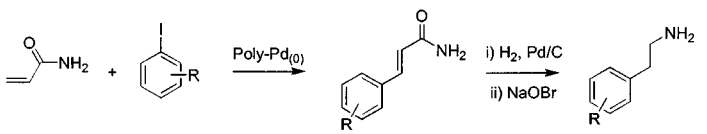
Table XLVI. Allylic Substitution of Allylic Esters Using a Polymer-Supported Catalyst



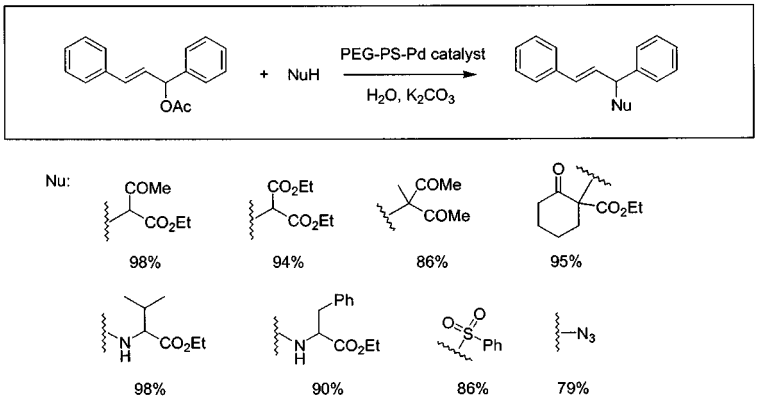
$X=CH_2$	100%
X=O	100%



Scheme 36. Synthesis of functionalized acetylenes using a polymer-supported catalyst.



Scheme 37. Synthesis of cinnamides using a polymer-supported palladium catalyst.



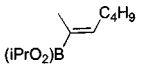
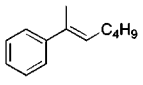
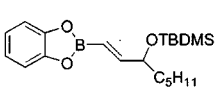
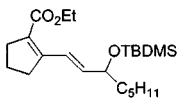
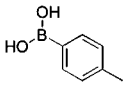
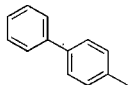
Scheme 38. Allylic substitution with a polymer-supported palladium-phosphine catalyst.

Recently, palladium-phosphine complexes on polyethylene glycol-polystyrene graft copolymer (PEG-PS) resin were designed and prepared. PEG-PS support was chosen in order to be able to carry out reactions in aqueous media.[112] The polymer-supported catalyst allowed for the allylic substitution of allyl acetates with a variety of nucleophiles. Scheme 38 shows the results for the reaction of 1,3-diphenyl-2-propenyl acetate and eight different nucleophiles. Because the reaction is carried out in water, nucleophiles that have limited solubility in organic solvents, such as the hydrochloride salt of phenylalanine ethyl ester and sodium azide, can be utilized successfully. Importantly, the catalyst could be reused with no loss in catalytic activity and continued high yields.

Polymer-bound palladium species have also been used for the Suzuki reaction, another very important carbon–carbon bond forming reaction.[113] The palladium (0) catalyst cleanly cross-coupled organoboranes with 1-alkenyl bromides, aryl halides, and aryl or alkenyl triflates (Table XLVII). The polymeric catalyst could be recovered by filtration and reused more than ten times with no decrease in activity. The polymer-supported reagent is comparable to $Pd(PPh_3)_4$.

A recent report describes a polymer-bound hydrogenation catalyst that is soluble and active in basic aqueous media, but insoluble and inactive in acidic aqueous media.[114] This unique property allows for homogeneous reactions in base, and catalyst recovery by acidification. The polymeric support is synthesized by reaction of a commercially available copolymer of maleic anhydride and methyl vinyl ether with a phosphine containing amine, and subsequent complexation with rhodium. Hydrogenation of N-isopropyl acrylamide proceeds in 94% yield.

