Preparation of Polymer-Supported Ligands and Metal Complexes for Use in Catalysis

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1. Introduction

Recent interest in the development of environmentally benign synthesis has evoked a renewed interest in developing polymer-bound metal catalysts and reagents for organic synthesis that maintain high activity and selectivity.[1−3] The immobilization of transition metals on polystyrene supports offers a number of advantages over traditional solution-phase chemistry. In an ideal case, the supported complexes can be recovered from reaction mixtures by simple filtration, they do not contaminate the product solution, they can be recycled, and they can help increase selectivity. As transition-metal complexes are often expensive to purchase or prepare, the immobilization on a support, thereby enabling simple extraction and recyclability, makes for commercial advantage as well as ease of manipulation. Supported catalysts have also been used for rapid production of compound libraries.[4,5] There are however a number of disadvantages including the fact that often there is metal leaching during the course of a reaction and they are often not recyclable. In addition, when considering asymmetric synthesis, the enantioselectivity of polymer-supported complexes can be less than that of the homogeneous analogue. As a result, much recent work has been focused on developing and screening new ligand-derivatized polystyrene supports for attachment of metals and on developing methods for increasing activity and selectivity. Also, there has been an increase in reports presenting the use of combinatorial methods to discover new catalysts, as discussed recently in the reviews by Senkan,[6] Reetz,[7] and Bräse and Dahmen.[8]

Over the past few years there have been a large number of reviews on solid-supported catalyst and reagent chemistry[9−15] including the recent major review of Ley and co-workers,[16] but these have been focused particularly on the *use* of the supported complexes rather than their *preparation*. It is the aim of this review to discuss the preparation of polymer-supported ligands and the organometallic complexes formed using them. The aim is to give an insight into how chemists have gone about the task of attaching

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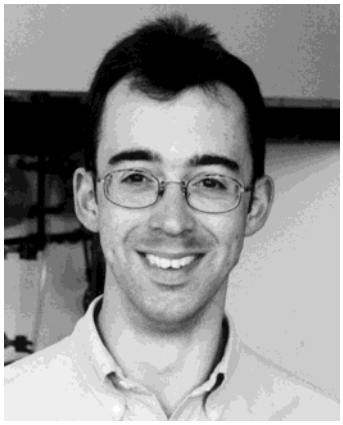


Dr. Nicholas E. Leadbeater was born in Birmingham, England, in 1972. He obtained his B.Sc. in chemistry from the University of Nottingham in 1993 and then moved to the University of Cambridge to carry out his Ph.D. on the use of photochemistry as a synthetic tool in organometallic chemistry under the supervision of Professor the Lord Lewis of Newnham and Professor Paul Raithby. On completion of his Ph.D. he took up a College Research Fellowship at Girton College, which he held until 1999. In 1997 he was awarded the Royal Society of Chemistry Laurie Vergnano award. Since 1999 he has been holding a Royal Society University Research Fellowship and a Lectureship at King's College London. In 2002 he was awarded the Royal Society of Chemistry Harrison Memorial Prize for chemistry conducted and published under the age of 30. The focus of his research lies in the broad field of synthetic chemistry, and he has published over 30 papers in the area. Specific research interests include metal-mediated organic synthesis, polymer-supported catalysis, the use of photochemistry as a synthetic tool for organometallic synthesis, and, more recently, microwave-mediated synthetic chemistry. His research has led to a range of novel complexes as well as new developments in synthetic methodology.

Maria Marco was born in Madrid, Spain, and obtained her Bachelor degree in chemistry from the Complutense University of Madrid in 1999. After spending a year working for GlaxoSmithKline in Madrid, she moved to London to start her Ph.D. working in Dr. Leadbeater's research group, which she will complete in 2003. The research area of her Ph.D. is the development of new synthetic methodologies for metal-mediated organic synthesis and has involved the development of *N*-heterocyclic carbenes as ligands and, more recently, microwave-mediated aqueous-phase catalysis.

ligands and metal complexes that have shown great promise in homogeneous catalysis to polymer supports. As is shown, this is often a far from trivial exercise, and the full synthetic tool kit is required. As well as grafting ligands onto prefabricated supports, the copolymerization of suitably derivatized ligand precursors with styrene and divinylbenzene (DVB) as a route to immobilized organometallics is also discussed. The scope of the review will be limited to ligands and their metal complexes attached to derivatized polystyrene supports as other supports are discussed elsewhere in this issue. The work covered herein will be further limited to six main areas together with some miscellaneous examples to show the scope of the preparative methods used and highlight the range of applications the supported complexes have found.

