

1999 Alfred Bader Award Lecture From early developments in multi-step organic synthesis on solid phases to multi-nuclear phthalocyanines¹

Clifford C. Leznoff

Abstract: Early developments in solid phase organic synthesis are traced. Particular emphasis is placed on the use of cross-linked polystyrene in the first general method of monoblocking symmetrical difunctional compounds. The monoprotected polymer-bound symmetrical starting materials were then used in multi-step syntheses of a variety of compounds, particularly insect pheromones. Asymmetric synthesis on polymer supports was demonstrated. Diels–Alder and 1,3-dipolar additions on polymer supports proceeded readily as did macrocyclic formation of porphyrins and phthalocyanines. All of these reactions clearly showed that most organic chemical reactions could be performed on solid phases and laid the basis for the development of combinatorial chemistry. The first unsymmetrical phthalocyanine was prepared using the solid phase method and this led eventually to solution phase methods of preparing bi-, tri-, tetra-, and even a dendritic-like pentanuclear phthalocyanine.

Key Words: solid phase organic synthesis (SPOS), phthalocyanines.

Résumé : On retrace les développements de la synthèse organique en phase solide. On insiste sur l'utilisation du polystyrène réticulé dans la première méthode générale de bloquer une seule des deux fonctions de composés bifonctionnels symétriques. Les produits de départ symétriques reliés par une seule liaison à un polymère étaient ensuite utilisés dans des synthèses en plusieurs étapes d'une grande variété de composés, en particulier des phéromones d'insectes. La possibilité de réaliser des synthèses asymétriques sur des polymères solides a été démontrée. On a aussi montré que, sur des supports solides, on peut effectuer facilement des additions de Diels–Alder et des additions 1,3-dipolaires ainsi que la formation de macrocycles, comme les porphyrines et les phthalocyanines. Toutes ces réactions ont clairement démontré que la plupart des réactions organiques peuvent être réalisées en phases solides et ont servi de base au développement de la chimie combinatoire. La première phthalocyanine non symétrique a été préparée en faisant appel à la phase solide et ceci a conduit aux préparations, par des méthodes de phase en solution, de bi-, tri-, tétra- et même d'une phthalocyanine pentanucléaire de nature dendritique.

Mots clés : synthèse organique en phase solide (SOPS), phthalocyanines.

[Traduit par la Rédaction]

Introduction

Organic chemists have long been wedded to the practice of performing chemical reactions in homogeneous media. Hence, the idea that organic reactions could be performed on insoluble polymer supports was indeed revolutionary (1, 2). This concept was initially applied to solid phase synthesis of polypeptides (1, 3), polynucleotides (4–6), and later polysaccharides (7). These topics have been reviewed often (8–10). The general advantage of organic synthesis on insoluble

polymer supports (usually cross-linked polystyrene) is particularly favourable for repetitive synthesis of like units such as the sequential addition of amino acids to a polymer support. Thus, polypeptides can be prepared on solid phases, whereby the only mechanical operations involved are stirring (or shaking), filtration, and washing. In some respects, these repetitive syntheses are easy in that only a very few different reactions at room temperature are required. It is so easy, in fact, that the process was automated even using pre-computer technology (11). Even so, difficulties abounded; however, multiple parallel synthesis of polypeptides using computer-controlled robotic systems is now routine (12, 13).

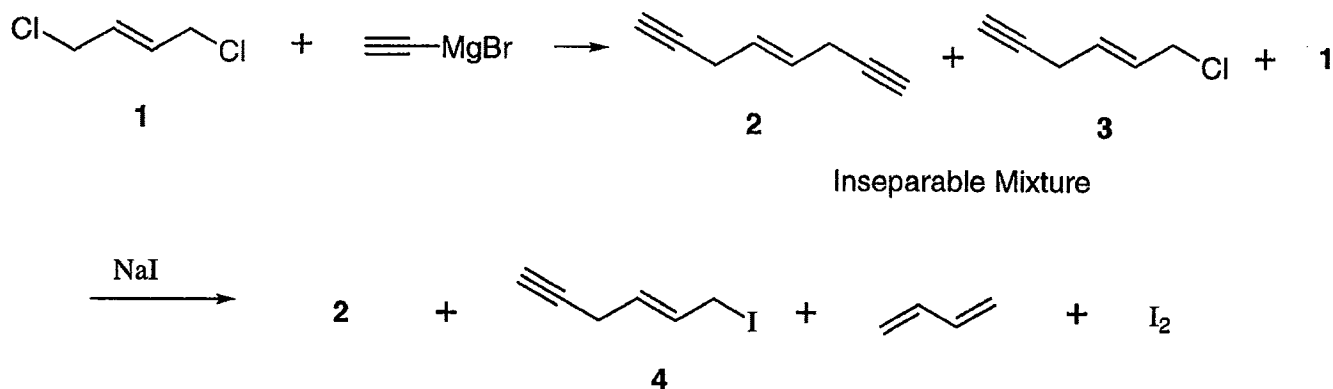
During this era, reagents attached to insoluble polymer supports, useful for organic synthesis, were developed. The work of Patchornik's group (14, 15) on the use of reagents for polypeptide synthesis was noteworthy. Polymer-bound reagents (15, 16) and catalysts (16, 17) in which the organic reagent or catalyst is bound to the polymer (with the organic substrate always remaining in solution) has found its place in many applications but is beyond the scope of this article.

C.C. Leznoff,² Department of Chemistry, York University, Toronto, ON M3J 1P3, Canada.

¹This paper is based on the Alfred Bader Award lecture presented May 30, 1999 by Professor Leznoff at the 82nd Annual Conference of the Canadian Society for Chemistry, Toronto, Ontario.

²Telephone: (416) 736-2100 ext. 33838. Fax: (416) 736-5936. e-mail: leznoff@yorku.ca

Scheme 1.



A post-doctoral fellowship in Letsinger's laboratory (2, 4) in 1964 piqued my curiosity to the possibility of using polymer supports in organic synthesis. Coincidentally, during our research project on the synthesis of annulenes in another post-doctoral sojourn in Sondheimer's group (18), we were faced with the problem of reacting *trans*-1,4-dichloro-2-butene (1) with ethynyl magnesium bromide. Invariably, an inseparable mixture of 1, the bis reacted product *trans*-4-octen-1,7-diyne (2) and the desired *trans*-6-chloro-4-hexen-1-yne (3) was obtained. These compounds had very similar boiling points and they could not be separated by distillation. Ultimately, conversion of the mixture of 1-3 with NaI led to I₂, butadiene, 2, and *trans*-6-iodo-4-hexen-1-yne (4) which was separable by distillation (Scheme 1). This problem led to the germination of an idea that insoluble polymer supports could be an advantage in addressing the whole concept of monoreactions of symmetrically difunctionalized organic compounds.

Insoluble polymers supports as blocking groups of symmetrically disubstituted compounds

Solid phase organic synthesis (SPOS) usually refers to general organic synthesis on polymer-supports, outside the repetitive syntheses of polypeptides, polynucleotides, and polysaccharides. The synthesis of a threaded rotaxane in 1967 (19) on a polymer support probably represents the first example of SPOS. Our own early efforts focussed on the use of polymer supports as monoblocking agents of completely symmetrical difunctional compounds. Monoreactions of reagents such as acetyl chloride with a compound such as 1,10-decanediol (5) in a 1:1 ratio would give 25% of the bis reacted product, 50% of the desired monoreacted product, and 25% of unreacted starting material. A large excess of (5), for example, would give mainly the desired monoreacted product and unreacted starting material but separating the

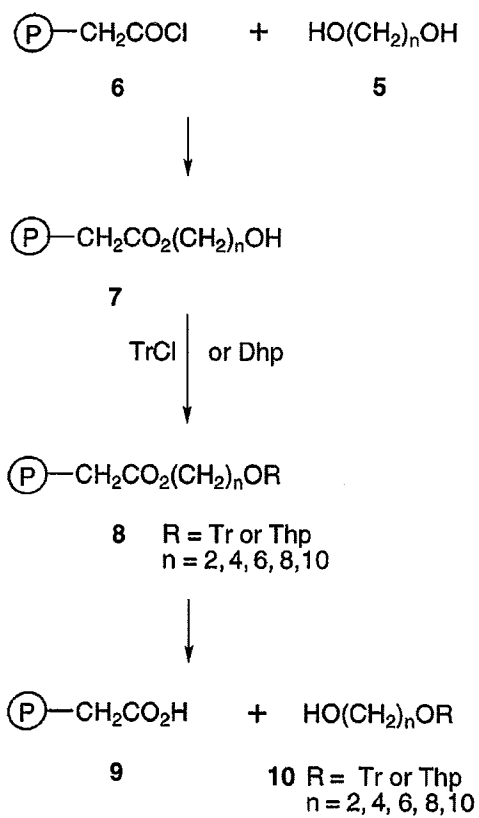
minor product (the monoreacted product) from a sea of unreacted starting material could be difficult. This separation could be readily achieved, however, by simple filtration if the monoreacted product remained attached to an insoluble polymer and "fished out" of the excess starting material which could be recovered. The process would be particularly important for the longer chain symmetrical difunctional compounds such as 5, as short chain monoreaction products of say ethylene glycol could be achieved by other methods such as ring opening reactions of ethylene oxide. Thus treatment of polymer-bound³ phenylacetylchloride (6) (20) with a large excess of symmetrical diols (5, *n* = 2, 4, 6, 8, 10) gave the polymer-bound monoprotected diols (7). Subsequent reaction of 7 with chlorotriphenylmethane (TrCl) or dihydropyran (dhp) gave polymer-protected monoether 8. Cleavage of 8 with NH₄OH gave polymer-bound phenylacetic acid (9) and the liberated monoprotected ethers of the symmetrical diols (10) (21, 22) (Scheme 2). Recovered 9 was converted back to 6 but the synthesis of 10 (*n* = 10) on once used 9 gave 10 in lower yield.