Table XLVII. Suzuki Reaction Using a Polymer-Bound Palladium Catalyst

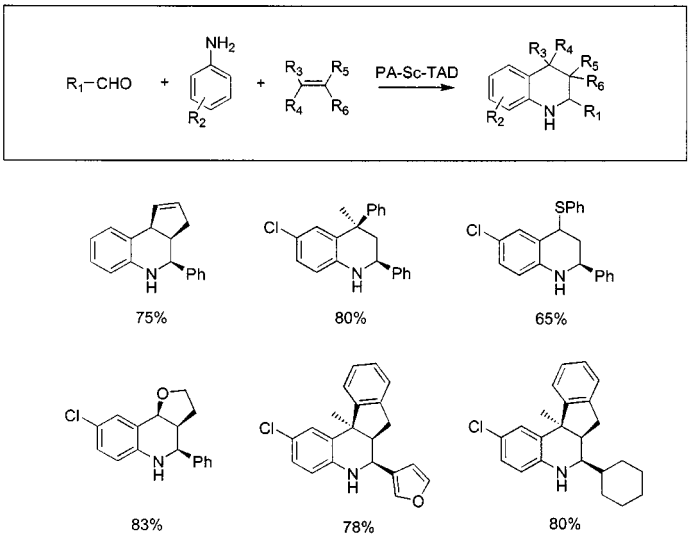
Triflate	*Organoborane*	*Product*	*Yield*
			85%
			97%
			90%

Other more conventionally supported catalysts have been used in asymmetric hydrogenations. Attachment of an acid functionalized (R)-BINAP to a polystyrene resin followed by treatment with a ruthenium complex afforded a catalyst, presumed to be the ruthenium dibromide species, which demonstrated similar activity to the solution phase catalyst.[115] Analysis of the reaction products for ruthenium content showed less than 1 mol% of the total amount of ruthenium leached into the reaction product.

A range of polymer-supported versions of chiral auxilaries or ligands have been prepared. Generally this has been achieved via attachment of catalyst at a position pendant to the polymer backbone. These have been successfully utilized in transfer hydrogenation,[116] allylation using allylboron reagents,[117] and alkylation reactions.[118] The incorporation of the catalytic ligand at the resin cross link has recently been investigated.[119] (R,R)-1,2-diaminocyclohexane was functionalized with styrenesulfonyl chloride and then copolymerized with styrene to afford resin with the ligand incorporated at the cross link. The resin was used in enantioselective alkylation of aldehydes and cyclopropanation of allylic alcohols and produced enantiomeric excesses slightly below the values obtained in solution.

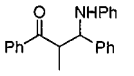
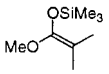
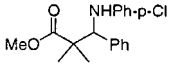
Two recent examples from the Kobayashi group highlight the utility of polymer-supported catalysts in the preparation of combinatorial libraries. A library of tetrahydroquinolines was prepared from the multicomponent condensation of aldehydes, anilines, and olefins in the presence of (polyallyl)scandium trifylamide di-triflate (PA-Sc-TAD).[120] The catalyst is synthesized in three steps from polyacrylonitrile. PA-Sc-TAD is partially soluble in the reaction solvent system (CH_2Cl_2—CH_3CN, 2:1), but can be precipitated by the addition of hexane. Fifteen examples are given in the article, with yields from 65 to 100%. Scheme 39 illustrates some of the products that can be formed using this chemistry.

Diverse amino ketones, amino esters, and amino nitriles are obtained from the multicomponent condensation of aldehydes, amines, and a silyl nucleophile in the presence of PA-Sc-TAD.[121] The reaction is performed at room temperature, yields are high, and products are quite pure after removal of the catalyst by filtration. Examples using three different silyl nucleophiles are shown in Table XLVIII. The PA-Sc-TAD has a lower reactivity than the monomeric Lewis acid and additional work has resulted in an alternative polymer-supported reagent, a microencapsulated Lewis acid.[122] The catalyst has been demonstrated to be effective in many carbon–carbon bond forming reactions and can be reused without loss of activity.



Scheme 39. Tetrahydroquinoline synthesis using a polymer-supported scandium catalyst.

