Supported Reagents

PREPARATION, ANALYSIS, AND APPLICATIONS

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Preface

Supported reagents have been known since Fetizon's original article describing silver carbonate-celite in 1968. The first comprehensive reviews on their applications in synthesis appeared in 1979 and the first entire book devoted to the subject was published in 1987. The last few years in particular have seen several significant breakthroughs in the subject including the discovery of truly catalytic supported reagents, their successful scale-up to an industrial scale, and the effective use of modern analytical techniques to probe the surfaces of the materials and to help optimize their performance in chemical reactions. The first International Symposium on Supported Reagent Chemistry was held in England in 1991 and it brought together chemists with many different backgrounds—in catalysis, organic synthesis, analysis and materials science, as well as from industry and academia. Added momentum to the development of the subject has come from new national and trans-national environmental legislation which is placing increasing demands on the chemical industry to replace outdated chemical processes with new cleaner technologies and thus reduce pollution at source. End-of-pipe solutions are now the least attractive option.

One important aspect of "Clean Technology" will be the use of "Environmentally Friendly Catalysis" typically involving the use of solid catalysts the use of which will lead to minimal pollution and waste and will themselves be environmentally benign. The application of such catalysis to fine chemicals manufacturing—an area where heterogeneous catalysis has traditionally been little used—is likely to be especially important in the future. Supported reagents should have an important role to play as environmentally friendly catalysts.

In many ways, supported reagent chemistry is coming of age and seems destined to play an increasingly important role in research and industrial process technology into the future. This book has been written as a guide to the chemist who is planning to use or is considering the possible use of supported reagents. One of the most difficult aspects of the subject is the number of choices available in the preparation; loading, support, method of preparation and activation are all important parameters. Chapters 1 and 2 focus the readers mind on the most important factors which need to be taken into account in selecting the particular combination of parameters most appropriate to the job involved. The importance of analysis in heterogeneous catalysis is well established but it is only in recent years that its value is improving the performance of supported reagents has become apparent. There are very many analytical techniques that can be applied to solids and Chapter 3 deals only with those which are most likely to be available and that give useful information quickly! As in Chapter 2, the emphasis is on the supported reagents rather than the methods or techniques and we are deliberately generous with our use of examples. Finally, in Chapter 4 three types of supported reagents which have received significant attention in the literature are used as case studies to help illustrate the various topics covered earlier.

This book should provide you with a unique guide and reference source for supported reagent chemistry. It should hopefully convince the reader to make use of these essentially simple but fascinating materials which in a little over twenty years are maturing from academic curiosities to important industrial materials.

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April 1992

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Appendix 1

1

Introduction to Supported Reagent Chemistry

1.1. Definitions

The term *supported reagent* has been used to describe a wide range of materials including both inorganic and organic "supports." The most general definition of the term is the adsorption on, dispersion over, or intercalation in an insoluble support material of a chemical reagent.[1] The interaction between reagent and support may be either by chemical bonding (chemisorption) or by other physical modes (physisorption). This book is predominantly devoted to those supported reagents and catalysts prepared using inorganic and generally high surface area support materials. The most common of these are aluminas, clays, silicas, and zeolites. In general, the reagents considered are inorganic, although there are some notable organic exceptions to this. The supported reagents of interest are those that are of use in synthetic organic chemistry, particularly for the formation of fine organics. The use of heavy metals as support materials or as reagents are generally excluded from consideration here.

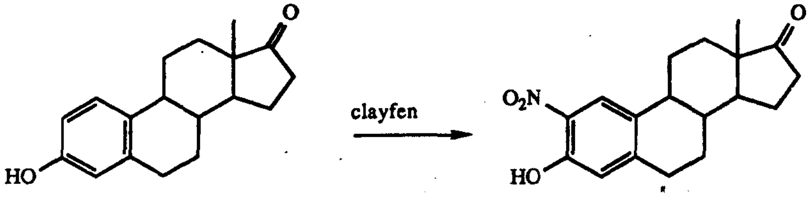
The subject of supported reagent chemistry is inherently difficult to search in the chemical literature or abstracts. There are several reasons for this, not the least being the diverse interests of the workers in the field covering the broad areas of theoretical, physical, inorganic, organic, and analytical chemistries. The use of the word *support* in titles or abstracts is not general or satisfactory as a search term. Search terms, such as *alumina* or *silica,* are impracticable, producing unwieldy results. Nevertheless, computer literature searching facilities may be useful when several search terms are combined.