In order to obtain a more recyclable polymer, a polymer-bound trityl chloride³ (11) was prepared by our direct lithiation method (23, 24). Treatment of 11 with symmetrical diols (5, *n* = 4, 7, 10) gave the polymer-bound monotrityl ether 12. Acetylation gave the polymer-bound monotrityl monoacetates (13) which on acid cleavage gave polymer-bound trityl alcohol (14) and the desired symmetrical diol monoacetates (15) (23, 24) (Scheme 3). Polymer 14 was readily recyclable to give products in undiminished yield from used 14.

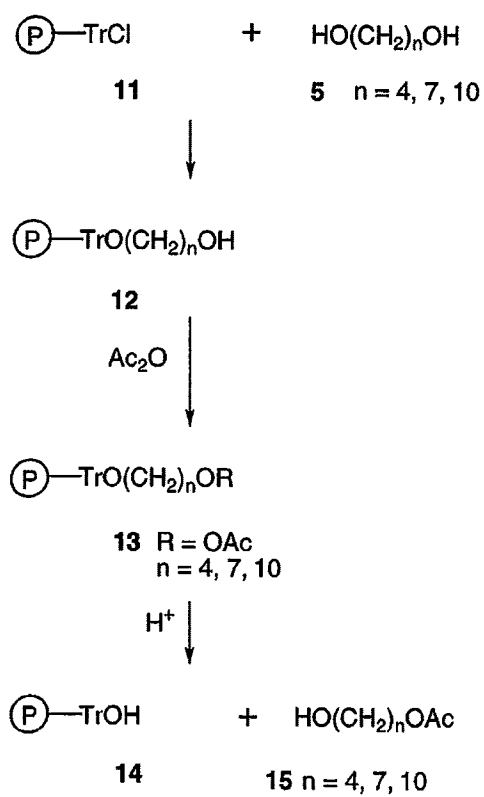
The successful monoprotection of symmetrical diols encouraged us to explore the monoprotection of other symmetrical difunctional compounds, particularly symmetrical dialdehydes. For this purpose, a polymer-bound 1,2-diol (16) was developed (25). Treatment of 16 with terephthalaldehyde (17) gave the polymer-bound monoacetal (18). It should be noted that such a reaction in solution gives only bis acetal and unreacted 17 as the mono product is normally more reactive

³The use of a P used by Merrifield, Letsinger and others to represent the polymer has in recent times been replaced by a solid sphere. It is unlikely that the P could be confused for phosphate in the context used and the more currently used symbol, the solid grey or black sphere, could also be confused with current representations of solid metallic clusters, the latter use being more reasonable as the solid ball is solid like the cluster. In addition, the P can be replaced by Si for silica polymers and PEG for polyethylene glycol polymers, etc., and, hence, is more flexible. In this paper the polymer is, polystyrene, cross-linked with 1-3% divinylbenzene. In the trityl containing polymer (11), one phenyl group of the polymer is actually part of the trityl group.

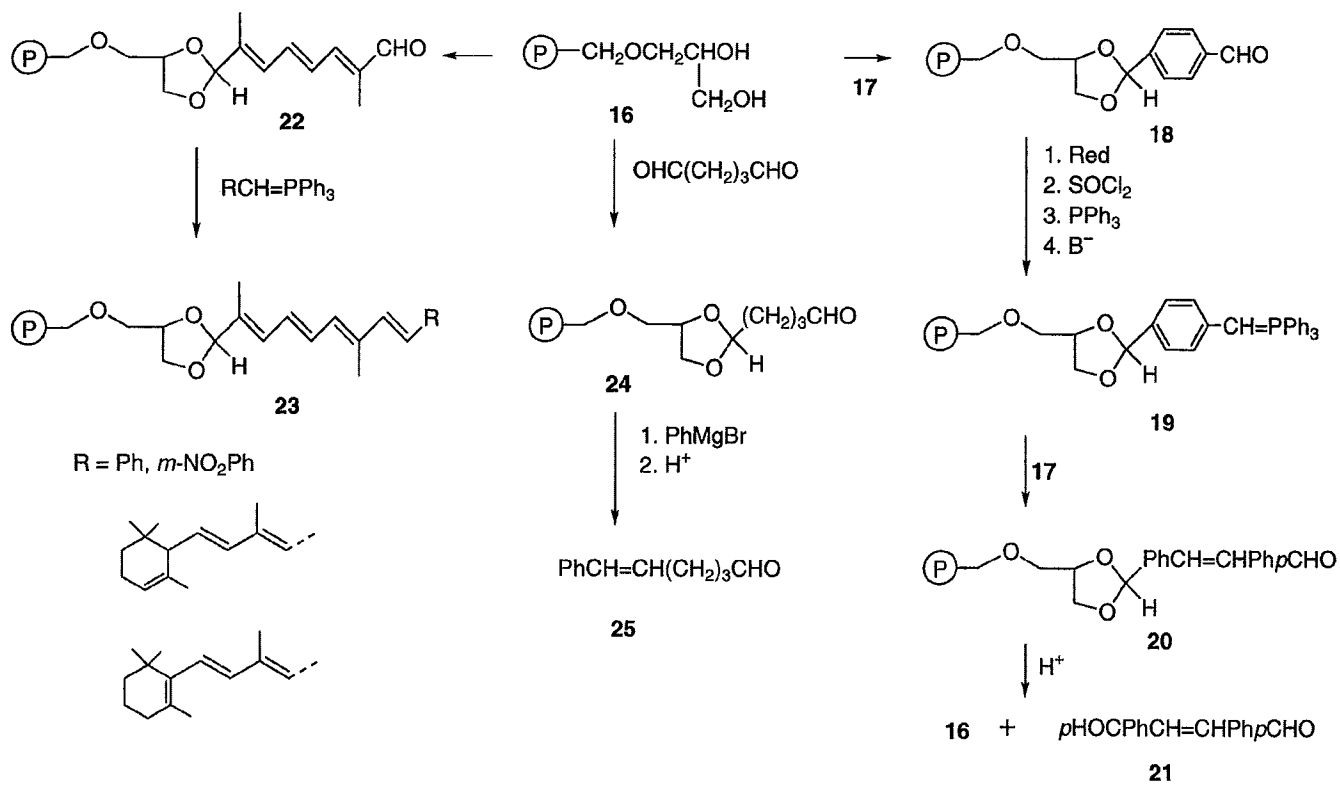
Scheme 2.



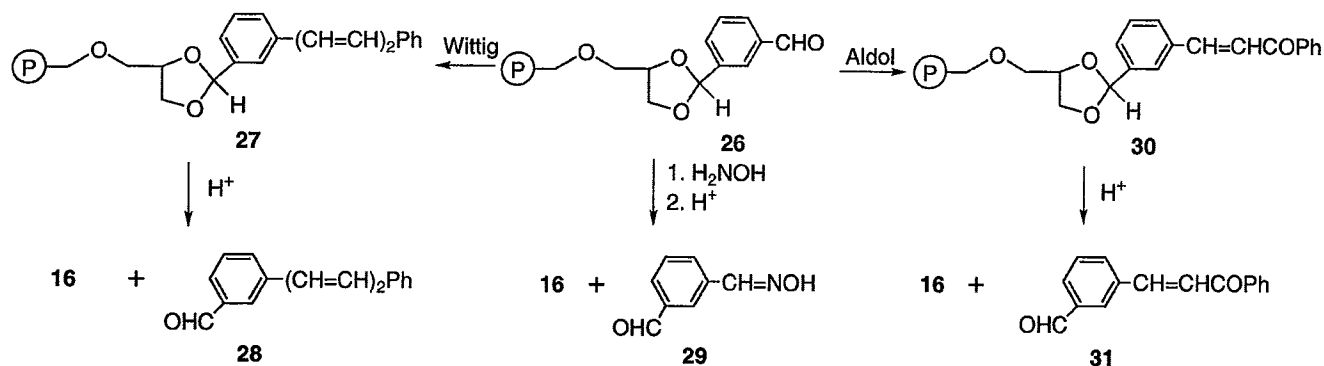
Scheme 3.