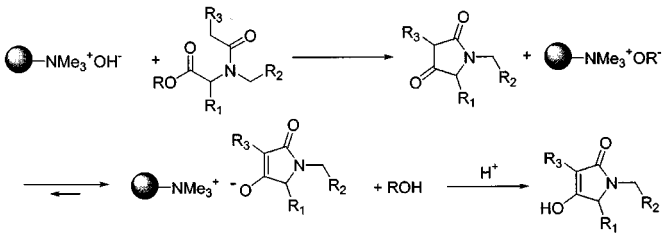
Table XLVIII. Three-Component Reaction Using a Polymer-Supported Scandium Catalyst

Aldehyde	*Amine*	*Silyl nucleophile*	*Product*	*Yield*
Ph—CHO	Ph—NH_2			91%
Ph—CHO	p-Cl-Ph—NH_2			88%
Ph—CHO	Ph—NH_2	Me_3Si-CN		86%

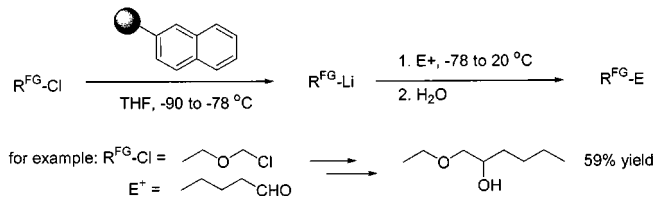
In addition to the solid-supported scandium examples outlined above, a number of other lanthanides have been supported on ion exchange resins.[123] Ytterbium resins catalyzed a variety of reactions including the reaction of indole with hexanal, the aldol condensation of benzaldehyde with a silyl enol ether, acetal formation, nucleophilic addition to imines, allylation of an aldehyde, aza-Diels Alder reaction, epoxide opening, and glycosylation with glycosyl fluorides. The broad range of chemistries catalyzed by lanthanides, combined with the convenience of the solid support, should lead to widespread utility and application.

The hydroxide form of Amberlyst A-26 resin can be used as a catalyst for the Dieckman cyclization to give 2,4-pyrrolidinediones (Scheme 40).[124] Cyclized material remains ionically bound to the resin, which can be washed to remove impurities. The pure product is removed from the resin by treatment with acid. It is interesting to note that the cyclization precursor is made in two steps (reductive amination and amide formation), both of which could be performed using solid supported reagents.

The use of catalytic quantities of arenes as electron carriers has been proven to be beneficial in lithiation reactions at low temperatures. Attachment of naphthalene to a polymer support has allowed the preparation and reaction of very reactive organolithium species to be achieved without contamination of the final product with the electron carrier.[125] (Scheme 41)



Scheme 40. Dieckman cyclization catalyzed by an ion exchange resin.



Scheme 41. Naphthalene resin for lithiation reactions.

A variety of transformations are promoted by alkali metals. A convenient procedure for the preparation of supported alkali metals via deposition of the corresponding metal on a support from a solution of the metal in liquid ammonia has been published.[126] The metals supported on polyethylene have been used in Dieckmann cyclization, lithiation, Barbier, and Reformatski reactions with high yields (Scheme 42).

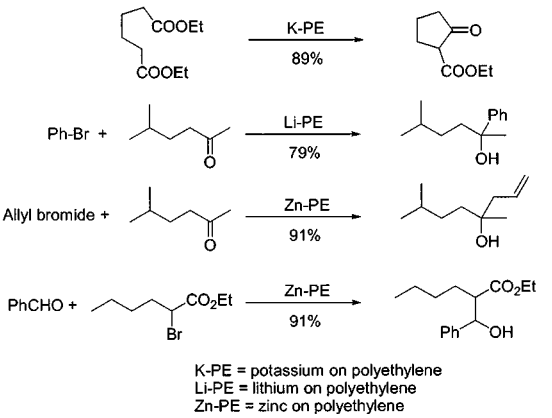
A polymer-supported selenium reagent prepared on polystyrene via lithiation and quenching with dimethyldiselenide has been used as both a traceless linker in SPOS and as a supported reagent.[127] The advantage of this reagent is the convenience of handling and the lack of odor when compared with the nonbound reagents.