A further reason for the difficulties involved in systematically searching the literature is that the supported reagent may not be of primary importance in the article. A particularly helpful starting point remains the review "Organic Synthesis Using Supported Reagents",[1] although the volume of material published since then is vast. A table of examples of the use of supported reagents is given in Appendix 1.

1.2. The Importance of Supported Reagents

There are several important factors that have influenced the great surge of work with supported reagents in organic synthesis. One major, and only recently appreciated, advantage of supported reagents is their potential as environmentally friendly alternatives to corrosive, wasteful, and difficult to dispose of conventional reagents.[64] Thus, clay-supported reagents have been used to replace aluminium trichloride for Friedel–Crafts catalysis.[2]

A number of general advantages of using supported reagents have been put forward. A supported reagent often has a high surface area and a layered or porous nature. These factors may have advantages to the reaction energetics, enabling reactions to be carried out rapidly and in high yields under mild conditions. In many cases the isomer selectivities of a reaction may be changed or enhanced by using a supported reagent. An example that demonstrates these effects is the nitration of estrone using clay-supported iron III nitrate (clayfen).[3]



The conventional route using concentrated nitric acid in glacial acetic acid may result in further nitration and lack regioselectivity. The use of clayfen achieved the best reported yields for the regioselective mononitration illustrated.

The advantages of supported reagents in terms of reaction energetics may be accounted for in many ways. At the simplest level the benefit may be considered by the dramatic increase in surface area achieved by simply dispersing an inorganic reagent over a high surface area material. Thus, KF (which has a surface area of 1.3 m^2/g for spray dried samples)[4] when efficiently dispersed on alumina of surface area ca. 150 m^2/g

may have a greater than 100-fold increase in its accessible sites. This is a vital consideration, especially for reagents that are insoluble in organic media.

The general effect of reduced dimensionality in heterogeneous catalysis is also vital in supported reagent chemistry. Thus, substrate and reagent are more likely to meet as a result of random motion in a two-dimensional space rather than in three dimensions. The consideration of fractal dimension *(D)* of a support material may lead to a qualitative assessment of its effectiveness, solids of lower *D* constraining diffusion of reactants more effectively. This principle has been described by Laszlo,[5] who also quotes a range of *D* values from 2.9 for silica gel (porous solid) to 1.9 for activated charcoal (layered solid).[5]

Furthermore, the surface area and the fractal dimension must be considered in combination with the actual chemical nature of support surface. The most important features of concern here are usually the Brönsted and Lewis acid sites, as well as the degree of hydration of the surface.[64] For example, alumina normally contains a large amount of physisorbed water, also polarized surface =Al-O-H groups providing Brönsted acidity, as well as the expected Lewis acid sites of the alumina.

A charcoal surface, although having a lower fractal dimension and a higher surface area, may in some cases be less effective as a support material because of its lack of OH sites. Furthermore, the activity of any supported reagent is determined by its preparation (discussed in detail in Chapter 2). It may not be possible in practice to achieve actual monolayer dispersion of a reagent over a surface to take full advantage of the benefits described earlier. Scanning electron microscopy has shown that alkali metal fluorides form microclusters on alumina surfaces, but, although an increased effective surface area is achieved, it is not actually as high as the support material itself[6] (see Chapter 3). In addition, internal microporous surfaces may be inaccessible to reagents owing to steric constraints.