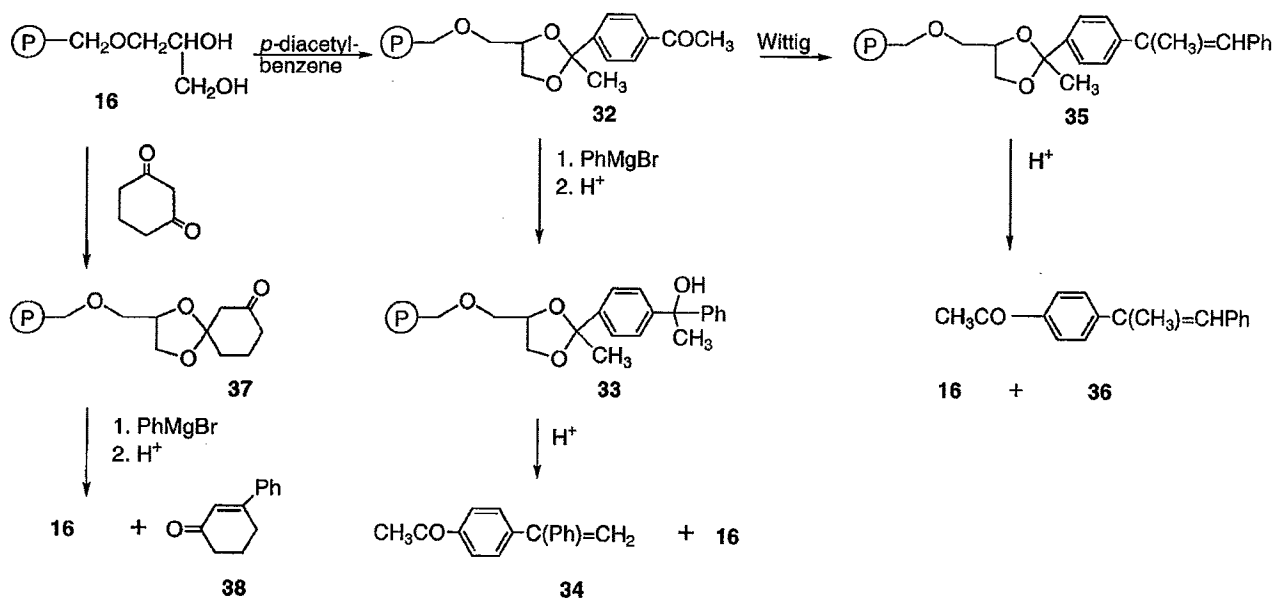
Scheme 4.



Scheme 5.



Scheme 6.



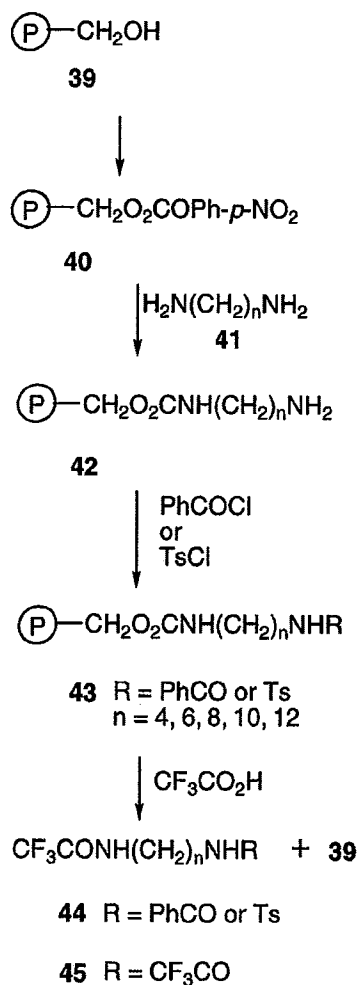
that the starting dial, containing two electron-withdrawing groups. Conversion of **18** to a polymer-bound Wittig reagent (**19**) in four steps and further reaction with symmetrical dial **17** led to polymer-bound **20**. Acid cleavage of **20** gave **16**, that could be recovered, and the symmetrical diformylstilbene (**21**) in the first multi-step (7 reactions) SPOS on polymer supports (**26**). Interestingly **18** was also converted to a helicene (**27**). A linear conjugated symmetrical dialdehyde, 2,7-dimethyl-2,4,6-octatrien-1,7-dial reacted with **16** to give the polymer-bound monoprotected **22**. The Wittig reaction of **22** gave the polymer-bound polyenes **23**, which on acid cleavage provided conjugated aldehydes, useful in carotenoid synthesis (**28**). Even symmetrical aliphatic dialdehydes may be monoprotected using **16** giving polymer-bound **24**, which with PhMgBr and acid cleavage, gives **25** (**29**) (Scheme 4). The symmetrical isophthalaldehyde can be monoprotected with **16** as well to give the polymer-bound monoblocked acetal **26**. Wittig reactions on **26** give the formyl diene **28** via polymer-bound butadiene **27**, oximation of **26** gives a polymer-bound acetal oxime which yields monooxime **29**, while an aldol con-

densation of **26** gives polymer-bound chalcone **30** and ultimately formyl chalcone **31** (**25**) (Scheme 5). In all cases recovered **16** is fully recyclable.

These formyl compounds **28**, **29**, and **31** and their *p*-analogs (**25**) are difficult to prepare in solution. Symmetrical diketones can be monoprotected with **16**. Thus, *p*-diacetylbenzene reacts with **16** to give the polymer-bound monoacetal (ketal) **32**, which with PhMgBr gives **33** and acid cleavage gives the *p*-acetylstyrene **34** (**30**). Alternatively, the Wittig reaction of **32** gives polymer **35** which liberates a *p*-acetylstilbene (**36**) (**31**). Symmetrical cyclic diketones such as 1,3-cyclohexanedione react with polymer **16** to give the monoprotected **37** which on Grignardization and acid cleavage liberates 3-phenyl-2-cyclohexen-1-one (**38**) (Scheme 6). Again polymer **16** is recovered for reuse with undiminished capacity. Recently, polymer **16** has been used in palladium coupling reactions (**32**).

Other polymer-bound 1,2 and 1,3-diols were also used in similar reactions but the polymers were not always recyclable (**33**). Interestingly, the reverse of the procedures described

Scheme 7.



in Schemes 4–6 has been described recently in which a polymer-bound aldehyde has been used to monoblock symmetrical tetraols (34). Polymer-bound boronic acids have been used to selectively extract *cis*-diols from mixtures (35).

Polymer supports have been used to monoprotect symmetrical diamines. Thus, polymer-bound benzyl alcohol (39) on treatment with *p*-nitrophenyl chloroformate yielded the polymer-bound carbonate (40) which on reaction with the symmetrical diamines (41, $n = 4, 6, 8, 10, 12$) yielded the polymer-bound monoprotected carbamates (42). Subsequent treatment with benzoyl chloride or *p*-toluenesulfonyl chloride (TsCl) gave polymers 43. Treatment of 43 with trifluoroacetic acid gave recyclable polymer 39, the desired unsymmetrical amides (44, $n = 4, 6, 8, 10, 12$), and some bistrifluoroacetamide (45) of their respective diamines (36) (Scheme 7). The trifluoroacetamido groups of 44 are easily cleaved by mild base. Some recent examples using polymer-bound monoprotected symmetrical diamines in SPOS have been reported (37).

Symmetrical diesters, diacids, and diacid chlorides can be monoblocked most readily using diacid chlorides, which is general for both linear and aromatic diacid chlorides. Thus, polymer 39 readily reacts with a series of diacid chlorides

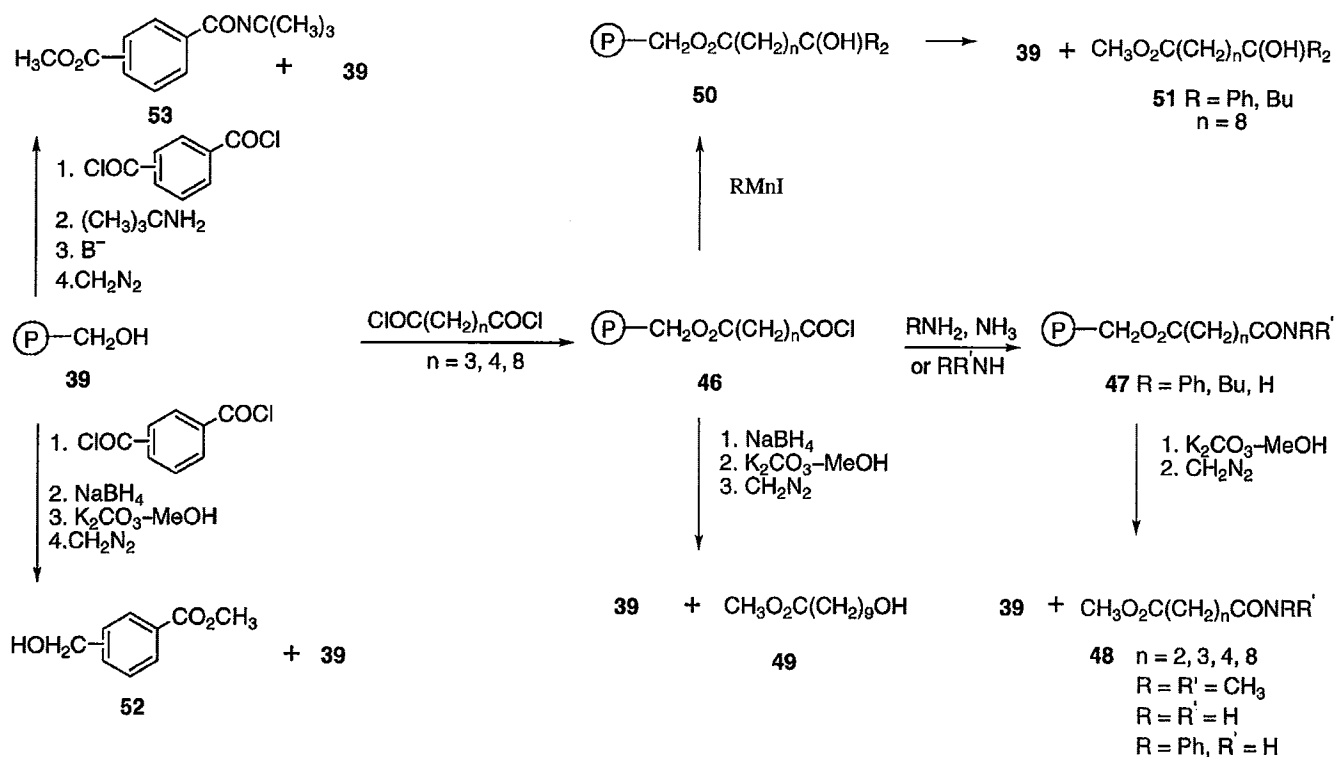
(ClOC(CH₂)_{*n*}COCl ($n = 2, 3, 4, 8$)) to give the polymer-bound monoester mono-acid chlorides (46). These versatile monoblocked derivatives (46) may be treated with amines to give polymer-bound ester amides (47) which can be cleaved and esterified to the free methyl ester amides (48). Alternatively, 46 ($n = 8$) may be reduced selectively to methyl 10-hydroxydecanoic acid (49) (38, 39). Treatment of 46 with phenyl or butylmanganese iodide (40) gave polymers (50) resulting from selective addition to the acid chloride. Cleavage and methylation readily yielded 51 (41). In all cases, 39 was recovered and was recyclable. Similarly, aromatic diacid chlorides such as terephthaloyl and isophthaloyl chloride provided the ester alcohols 52 and aromatic ester amides 53 (Scheme 8). Polymer-bound monoester succinic acid was formed via succinic anhydride (42) and recently the malonic analog via Meldrum's acid (43) and other activated acids (44) were monoprotected using polymers. Only rigid diacids such as fumaric and 2-butyne-1,4-dioic acid can be reacted directly with a polymer support (45, 46) as intraserial reactions strongly interfere (47, 48).