9. AMIDE BOND FORMATION USING POLYMER-SUPPORTED REAGENTS

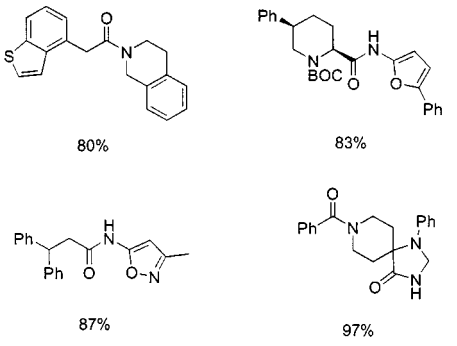
The amide bond is present in a very large number of pharmacologically active compounds, and a wide range of amines and carboxylic acids are commercially available. These factors have contributed to the development of a number of methods to prepare amides using solid-supported reagents. An important advantage to the utilization of solid-supported reagents for this coupling is the fact that neither starting material needs a point of attachment to the solid support, thus greatly expanding the diversity that can be obtained in a two component amide library.

The carbodiimide coupling method is both popular and versatile, and the first report of a carbodiimide on a crosslinked polystyrene support appeared in the early 1970s.[128] The resin showed some utility in converting carboxylic acids into anhydrides. More recently, the preparation and utility of polymer-bound 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (P-EDC) was reported.[129] This resin is prepared in one step from commercially available chloromethyl polystyrene and the free base of commercially available EDC hydrochloride. The resin cleanly and efficiently couples amines and carboxylic acids (Scheme 43). The reaction is carried out in chloroform in order to obtain adequate swelling of the resin, and up to 25% t-butanol can be added to aid in solubility of monomers if needed. This resin has also been used to prepare Mosher amides,[130] hapten active esters,[131] benzoxazines,[132] and benzoxazinones.[133] A related carbodiimide, 1-(3-pyrrolidinylpropyl)-3-ethylcarbodiimide (P-EPC), has also been disclosed in the literature and is useful for amide formation.[3f]

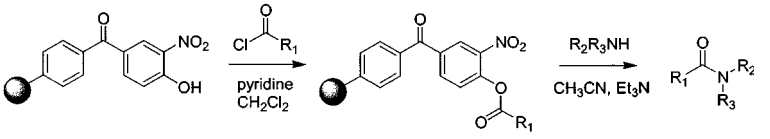
A library of 8000 amides and esters was prepared using polymer-bound 4-hydroxy-3-nitrobenzophenone (Scheme 44).[134] The polymer-bound phenol was first acylated with a mixture of ten acid



Scheme 42. Transformations using supported alkali metals.



Scheme 43. Examples of amides made using polymer-supported EDC (P–EDC).



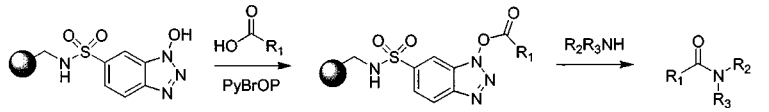
Scheme 44. Synthesis of amides from polymer-bound 4-hydroxy-3-nitrobenzophenone esters.

chlorides, and the resulting mixture of active esters was treated with amines and alcohols. The reaction with the active ester was carried out at 70°C in acetonitrile in the presence of triethylamine, and the products were obtained by simple filtration of the reaction mixture. A substoichiometric amount of amine or alcohol nucleophile was employed in the transformation.