It may be reasonably argued that supported reagent chemistry has its origins in pure serendipity. For example, water present in chromatographic silica gel may function as an inefficient supported reagent, causing reactions where simple separations were intended. The development of the subject is such that careful design and characterization may achive highly efficient and selective catalysis. An example of this latter case is a new solid acid catalyst prepared by reacting an inorganic oxide with aluminium tri-chloride in refluxing carbon tetrachloride.[7] In this case the careful choice of a solvent for preparation resulted in a catalyst with considerably greater activity than that produced using other solvents (Table 1.1). In this case infrared and NMR spectroscopies demonstrated the active species to be surface (-O-)$AlCl_2$. This species is stable and does not evolve $AlCl_3$ from the surface.

A further example of the formation of a highly acidic supported reagent is the use of molybdenum oxide supported on zirconia.[8] This solid super-

Table 1.1 Relative Activities of $AlCl_2$-Functionalized Supports in the Cracking of Hexadecane

Support	Solvent	Relative Activity
Al_2O_3	CCl_4	5.9×10^6
Zeolite[a]	CCl_4	1.3×10^7
B_2O_3	CCl_4	6.1×10^6
TiO_2	CCl_4	5.0×10^4
MgO	CCl_4	7.8×10^3
Al_2Cl_6[b]	CCl_4	1.1×10^7
SiO_2	CCl_4	7.5×10^6
SiO_2	$CHCl_3$	8.2×10^3
SiO_2	CH_2Cl_2	1.1×10^2
SiO_2	$ClCH_2CHCl$	2.4
SiO_2	C_6H_6	1.0

[a] High silica zeolite.
[b] Unsupported Al_2Cl_6.

acid was prepared by impregnating H_2MoO_4 in aqueous ammonia onto $Zr(OH)_4$. Drying and air calcining the resulting solid produced an active catalyst for the liquid phase acylation of toluene with benzoic anhydride. The MoO_3–ZrO_2 catalyst was characterized using X-ray diffraction (XRD) and compared with a preparation commencing with the zirconium oxide. The XRD patterns were significantly different and zirconium oxide was inactive in the benzoylation. The authors also reported that the use of TiO_2, SiO_2, Al_2O_3, and MgO as support materials for the molybdenum oxide result in inactive reagents in the Friedel–Crafts reaction. These observations illustrate the importance of the choice of the support, the preparation method, and the characterization of the material, as well as the great potential of supported reagents. The acylation described generally requires strong acid catalysis, creating handling and disposal problems.

An interesting example of the selectivity achievable using support materials is the preferential esterification of longer chain dicarboxylic acids in the presence of shorter chain molecules.[9] In this case there is an interesting reversal of the usual supported reagent concept. The selectivity is in fact achieved by supporting the reactant while the reagent (diazomethane) remains in solution. One end of the diacid absorbs onto the alumina surface, leaving the opposite end of the molecule free to esterify. The greatest selectivity was found for mixtures of two diacids with the greatest difference in chain length. For example, the authors report that a mixture of C_{12} and C_5 diacids gave 89% formation of the monomethyl C_{12} ester with only 9% of the monomethyl C_5 ester.

A similar concept to the one described earlier has been applied to the methylation of alcohols and phenols with diazomethane.[10] Alcohols and phenols are adsorbed onto silica gel either by a strong hydrogen bond or by formation of the alkoxide. Here, the silica gel replaces the more conventional Lewis acid catalysts in the quantitative formation of methyl ethers using (in this case) gaseous diazomethane. Again, there is a strong dependence on the choice of support with alumina and titania promoting the reaction to a lesser extent. Zeolite, celite, and zinc oxide were less effective and magnesium oxide was totally inactive. The esterification and methylation reactions described are important reminders that the support materials themselves should not be regarded as being simply inert when actual supported reagents are considered.