Dihydroxy aromatic compounds are also readily monoprotected using a polymer-bound benzoyl chloride (54). Thus, treatment of 54 with 2,7-dihydroxynaphthalene (55) gave the polymer-bound monoester mononaphthol (56), which on reaction with diazomethane and cleavage gave recovered polymer-bound benzoic acid (57) and 7-methoxy-2-naphthol (58). Simpler phenols such as resorcinol and hydroquinone also gave polymer-bound monoprotected phenols 59 which on alkylation gave 60 and cleavage yielded the *m*- or *p*-monoalkyl ethers of phenol (61) (50) (Scheme 9).

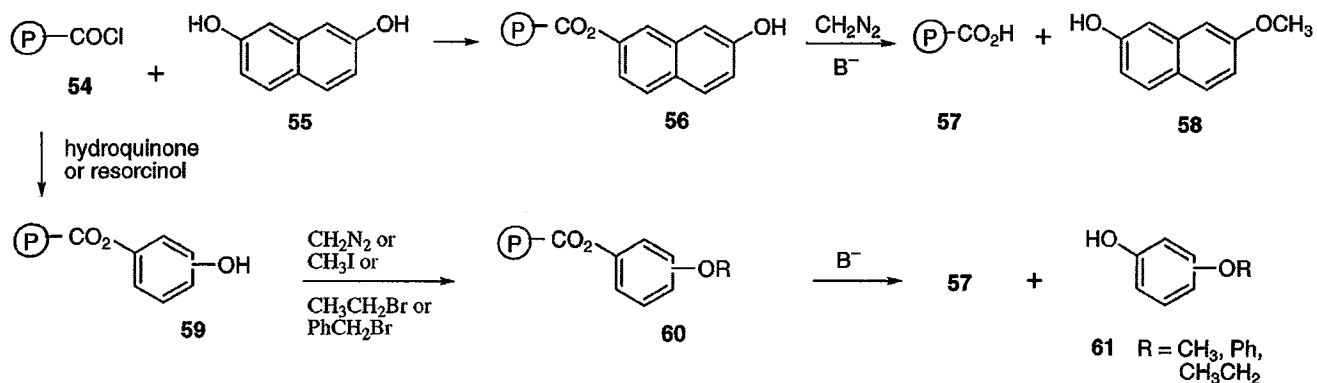
In all of the above examples, it is possible for the polymer support to react with both ends of the insoluble polymer support, the so called "double binding" problem. This problem has been discussed in some of the earliest reviews on SPOS (47–49) and in more recent reviews (49). Double binding can usually be diminished greatly by using a vast excess of starting symmetrical difunctional compound and indeed most of the examples listed show minimal double binding, but symmetrical diols can give up to 40% double binding and aliphatic diacids up to 100% double binding (47–50). Even when double binding occurs, it usually doesn't interfere in the reactions of SPOS but does reduce capacity. Although double binding can be eliminated by putting the polymer-bound functional group at a cross-linked position, capacity is reduced (23, 51).

New methods of monoprotecting symmetrical difunctional compounds *in solution* have been developed, particularly with respect to diols (52–55), tetraols (56), dihydroxyaromatic compounds (57, 58), diols (59, 60), diones (61), diamines (62–64), diesters (65, 66), diacids (67, 68), and dihalides (69, 70). Some of these methods still rely on statistical strategies using excess substrate (69, 70); others rely on specific properties of the monoprotected products such as precipitation (52*a*), solubility (54*b*), and enzymatic activity (55), while additional routes feature reactivity profiles (53), solid phase catalysis (54*c*, 65, 68), or alternative synthesis (69). All of these solution methods are, unfortunately, applicable not only to a specific symmetrical difunctional group, but to defined sub classes of that group and hence, are not general methods like the polymer support method. Despite this, specific methods are used more generally both

Scheme 8.



Scheme 9.



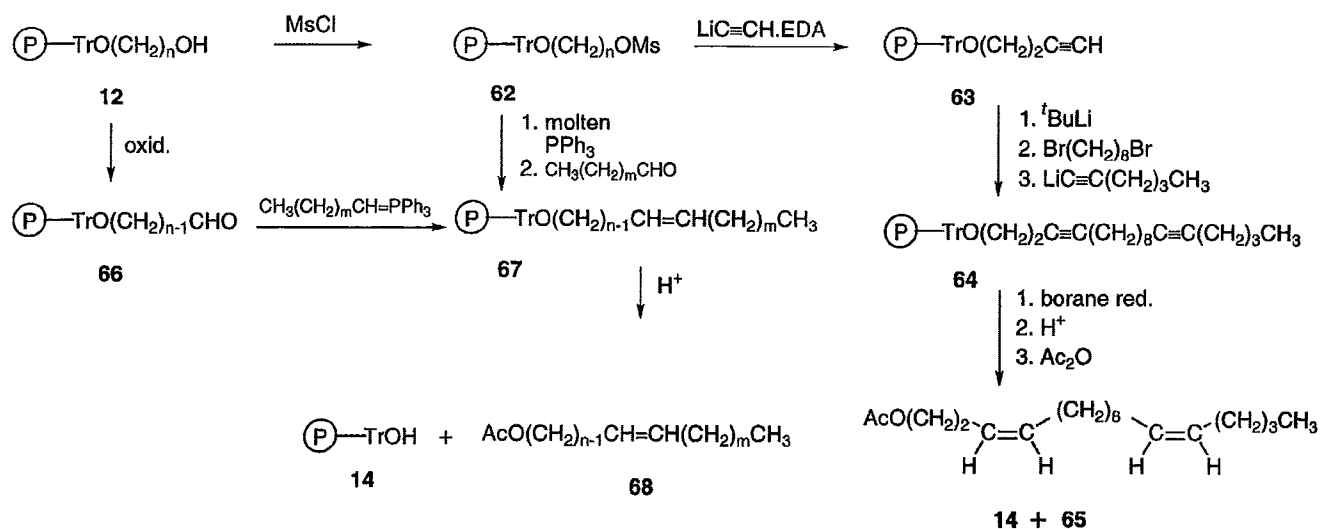
academically and industrially where a single particular difunctional compound can be monoblocked by methods peculiar to that compound. With the advent of combinatorial chemistry (71–73), it is important to have a general method of monoprotection of symmetrical substrates for elaboration into the preparation of chemistry libraries and this method is being used now in this context (37b, c).

Multi-step solid phase organic synthesis

The synthesis of polypeptides, polynucleotides, and polysaccharides all depend on the selective attachment to the polymer support of a difunctional compound containing two

different functional groups. The monoblocking of symmetrical difunctional compounds, having two identical functional groups, on solid phases opened the way to using simple inexpensive materials in multi-step solid phase organic synthesis (SPOS). Although **21** (Scheme 4) was synthesized before in a multi-step synthesis, our major effort was devoted to SPOS of insect pheromones (74–80), which has been reviewed (77) previously. Three routes to insect pheromones on solid phases were paramount. Thus, polymer-bound trityl-blocked symmetrical diols (**12**) (**23**), were treated with mesyl chloride to yield to polymer-bound mesylate (**62**) which, in the alkyne route, reacted with lithioacetylide to

Scheme 10.



give the polymer-bound terminal alkyne (**63**, $n = 2$). Lithiation of **63**, followed by treatment with the symmetrical alkylating agent, 1,8-dibromooctane, gave the monoalkylated product, which was coupled with 1-lithio-1-hexyne to give the polymer-bound diyne (**64**). Although catalytic reduction of **64** with insoluble Pd or Pt catalysts was not possible, borane reduction proceeded even more easily than in solution as organoborane by-products were easily removed by simple filtration. Acid cleavage and acetylation readily gave **65**, an insect sex attractant of the lesser peach borer, *Synanthedon pictipes* (**76**, **77**) (Scheme 10). Alternatively, polymer **12** can be oxidized with di-*tert*-butyl chromate to give the polymer protected ether aldehyde **66**. Reaction of **66** with Wittig reagents, the Wittig route, give a variety of polymer-bound insect pheromones **67**, containing up to 33% of the *E* isomer. On the other hand, in a "reverse" Wittig route, conversion of **62** with molten PPh_3 gave a polymer bound Wittig reagent, which on treatment with aliphatic aldehydes again gave **67** ($n = 10$, $m = 2$) with less than 9% of the *E* isomer. Acid treatment and acetylation of **67** gave recovered polymer **14** and insect attractants (**68**) (**78**) (Scheme 10). It is notable, in the alkyne route, that the polymer-bound synthesis uses two steps to monoreact symmetrical disubstituted substrates and a borane reduction step to such an advantage that this sequence cannot be readily performed in solution. Natural insect pheromones often contain mixtures of *E*, *Z* components so that the Wittig routes can be selected to give the desired mixture. The polymer support does affect the stereochemistry of the Wittig reactions (**79**). Large scale synthesis of pheromones using over 50 g of polymer supports and yielding up to 5 g of product have been reported (**80**). The synthesis of an insect pheromone using a polymer-bound silyl chloride and a more convenient Moffatt-Swern oxidation is interesting (**81**) as is the recent related polymer-supported Cadiot-Chodkiewicz coupling (**82**) giving conjugated unsymmetrical diynes, suitable for pheromones (**82**, **83**).