A number of variants of polymer-supported 1-hydroxybenzotriazole have been used in amide synthesis. Tartar and colleagues have synthesized the reagent via reaction of aminomethylated polystyrene with 4-chloro-3-nitrobenzenesulfonyl chloride to give a sulfonamide, and then conversion of the ortho-chloro nitro functionality into the hydroxybenzotriazole moiety in two steps.[135] Carboxylic acids are converted to the polymer-supported active esters using the soluble coupling agent PyBrOP, and then treated with an amine in a second step to give the amide. Filtration affords the desired products in high purity (Scheme 45). The scope of the methodology was explored with a range of carboxylic acids and amines. It was found that acids with an acidic alpha proton and acids possessing a nucleophilic group did not perform well in the reaction. Highly deactivated anilines, 2-aminopyridines, and 2-aminopyrimidines did not give satisfactory results as the nucleophilic component.

The use of polystyrene resins can limit the choice of reaction solvent to one that will swell the resin. HOBt immobilized on a macroporous support has been synthesized and can be used to synthesize amides in excellent yields in a variety of solvents.[136]

In a slightly different approach, Gayo and Suto have found that Amberlite IRA-68, a weakly basic ion-exchange resin, can be used in the solution phase synthesis of amides.[2d] A slight excess of



Scheme 45. Synthesis of amides using a polymer-supported 1-hydroxybenzotriazole derivative.

acid chloride is treated with an amine in the presence of the resin, to afford the amide product. A small amount of water is added to hydrolyze excess acid chloride, and the resulting carboxylic acid and HCl are absorbed onto the resin; filtration affords clean product in solution. A further development was the synthesis of amides via the mixed anhydride prepared from the carboxylic acid and ethyl chloroformate in the presence of Amberlyst 21.[137]

10. POLYMER-SUPPORTED SCAVENGER REAGENTS

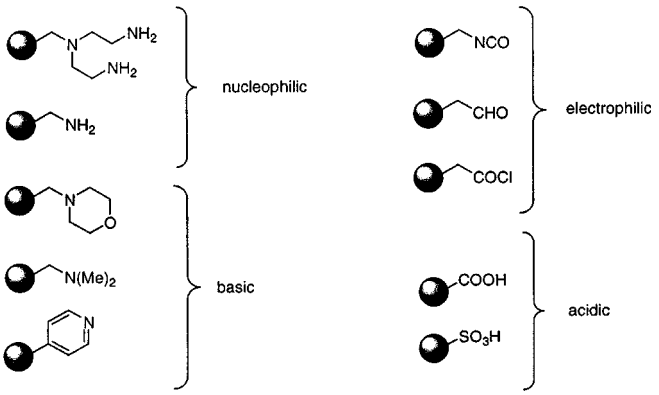
A new technique for the parallel purification of arrays of compounds made by solution phase methodologies has recently been reported by several groups. The strategy involves synthesizing a reaction product in solution, and then sequestering, or scavenging, unreacted starting material and or by-products by immobilization onto a solid support. Filtration then removes the now resin-bound impurity, leaving pure product in solution. This technique has been referred to as solid-supported scavengers,[2b,138] polymer-supported quench (PSQ),[2h] and complementary molecular reactivity and molecular recognition (CMR/R).[2g,139]

The advantages of this technique are the ability to use one starting material in excess in order to drive the reaction to completion. Excess reactant can be sequestered, therefore product purity is not compromised, and one does not have to resort to aqueous workup or chromatography. A range of electrophilic, nucleophilic, acidic, and basic solid supported scavengers have been reported in the literature, allowing flexibility in the choice of reagent used in excess. Scheme 46 lists some of the solid-supported reagents.

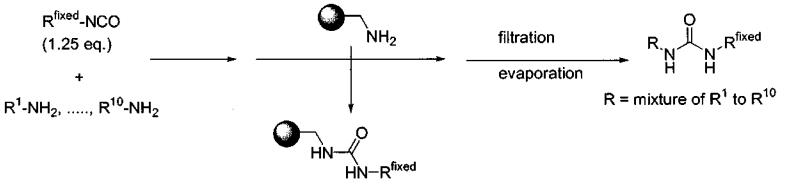
The range of functional groups that can be produced in pure form using scavenging reagents alone includes ureas (from amines and isocyanates), thioureas (from amines and isothiocyanates, ketones (from Moffatt oxidation), amino alcohols (from epoxides and amines), and secondary alcohols (from organometallic reagents and aldehydes). In a recent example, the major contaminants in the synthesis of perhydroxazin-4-ones via a Diels–Alder reaction were minimized in the final product by using an aminomethyl polystyrene in the presence of trimethylorthoformate.[140]