The formation of supported ionenes on silica gel illustrates another useful attribute of supported reagents. Ionenes (polycations where quaternary ammonium functions form part of a polymer chain, or side groups on a chain) are generally hydrophilic and are used as catalysts in aqueous solutions. It has been reported, however, that supporting ionenes on silica gel enables them to be used as phase transfer catalysts in toluene solutions.[11] This enabled a number of substitution reactions, such as:

$C_{10}H_{21}OMs$ + ionene, Br^-/silica gel $\longrightarrow$
$C_{10}H_{21}Br$ + ionenes, , OMs^-/silica gel

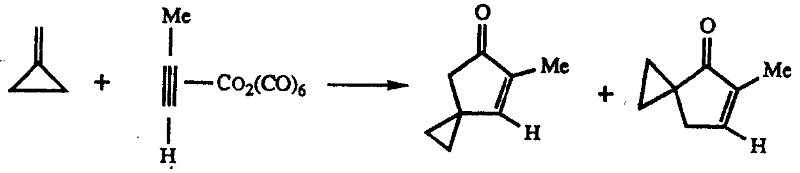
There is some ambiguity in the formal definition of a supported reagent, but one reasonable category of materials to include is those that are formally ion exchanged. For example, considerable literature is available describing the use of ion-exchanged clays in organic synthesis. Thus, a methyl-*t*-butyl ether has been produced using either ion-exchanged resins or clays[12] and Friedel–Crafts alkylations have been accomplished using montmorillonite exchanged with transition metal cations.[13]

Zeolites have been used mostly as catalysts for large-scale, typically petrochemical syntheses; however, examples of applications in fine chemistry are available.[14] Zeolites are designated as support reagents with their acidic and basic properties as well as by virtue of supporting further reagents or catalysts. The acid strength of a zeolite may be altered by ion exchange and thermal treatments, and in a series of reactions it was possible to vary the products of the *t*-butylation of phenol according to zeolite acid strength.[15] This is a result of the *C*-alkylation requiring greater acidity than *O*-alkylation. All the acid sites are active for ether formation, whereas only a fraction of the Brönsted sites are active in *C*-alkylation. This fraction was found to increase exponentially with the extent of Na^+ exchange. The zeolite Si:Al ratio is also important in the determination of reaction products by zeolite catalysis. An example of this effect is described where HY zeolites (Na^+) only catalyze the alkylation of benzene by formaldehyde when the $pK_a > 0$.[16] In this case the authors describe the necessity for 0 or 1 Al to be in the next nearest site to the acid center for the reaction to proceed. This is an interesting example of extremely well defined supported reagents.

An example of the use of a reagent supported onto a zeolite is the use of *t*-butyl hypochlorite on zeolite X.[17] Here paraselective monochlorination of the aromatic compound was achieved under mild conditions.

Although this book concentrates on inorganic supports, it is important to recognize the wide use of organic materials as supports. For example, heterogeneous phase transfer catalysts, such as phosphonium salts or crown ethers, have been supported on polystyrene using long spacer chains.[18] In this way good catalytic activity was maintained while immobilizing them. Also, dimethyl sulfoxide has been supported on cross-linked polystyrenes as a phase transfer catalyst for the reaction of bromooctane with SCN^-, I^-, and CN^- as nucleophiles.[19] The cyanation of benzoyl chloride has been described where the cyanide is impregnated onto Amberlite resins.[20] This supported reagent was useful for the formation of acyl cyanides, but not aliphatic acyl cyanides. Indeed, it produced considerably superior reactivity and selectivity compared with alumina, silica, or activated charcoal as support materials.

The examples set out previously intended to show the variety of supported reagents described in the literature. Other ways of using supports and supported reagents exist, such as the in situ mixing of support (silica gel), reagent ($NaBH_4$), and reactant for the reduction of nitrostyrenes.[21] Also the existence of physisorbed non catalytic as well as chemisorbed catalytic sites in one supported reagent (dichromate or permanganate on alumina) has been described for the oxidation of diphenylmethane and other substrates.[22] Organometallic reactions have also been described that take place on the surface of a solid support:[23]



It has not been possible to absolutely define the term supported reagent. The chemistry considered has been wide ranging with a variety of supports, many reagents, and numerous categories of reactions promoted. Supported reagents have been shown to frequently enable increased yields and selectivities in synthesis.