One early example of a polymer-supported asymmetric synthesis (**84**) and high enantiomeric excesses (ee) achieved

in solution (**85**) encouraged us to apply solid phases in asymmetric synthesis. Thus, Merrifield's polymer **69** reacted with the chiral blocked aminoalcohols **70** to give the polymer-bound chiral reagents **71**. Some unreacted chloro groups in **71** interfered with subsequent asymmetric synthesis, but these were converted to inactive methyl groups by treatment with NaI and reduction with tri-*n*-butyltin hydride. Deblocking with hydrazine gave the polymer-bound chiral reagents **72**. Treatment of **72** with cyclohexanone gave polymer-bound chiral imine **73** which on alkylation and cleavage gave the valuable recovered polymer-bound chiral reagent **72** and (*S*)-2-methylcyclohexanone (**74**) (**86**). Alternatively, in the first example of an asymmetric protonation (**87**) on polymer supports (**88**), addition of racemic 2-methylcyclohexanone to **72** gave **73** which on deprotonation and asymmetric protonation gave **74** (Scheme 11). The ee of **74** was comparable to that obtained using solution methods (**85**). As in polypeptide syntheses, partially reacted substrates on the polymer may be carried forward and interfere in a polymer-supported multi-step synthesis and awareness of this problem (**71**→**72**) is a necessity.

Multi-step synthesis of cyclic compounds on solid phases became our next priority. Although a few Diels-Alder reactions had been performed on solid phases for mechanistic (**89**) or environmental purposes (**89d**), we wished to examine the effect of the polymer on regioselectivity in cycloaddition reactions (**90**). Thus, **69** reacted with acryloyl chloride to give polymer-bound acrylate (**75**), which on treatment with 1-phenyl-1,3-butadiene or methyl 2,4-pentadienoate gave the polymer-bound cyclohexenes **76** in good yield. Base cleavage and treatment with diazomethane gave a ratio of the *ortho* to *meta* Diels-Alder adducts **77**, similar to that achieved in solution, and hence the polymer support in this reaction did not affect the regiochemistry (Scheme 12). A polymer-bound chiral acrylate (**78**) was achieved by treatment of **69** with chiral 2-methyl-1,3-butanediol, esterification with acryloyl chloride, and blocking of unwanted primary alcohol groups with trityl chloride. Asymmetric Diels-Alder reactions of **78** using various titanium isopropoxy chlorides

gave the polymer-bound chiral cyclohexenes **79**. Reduction with LiAlH_4 liberated the free chiral 3-cyclohexenylmethanols **80** plus recovered polymer **39**.

In this example the polymer-bound asymmetric synthesis also yielded product having a similar ee to that achieved in solution and hence the bulk of the polymer did not aid in giving higher ee's (**91**). Again note that side reactions encountered in going from **69**→**78** caused difficulties in this synthesis, but it was possible to take countervailing measures (Scheme 12).

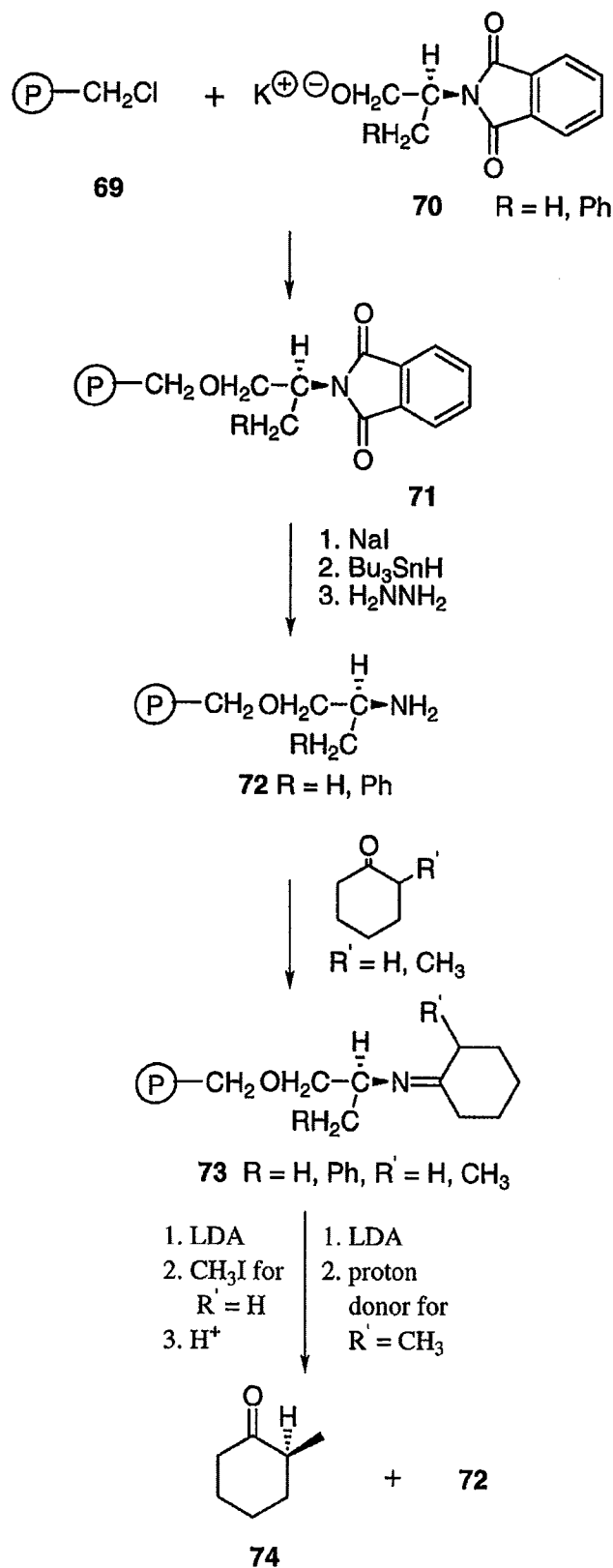
Cycloaddition of 1,3-dipolarophiles on polymer supported alkynes gave simple heterocyclic compounds. Thus, **39** was treated with propiolic acid (**81** R = H) or phenylpropionic acid (**81** R = Ph) with an acid catalyst to give the polymer-bound alkynes **82**. The 1,3-dipolar addition (**90**) with benzonitrile *N*-oxide gave the polymer-bound isoxazoles **83** (from **82** R = H) and **84** (from **82** = Ph). Base cleavage of **83** and **84** and esterification with diazomethane gave the pure regioisomeric isoxazoles **85** and **86**. The regioselectivity of **86** via the solid phase method was opposite to that observed in solution and hence, polymer-supported reactions can be different than their solution analogs (**92**, **93**) (Scheme 13).

A report on the synthesis in very low yield of an unsymmetrical tetraarylporphyrin in solution (**94**) led us to examine the syntheses of heterocyclic macrocyclic compounds on polymer supports. Thus, polymer-bound acid chloride **54** was treated with *m*- or *p*-hydroxybenzaldehyde (**87**) to give the polymer-bound aldehydes **88**. Treatment of **88** with pyrrole and excess tolualdehyde gave, after filtration from the excess symmetrical *meso*-tetratolylporphyrin produced, the unsymmetrical polymer-bound porphyrins **89**. Cleavage of **89** with base gave in higher yield the unsymmetrical *m*- and *p*-hydroxyphenyl tritolylporphyrins **90** (**95**) (Scheme 14). This synthesis represents another example of the "fishhook" principle (**47**), whereby the minor desired component **89** on the polymer is fished out from the major symmetrical product in solution.