Kaldor *et al.* used this approach in the discovery of antirhinoviral leads. A library of 4000 ureas was prepared as 400 pools of ten compounds and ten of the pools deconvoluted using an identical approach.[142] The biological data for two of the combinatorial samples shown excellent correlation with that obtained for material prepared using standard synthetic protocols (Scheme 47).

The oxidation of secondary alcohols to ketones via reaction with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC), dimethylsulfoxide, and catalytic dichloroacetic acid, illustrates the si-



Scheme 46. Some solid-supported scavenger reagents.

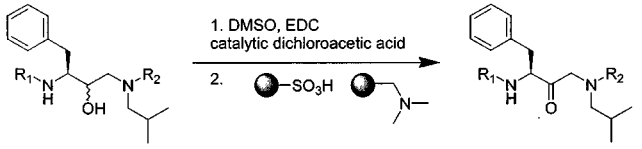


Scheme 47. Urea library using scavenger reagents.

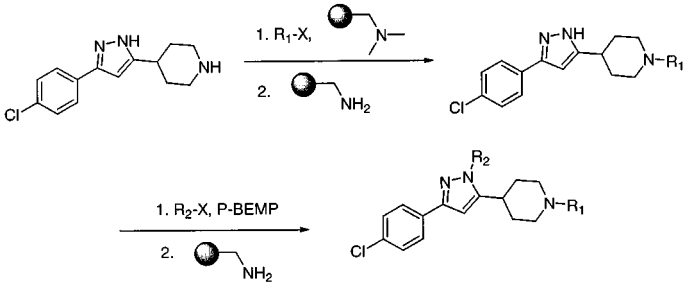
multaneous use of resins which contain incompatible functional groups (Scheme 48). After complete consumption of the alcohol, the excess carbodiimide and the by-product urea were sequestered using a sulfonic acid resin and a tertiary amine resin. The quenching and purification of tetrabutylammonium fluoride mediated desilylation reactions utilizes a mixed-resin bed.[142] A combination of Amberlyst A-15 calcium sulfonate, which sequesters extra tetrabutylammonium fluoride reagent, and Amberlyst A-15 sulfonic acid, which performs efficient proton tetrabutylammonium exchange, eliminates the requirement for a liquid-phase extractive protocol. Two resins are also used in the generation of 4-thiazolidinones.[143]

The ability to combine the use of supported reagents and scavengers (supported reagents delivering an additional reactant necessary for the reaction to proceed, and scavengers removing starting materials and by-products) enhances the utility of this approach for medicinal chemists. For example, the use of polymer-supported amine bases and nucleophilic or electrophilic scavenger resins has been reported by a number of groups in the synthesis of amides (from amines and acid chlorides), sulfonamides (from amines and sulfonyl chlorides), tertiary amines (from secondary amines and alkylating agents) and pyrazoles (from β-diketones and hydrazines) (see Refs. 2b, 2g, and 2h).

Another useful illustration comes from the work of Xu et al.[144] Polystyrene-supported—*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (P-BEMP) is utilized for the N-alkylation of a weakly acidic aromatic heterocyclic compound, followed by scavenging the excess alkylating agent using aminomethyl polystyrene (Scheme 49). In addition to N-alkylation, secondary amines can be prepared by a reductive amination procedure using supported borohydride and a polymer-supported benzaldehyde as a scavenger.



Scheme 48. Moffat oxidation using solid-supported reagents.



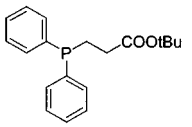
Scheme 49. Nitrogen alkylation using polymer-supported bases.