1.3. Choice of Support Material

There are relatively few systematic explanations available to account for the successful combination of a support and a reagent, although numerous works describe comparisons between various supports for a particular reaction. A number of supports have been described in the previous section and in his 1979 review McKillop included celite, silica, alumina, graphite, carbon, montmorillonite K10 clay, Girdler KSF clay, molecular sieves (zeolites), and kieselguhr. Posner[24] reviewed the use of alumina reagents for organic reactions, and more recently, Cornelis and Laszlo[3] reviewed their own extensive work using montmorillonite reagents, and zeolite reagents have been reviewed by Perot and Guisnet.[14] The first supported reagent book also describes a variety of support materials and their uses.[25] Bram and co-workers[26] have also reviewed the use of a number of support materials for reduction.

The effectiveness of a particular support material for a given reagent and reaction is likely to be the result of a combination of factors including surface area, porosity, acidity–basicity, as well as the crystalline or amorphous nature of the material.[27] The surfaces of the materials under consideration here are generally irregular with voids, steps, pores, and other surface imperfections. In contrast, zeolites have well-defined crystalline characteristics. Particle size and shape contribute to the surface area of crystals or powders as does the material's porosity (usually defined as surface imperfections that are deeper than they are wide).

The physical adsorption of gases is the usual method of surface area determinations, although this may only measure external and not internal surfaces, as in the case of layered clays. Table 1.2 shows a variety of support surface areas. In each case a range of values is given, reflecting the great differences that may exist between samples.

Support pore structure is, in some cases (notably with zeolites), a critical factor in the choice of the support material. Specific channel structures may result in molecular shape selectivity where the size and the shape of a diffusing substrate or product are closely matched to the support pore diameter. The regioselective chlorination of toluene using a zeolite-supported reagent is an example of this effect.[17] Selectivity is also induced by the void structure of zeolites in decane hydroconversion.[32] In the case of silicas pore sizes range from less than 2 nm to greater than 200 nm.[29]

Clay (montmorillonites) and graphite are support materials with layered structures. With montmorillonite-supported reagents reactions may occur in the interlamellar region of the crystals. This situation is important in terms of the reduced dimensionality of the reaction (fractal dimen-

Table 1.2 Support Surface Areas

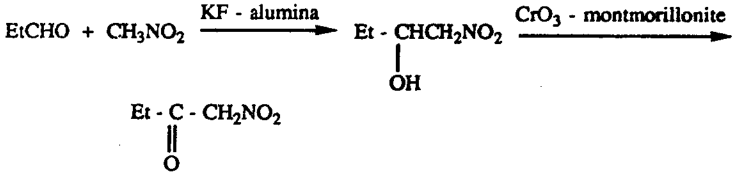
Support	Surface Area (m^2/g)	Reference
Alumina	120–300	28,30
Silica	50–420	29
Montmorillonite	10–270	30
Montmorillonite K10	220–270	30
Activated carbon	610–790	31

sion, described earlier) compared with a homogeneous reaction or one occurring on an external supported reagent surface. Montmorillonite may be pillared (layers permanently fixed apart) and thus achieve some degree of zeolitic character. For example, a large and sharp pore size distribution of ca. 3 nm was achieved by using an aluminium chlorohydroxy oligomer pillar in the presence of polyvinylalcohol (PVA). The PVA was used to wrap the oligomer to achieve a large layer swelling of the clay and was then removed by calcination.[33]

The careful choice of a support material is frequently critical to achieve satisfactory results in organic syntheses. It is also well established that the support chosen within a category may be important. For example, neutral, acidic, and basic aluminas from a variety of suppliers may give differing results.

An example of a systematic study of 10 support materials for sodium metaperiodate has been described.[34] Here, the identically prepared supported reagents were used for selective oxidations of sulfides to sulfoxides. The inorganic supports tested included alumina, celite, charcoal, florisil, montmorillonite clay, and silica gel, from which Merck acidic alumina was chosen for a series of sulfide oxidations.