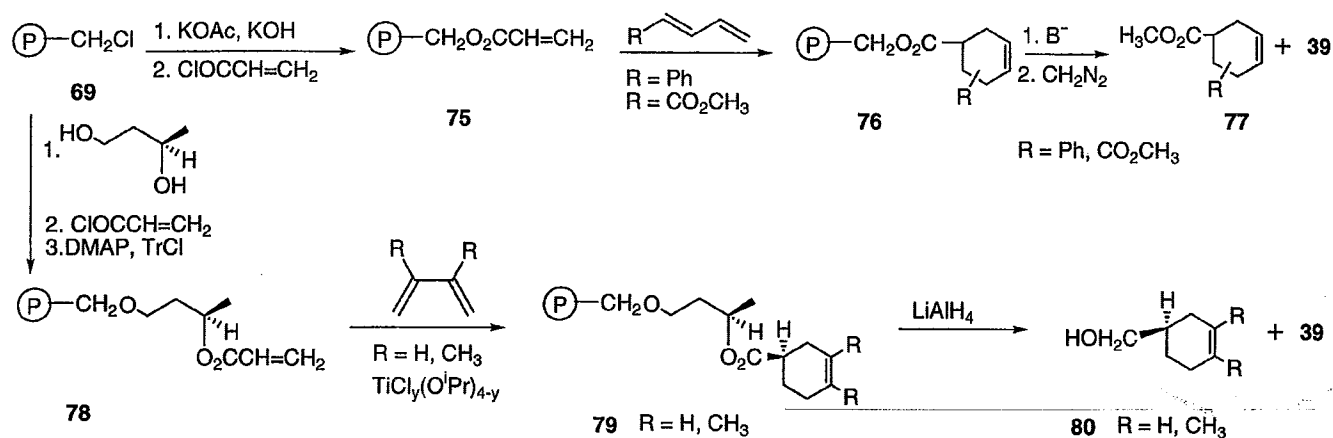
Pure unsymmetrical phthalocyanines were virtually unknown prior to 1980 and hence the polymer supported synthesis of porphyrins, described above, is eminently suited to be applied to the more complex heterocyclic macrocycles, the phthalocyanines (Pcs). For example, polymer-supported monotrityl hexanediol (**12**) underwent an aromatic nucleophilic displacement reaction with 4-nitrophthalonitrile and a phase transfer reagent in nitrobenzene to give the polymer-bound phthalonitrile (**91**). Conversion of **91** with base and NH_3 gave the polymer-bound diiminoisoindoline (**92**). Treatment of **92** with a large excess of the isoindoline of 4-isopropoxyphthalonitrile gave the polymer-bound unsymmetrically substituted phthalocyanine **93** as the minor product and a large excess of the symmetrical phthalocyanine (Pc) (**94**). Again, simple filtration afforded pure **93** by the fishhook principle. Acid cleavage of **93** provided the first pure unsymmetrical Pc **95** (**96**) (Scheme 15). Other examples followed (**97**, **98**).

Our early forays into the use of polymer-supports as monoblocking agents of symmetrical difunctional compounds led us to develop multi-step synthesis of linear compounds, such as insect pheromones and carotenoids, cyclic and heterocyclic compounds, such as cyclohexanes and isoxazoles, chiral compounds, and finally macrocyclic

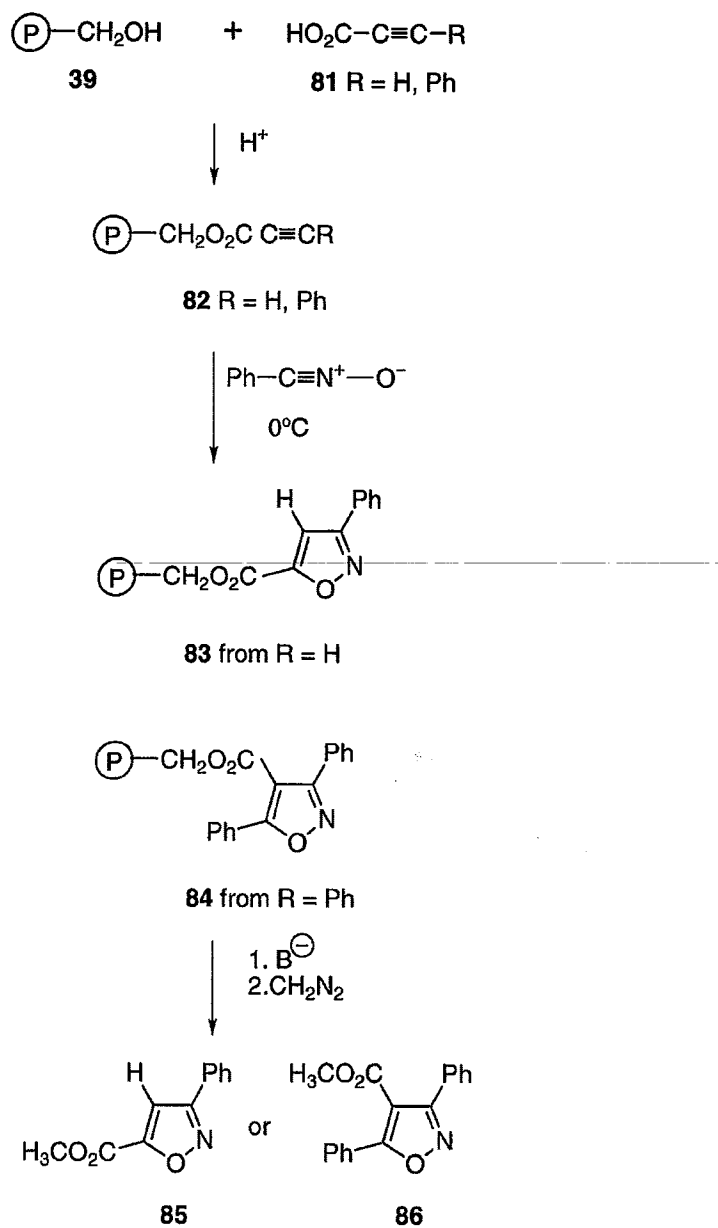
Scheme 11.



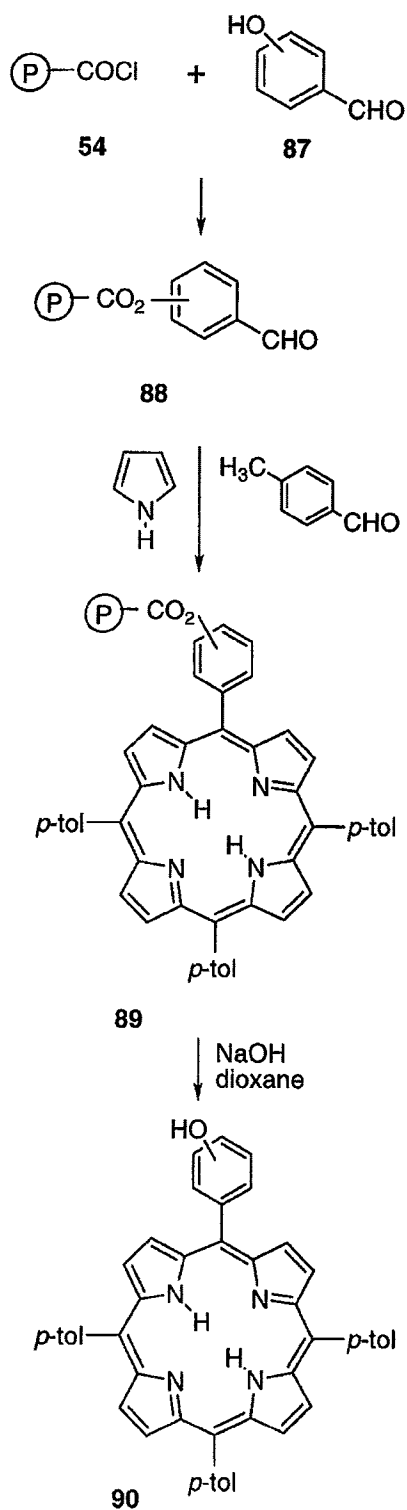
Scheme 12.



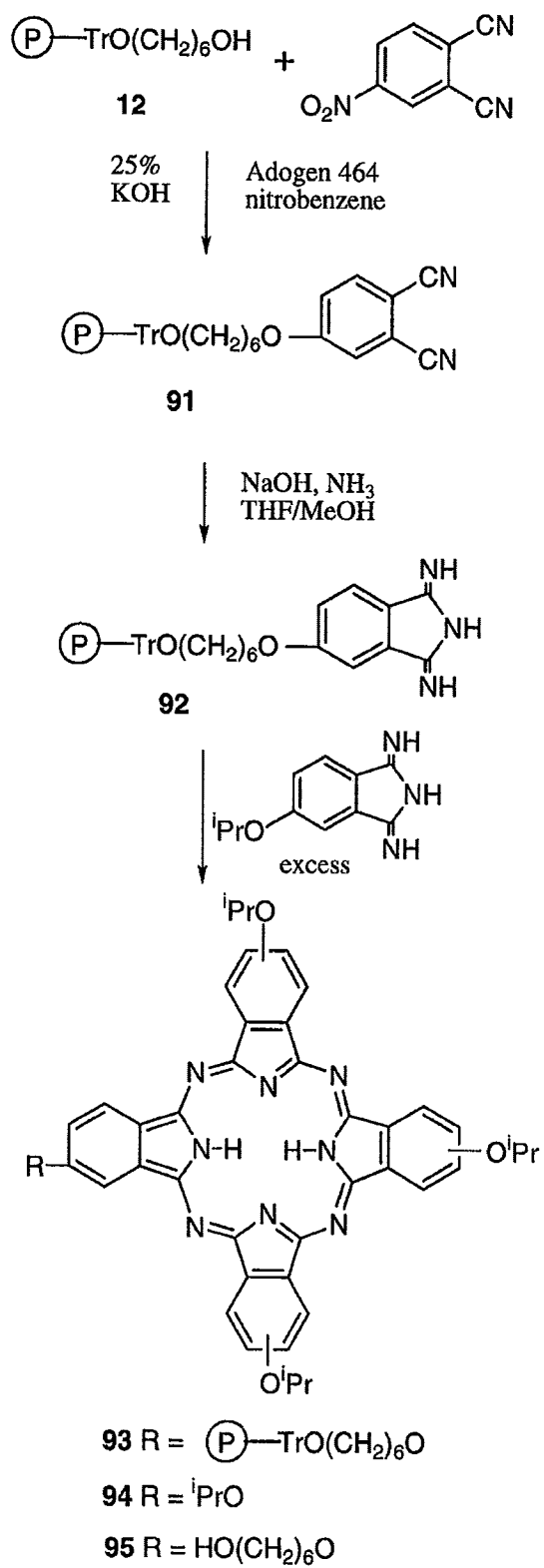
Scheme 13.