The use of less reactive amines (sterically hindered and/or electron deficient) may lead to complications in that reactions may not proceed to completion even with excess reagents, and scavenging of unreacted material may be more difficult. Parlow and co-workers have described one potential solution to this problem using what they call a sequestration enabling reagent (SER).[145] In this method, excess tetrafluorophthalic anhydride (the SER) is added to the incomplete reaction mixture. Because of the high reactivity of this SER, even poorly nucleophilic amines add to give a derivatized amine with a carboxylic tag. This tagged amine (and excess anhydride) can now be removed with a solid supported amine resin.

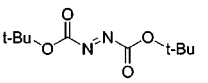
The methodology outlined is currently being extended to a wider range of reactions by the introduction of artificially introduced reagent tags which are complementary to functionality on commercially available ion exchange resins. The incorporation of masked carboxylic acid groups on both triphenylphosphine and dialkylazodicarboxylate allows the purification of a Mitsunobu reaction by a simple postreaction treatment with acid followed by sequestration of excess reagents and by-products on a basic ion exchange resin[146] (Scheme 50). In reactions involving relatively unreactive alcohol and nucleophile combinations the use of a SER allows for the isolation of material in excellent purity.

11. MULTISTEP SEQUENCES USING POLYMER-SUPPORTED REAGENTS

The number of examples in the literature which contain multistep sequences using polymer-supported reagents is currently very low. However the potential of using the approach to prepare arrays of complex molecules has been realized, and there is an increase in the reports appearing which have adopted this methodology. A synthesis of a substituted phenylethanone (Scheme 51) involving three

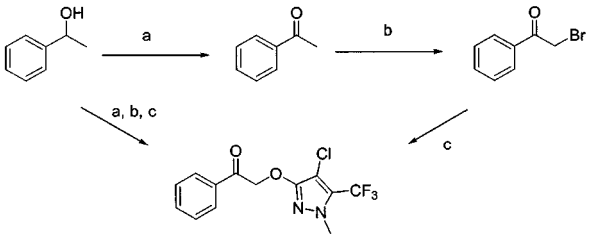


tagged phosphine reagent



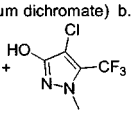
tagged azodicarboxylate reagent

Scheme 50. Use of chemically tagged reagents in the Mitsunobu reaction.
Method: After the Mitsunobu reaction, hydrolyze the t-butyl eaters to unmask the acid tag, and sequester the acidic byproducts with a basic resin.



a. poly(4-vinylpyridinium dichromate) b. Perbromide on Amberlyst A26

c. Amberlite IRA-900 +



Scheme 51. Multistep synthesis using solid-supported reagents.

transformations was achieved using three different polymer-supported reagents either in sequence or simultaneously.[147] The use of polymeric reagents in combination avoided the need to isolate the intermediate and illustrates that by immobilization on a polymer, mutually incompatible reagents can be present concurrently.

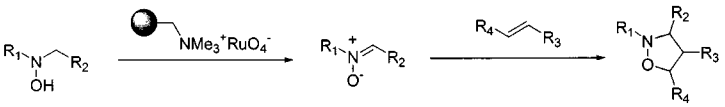
The additional examples of multistep sequences use a combination of supported reagents and scavenger resins in sequence. Although this requires the isolation of the intermediates by filtration it allows the incorporation of diversity elements into the final array of compounds. A dihydropyridone library was synthesized via hetero-Diels–Alder reaction using a an aminomethyl scavenger in conjunction with an aqueous workup.[148] After reduction of the conjugated double bond further libraries of aminopiperidine were prepared by reductive amination and acylation reaction using BER resin and appropriate scavengers.