In the preparation and subsequent oxidation of 2-nitroalcohols two different support materials were found effective to use for the two reactions.[35] Thus, KF supported on alumina was used for the condensation and CrO_3 on montmorillonite for the oxidation.



$$\mathrm{EtCHO} + \mathrm{CH_3NO_2} \xrightarrow{\text{KF - alumina}} \mathrm{Et\text{-}\underset{\displaystyle OH}{\underset{|}{C}}HCH_2NO_2} \xrightarrow{\mathrm{CrO_3}\text{ - montmorillonite}} \mathrm{Et\text{-}\underset{\displaystyle O}{\underset{\|}{C}}\text{-}CH_2NO_2}$$

The KF–alumina reagent was chosen as an already established catalyst of aldol and Michael reactions. The use of alumina for the condensation reaction gave improved yields compared with homogeneous catalysts and the supported reagent was again superior to the untreated support. For the oxidation stage, montmorillonite was the support of choice as silica resulted in an unstable CrO_3 catalyst and CrO_3–alumina gave poor yields.

As mentioned in the previous example the support material can have catalytic activity itself. Alumina catalyzes the formation of iodooctane from bromooctane in the presence of NaI (also chlorination, acetylation, and cyanation).[36] In this case the use of silica gel may also promote the reaction, but with lower yields than alumina, 34% versus 95% for iodooctane formation. Elimination reactions (cyclohexyltosylates to cyclohexenes)[37] have been effected by dehydrated chromatographic alumina. Such a heterogeneous reagent was found to be suitable to introduce double bonds into polyfunctional compounds.[38]

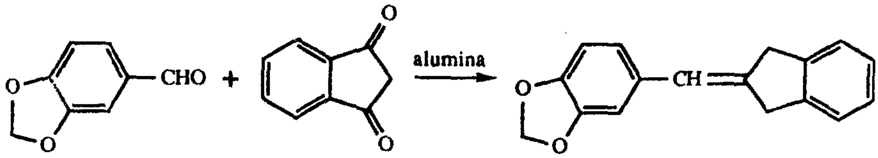
The inorganic materials used as supports for catalyst preparations are often those used for chromatography, as such, alumina was found to promote an oxidation and reduction reaction on an eluted molecule (a Cannizzaro type reaction).[39]

$$2\ \mathrm{RCH_2CHO} \xrightarrow{\text{Alumina}} \mathrm{RCH_2CH_2OH} + (\mathrm{RCH_2CO_2})_3\mathrm{Al}$$

$\mathrm{R} = [9\text{-}(p\text{-methoxyphenyl})\text{-}9\text{-fluorenyl}]$

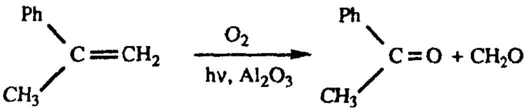
It is noteworthy that this reaction does not proceed under normal base-catalyzed Cannizzaro reaction conditions.

Furthermore base-catalyzed condensation reactions have been promoted by neutral alumina (in preference to silica), such as the Knoevenagel reaction.[40]



With less acidic compounds, KF–alumina was used.

A photochemical cleavage reaction has also been promoted by the inorganic support materials silica, $\mathrm{AlPO_4}$, $\mathrm{BPO_4{-}AlPO_4}$, and barium hydroxides.[41]



$$\mathrm{Ph(CH_3)C{=}CH_2} \xrightarrow[h\nu,\ \mathrm{Al_2O_3}]{\mathrm{O_2}} \mathrm{Ph(CH_3)C{=}O} + \mathrm{CH_2O}$$

Here the microcrystalline $\mathrm{BPO_4{-}AlPO_4}$ solids (of various compositions) were found to be more active than the amorphous silica or $\mathrm{AlPO_4}$ materials. The reaction proceeded on either acidic or basic solids using electron acceptor and electron donor sites, respectively.

Table 1.3 describes a selection of reactions promoted by supported reagents and illustrates the relative effectiveness of particular support materials.

Not only can silica and alumina produce different types of reagent, variations in supported reagent can also be found using different versions of the same support material. For example, alumina is available in acidic, neutral, and basic varieties. The differences between these are due to the relative numbers of sites on the alumina surface. The surface of any alumina has amphoteric AlOH sites that can be converted into either basic or acidic sites (Fig. 1.1). All aluminas contain some of each type of site and the differences between acidic, neutral, and basic aluminas stem from the amounts of each type of site, rather than from the presence or absence of