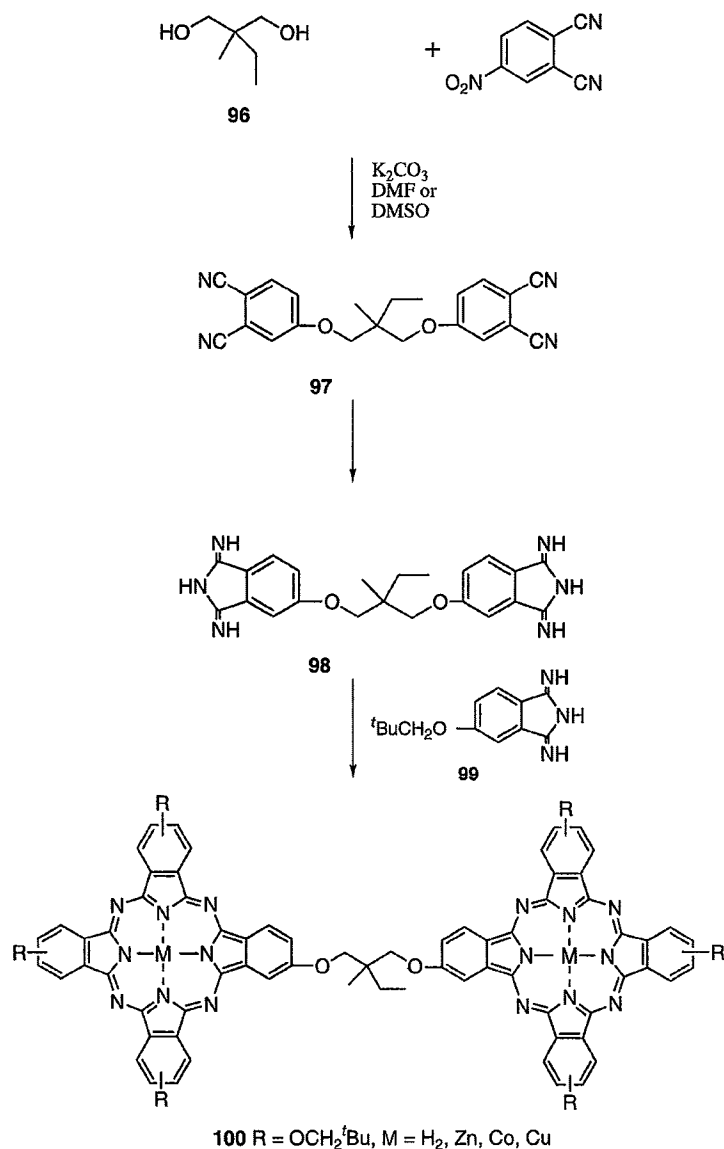
Scheme 14.



Scheme 15.



Scheme 16.



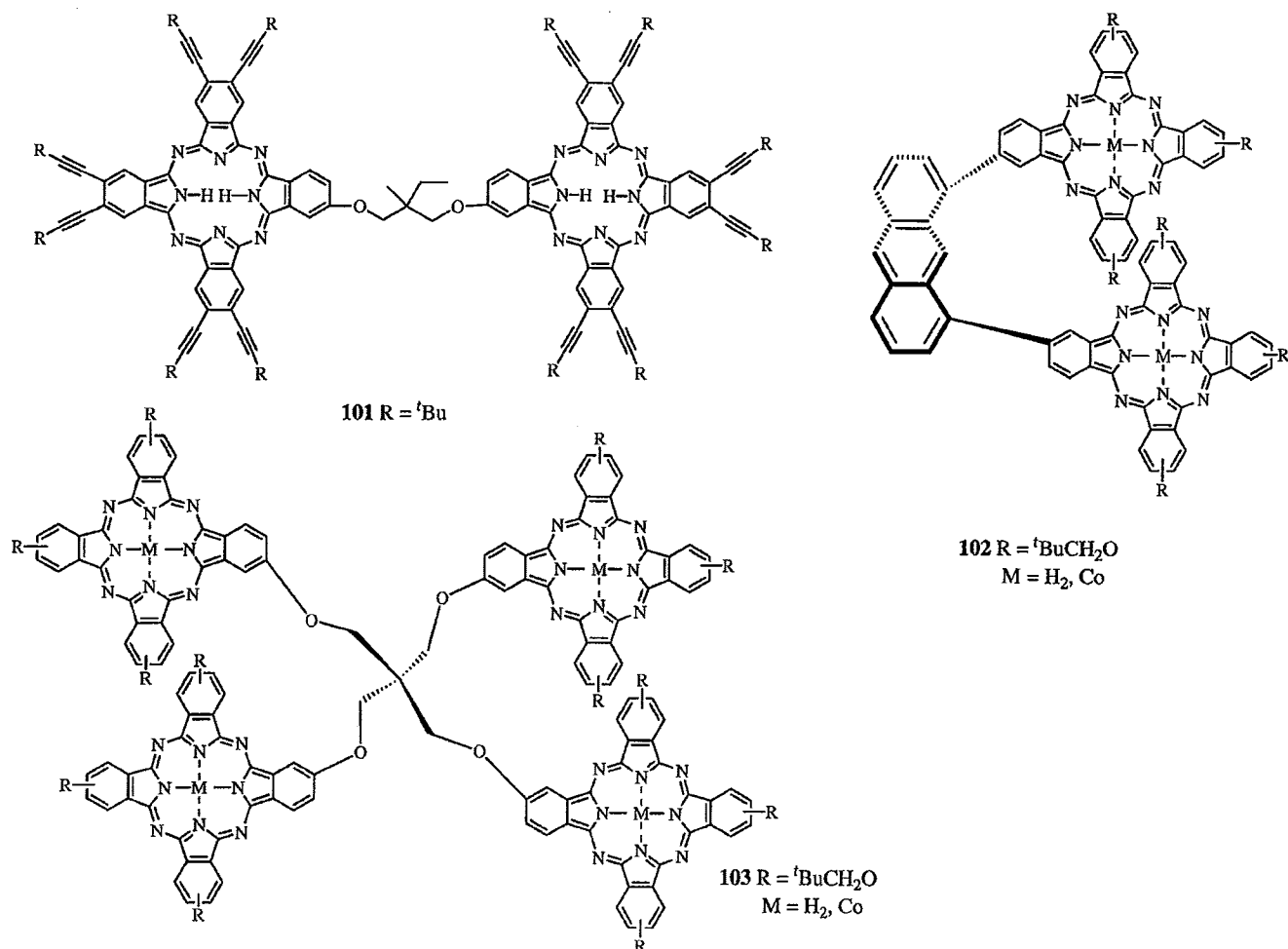
compounds such as porphyrins and phthalocyanines. Perhaps most importantly, it was demonstrated that a wide variety of common organic reactions could be performed readily on solid phases. These included ether and ester formation, Wittig and organometallic reactions, aldol condensations, oximation, amide formation, borane, borohydride and tin hydride reductions, non-chiral and chiral alkylations, mesylations, alkyne couplings, oxidations, Diels–Alder and 1,3-dipolar additions, and finally Rothemund type (99, 100) porphyrin and Linstead (101) phthalocyanine macrocyclic formations. Some more recent reactions that are noteworthy include the “traceless” attachment of substrates to polymer supports (102, 103), the four component Ugi reaction (104), the Pauson–Khand reaction (105), soluble palladium coupling reactions (106), and other protocols on solid phases (107). Other reactions are outlined in a number of early (47–49) and

more recent reviews on SPOS (108, 109) and in reviews on the applications of polymer-supported synthesis in combinatorial chemistry (71–73, 109).

Phthalocyanines

Our synthesis of the first characterized unsymmetrically substituted Pc (96) whetted our appetite for further studies in phthalocyanine chemistry (110–113). During this time, it was shown that certain bridged binuclear porphyrins (114–116) were able to act as catalysts in the 4e-reduction of H_2O to hydrogen and oxygen, although the catalysts tended to decompose with time. Since it was known that Pcs are very much more robust than porphyrins and Pcs can even be used as paint coatings for automobiles, we embarked on a program to make hitherto unknown bridged binuclear phthalocyanines and study their electrocatalytic properties. To

Scheme 17.