Polymer-supported perruthenate (PSP) has been used in a number of multistep sequences. The oxidation of secondary hydroxylamines in the presence of electron-poor dipolarophiles afforded the corresponding isoxazolidine in good yield as shown in Scheme 52.[149]

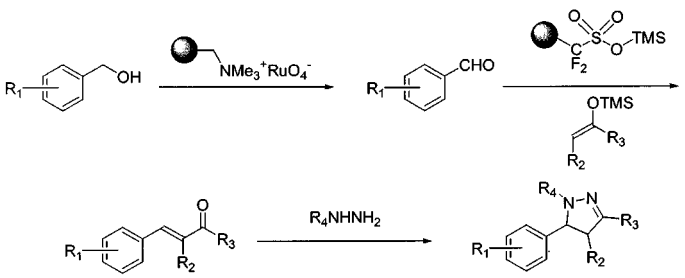
The aldehydes obtained from the oxidation of alcohols using PSP have been used in three different reaction sequences. The aldehydes were reacted with silyl enol ethers in a Mukiayama aldol reaction using Nafion-TMS as a supported Lewis acid, followed by treatment with hydrazine or methylhydrazine to yield 4,5-dihydro1H-pyrazoles[150] (Scheme 53).

The use of the PSP oxidation of alcohols was the initial step in the transformation of simple alcohols into complex amines[151] and amino alcohols.[152] Reductive amination using polymer-supported cyanoborohydride resulted in a number of amines which could be derivatized with polymer-bound sulfonylpyridinium chlorides (Scheme 54). Olefination using a polymer-supported Wittig reagents followed by epoxidation using dimethyldioxirane and aminolysis afforded a number of amino alcohols (Scheme 55).

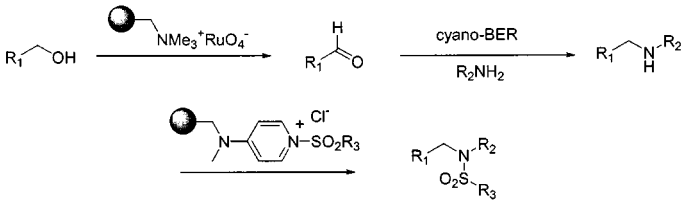
The methodology has been extended in two examples to sequences containing more than five steps; in these cases the purification of the intermediates and products is achieved by filtration after treatment with appropriate solid-supported reagents. A benzoxazinone library was synthesized in five steps from protected aniline[133] (Scheme 56) and a piperidino-thiomorpholine library was prepared in six steps from 4-piperidone hydrochloride[153] (Scheme 57).



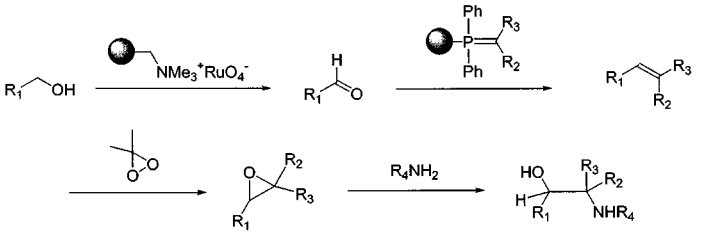
Scheme 52. Synthesis of isoxazolidines using polymer-supported reagents.



Scheme 53. Three-step synthesis of 4,5-dihydro-1H-pyrazoles using solid-supported reagents.

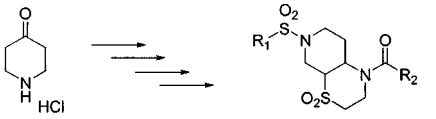


Scheme 54. Preparation of amines and amine derivatives from alcohols using solid-supported reagents.



Scheme 55. Use of polymer-bound Wittig reagent in a multistep synthesis.

Scheme 56. Parallel synthesis of benzoxazinones using solid-supported reagents.



Scheme 57. Parallel synthesis of a piperidinothiomorpholine library using solid-supported reagents.

12. CONCLUSIONS

Solid-supported reagents have been in use for decades, and have proven to be useful for a wide variety of transformations important to chemists. Recently, they have experienced a surge in popularity. With the increased emphasis on parallel synthesis as a means to increase productivity in medicinal chemistry labs, this technique will become a key component of a medicinal chemist's arsenal. In addition, the increased awareness of the advantages of solid-supported reagents will no doubt spur on the development of valuable new reagents.

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