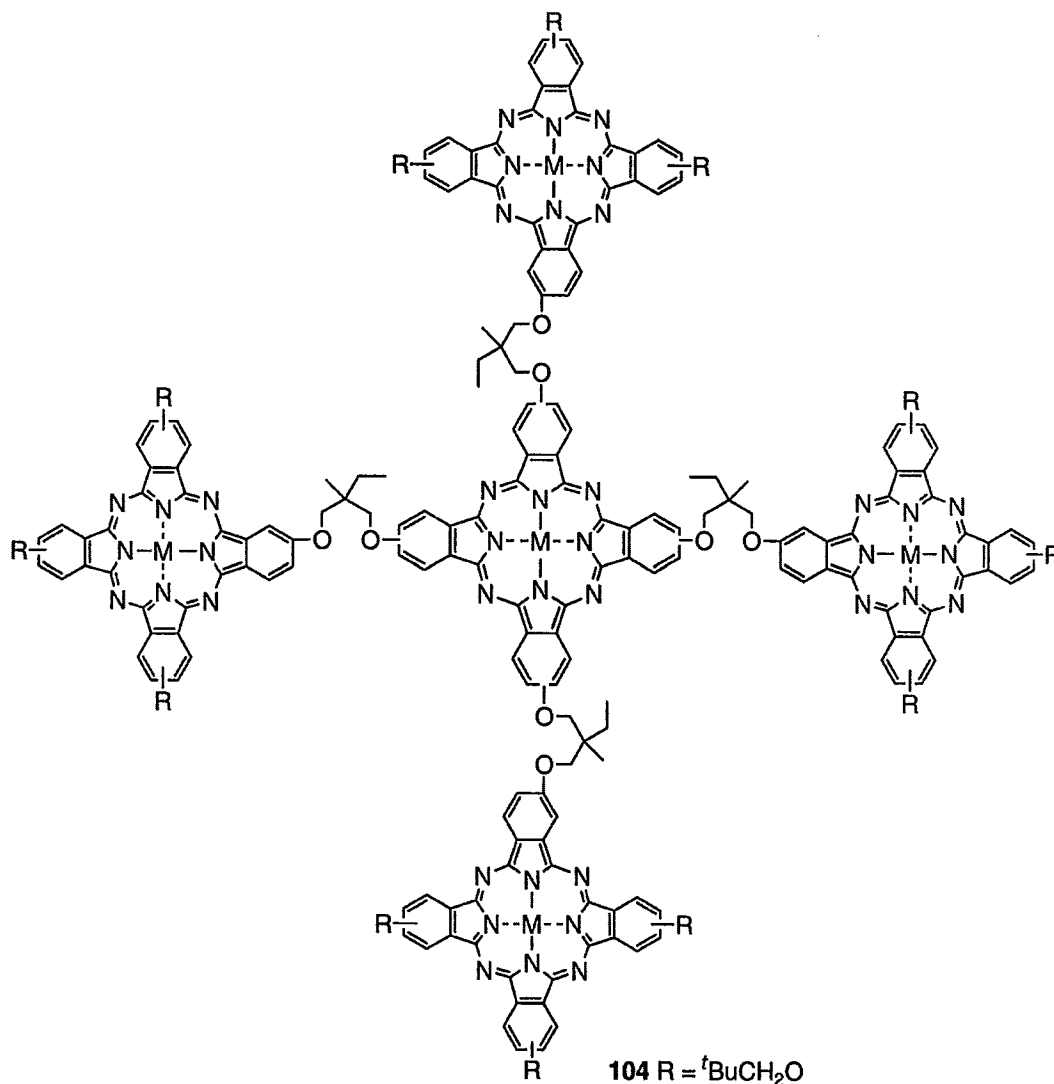
solubilize the rather insoluble phthalocyanines, we used the bulky neopentoxy (2,2-dimethyl-1-propoxy) group as a solubilizing substituent. Since bridged binuclear Pcs are essentially unsymmetrical Pcs in which one substituent is simply another Pc group, our prior experience in synthesizing an unsymmetrical Pc on a polymer support served us well. Thus, treatment of 2-ethyl-2-methyl-1,3-propanediol (**96**) with base and 4-nitrophthalonitrile gave the bisphthalonitrile (**97**). Conversion of **97** to its bisdiiminoisoindoline (**98**) as before, followed by condensation with a large excess of the diiminoisoindoline (**99**) of 4-neopentoxyphthalonitrile, resulted in a mixture of a large amount of mononuclear 2,9,16,23-tetraepentoxyphthalocyanine and some binuclear phthalocyanines (**100**) as a metal-free derivative into which various metals could be inserted (117, 118). Amusingly, gel permeation chromatography (94, 118), using the same 2% cross-linked polystyrene used in SPOS, was crucial in separating the mono- and binuclear Pcs in a final purification step (Scheme 16) in this and other polynuclear phthalocyanines (119–122). The method of synthesis of **100** gives the binuclear Pcs as a mixture of regioisomers which is actu-

ally beneficial as this mixture helps promote the solubility of **100**. More recently, we substituted the *tert*-butylalkynyl group for the neopentoxy group and we were able to make a binuclear Pc as the pure single isomer **101** (123) (Scheme 17).

Other rigid bridged binuclear Pcs based on attachment of Pcs to the 1,8-positions of anthracene (**102**) (124), naphthalene (125), and phenanthrene (126) were also synthesized (Scheme 17). Trinuclear (121), tetranuclear **103** (127) (Scheme 17), and even a dendritic-like pentanuclear phthalocyanine (**104**) (128) succumbed to the synthetic anvil (Scheme 18). Cyclic voltammetry (128, 129) and Langmuir-Blodgett studies (130) of the polynuclear phthalocyanines yielded many insights on intraphthalocyanine interactions (128) including step by step oxidation-reductions of the Pcs rings. However, in all cases, the two electron reduction of O₂ to H₂O₂ was observed (most efficiently with tetranuclear Pc **104**).

Currently, we are interested in preparing polyalkynyl phthalocyanines (122*b*, 123, 131–33) for use in nonlinear optics (134) and in shifting the absorption maxima of Pcs towards longer wavelengths. To this end, the 2,3,9,10,16,

Scheme 18.



17,23,24-octaphenylethynylphthalocyanines **105** and **106** have been prepared. Phthalocyanine **105** is extremely insoluble, but again, the neopentoxo groups in **106** provide this very planar Pc with enough bulkiness to prevent aggregation and enhance solubility. The polyoctabutadiynyl Pc **107**, although soluble, is fairly unstable and decomposes slowly (135).

Conclusions

In the 1970's, SPOS was considered as unusual and impractical, but through the advent of combinatorial chemistry, has become an important endeavour in the 1990's. I have shown how our curiosity-driven research later came to have important practical considerations, and led us to develop a new interest in phthalocyanine chemistry, the applications of which are only now beginning to be realized.

Acknowledgement

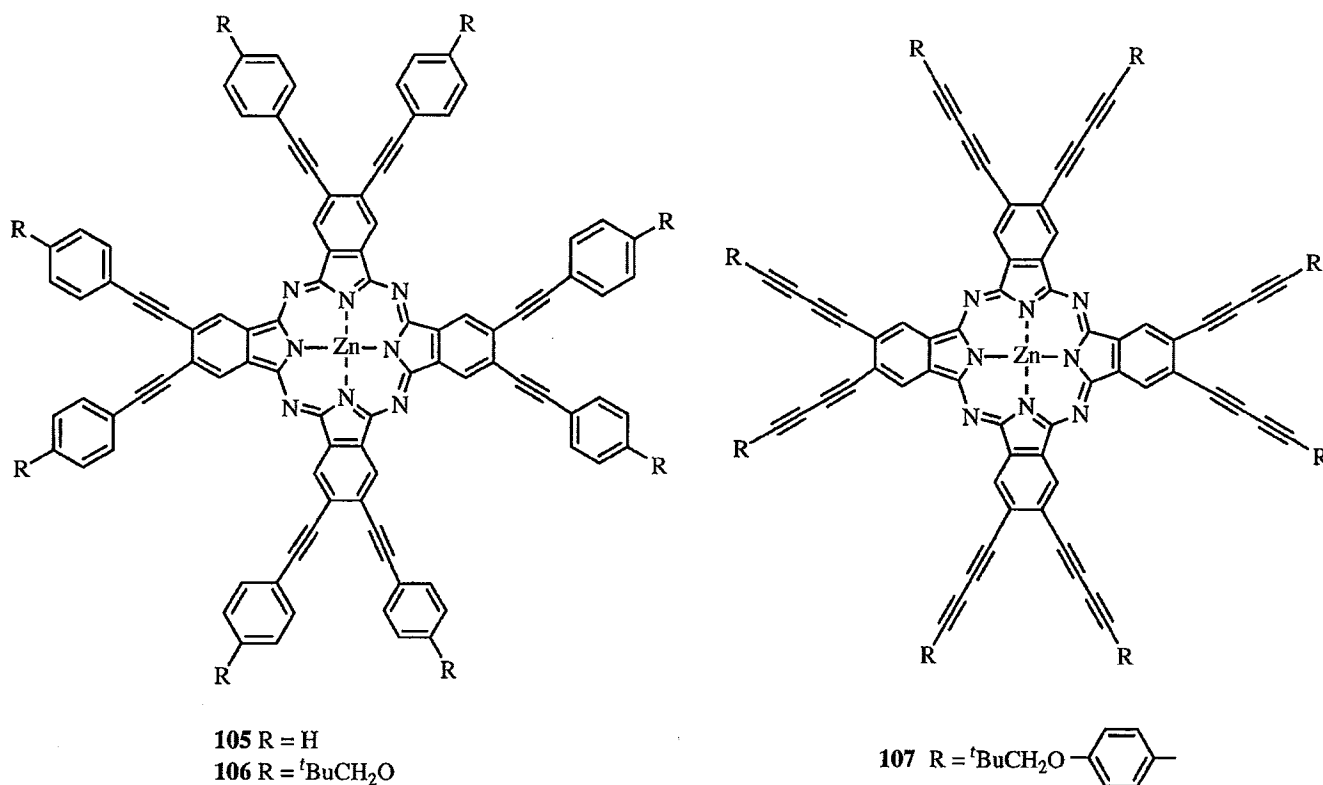
I would like to thank the many outstanding graduate students, postdoctoral fellows, research associates, and collabo-

rators at York, as well as those at other institutions who have made this work possible and indeed enjoyable and whose names appear in the references quoted. We thank the Natural Sciences and Engineering Research Council of Canada for major support through operating, strategic, and collaborative grants. Other agencies supporting this research included the Petroleum Research Fund, the Ontario Ministry of the Environment, and the Office of Naval Research (U.S.A.).

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Scheme 19.



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