2. Polymer-Supported Metal Phosphine Complexes

2.1. Introduction

The number and diversity of transition-metal phosphine complexes are very large, and a wide range have been used as catalysts for synthetic organic transformations for many years. It therefore comes as little surprise that the preparation of polymer-supported metal phosphine complexes and assessment of their catalytic activity has attracted much attention. Polymer-supported phosphine ligands and their metal complexes prepared from 1981 to date are shown in Table 1, with those discussed in the text being highlighted with an asterisk. Included in each entry is the chemical structure of the supported phosphine ligand and, where available, the supported complex and a brief outline of the synthesis. Discussed in the text are examples from 1996 to the present together with a selected number of those from 1981 to 1996 where particularly notable synthetic methods have been used or where key points should be raised. For supported complexes prepared before 1981 the reader is directed to the reviews by Pittman[17] and Bailey and Langer.[18]

One of the simplest ways to prepare a polymer-immobilized phosphine ligand is direct reaction of a simple functionalized polymer such as bromopolystyrene or Merrifield's resin with a derivative of the desired ligand.[19] This route has been used many times and is often still the preparative method of choice. The ready commercial availability of polystyrene resins in a variety of cross-link densities, particle sizes, and types permits investigation of these variables on catalytic performance. Simple ligands such as **1** are relatively easily prepared from bromopolystyrene by initial lithiation of the support to form lithiated polystyrene and then reaction with PPh_2Cl. There are however disadvantages with the lithiation approach. Treatment of cross-linked polystyrene or bromopolystyrene with butyllithium can often lead to unwanted side reactions such as attack on the C=C bonds of the divinylbenzene cross-linking. As a result, often the product resin formed becomes contaminated and has poor swelling properties. An alternative way to introduce phosphines is by reacting brominated or chloromethylated resins with $LiPR_2$ or KPR_2. This offers a useful route for the preparation of a wide range of polymer-supported phosphines and is the more common method for attachment of simple monodentate phosphines to polymer supports. Attachment of metals to a phosphine-derivatized polymer support is often achieved by one of two methods, namely, via a phosphine substitution reaction or by direct formation of the phosphine complex by reaction with an organome-

Table 1[a]

POLYMER SUPPORT	SUPPORTED PHOSPHINE	METAL	PREPARATION	USE IN CATALYSIS	REF
Polystyrene		Cu(I)	Ligand exchange wih $(n\text{-}Bu_2S)_2CuI$	Preparation of organocopper reagents	A
Polystyrene		Cu(I)	Ligand exchange with CuCl-TMEDA and then reduction with $NaBH_4$	Reduction of carboxylic acid chlorides to aldehydes with no production of alcohol	B
Polystyrene + DVB		Li and Cu	Ligand association with $LiCuR_2$	Reactions with α,β- unsaturated carbonyls, vinyl halides and epoxides	C
Poly(styrene-divinyl-benzene)$_s$ (SDVB)		Ni	Ligand exchange with $Ni(PPh_3)_4$	Oligomerization of 1, 2-dienes	D
Polystyrene		Ni	Ligand exchange with $Ni(cod)_2$	Ethene oligomerization	E
Polyvinylchloride or polybromostyrene	 *R = Me, Ph*	Mn (II)	Ligand association with MnX_2 (X = Hal)	Oxidation catalysts and adsorbent for removing oxygen from the air	F
Polystyrene		Pd	Ligand association with $PdCl_2$	Telomerization of butadiene with various nucleophiles	G
Polystyrene		Pd	Ligand exchange with $PdCl_2(PPh_3)_2$	Heck arylation	23(*)
Polystyrene+ 2% DVB		Pd	Ligand association using $PdCl_2$	Hydrogen transfer reactions for steroidal synthesis	H
Polystyrene+ (2-20)% DVB		Pd	Ligand association with $Pd(acac)_2$	Telomerization of isoprene with water to synthesize terpenols	I
Polystyrene		Pd	Ligand exchange with $PdCl_2(cod)$	Cross coupling reactions involving chloropyridines and activated aryl chlorides	24(*)
Polystyrene		Pd	Ligand exchange with $PdCl_2$ and PPh_3 then treatment with hydrazine hydrate	Coupling of allylic alcohols with hypervalent iodonium salts	27(*)
				Cross coupling reactions of organoboron compounds with organic halides and triflates	28(*)
Polystyrene		Pd	*In situ* synthesis using $Pd(\eta^5\text{-}C_5H_6)(\eta^3\text{-}C_3H_5)$	Co-oligomerization of 1, 3-butadiene and CO_2	29(*)
Polystyrene+ DVB		Rh	Ligand exchange with $[Rh_2(\mu\text{-}S^tBu)_2(CO)_4]$	Hydroformylation of alkenes	J
Polystyrene+ 1.8% DVB		Rh	Ligand exchange with $[RhH(CO)(PPh_3)_3]$	Hydroformylation reactions	K
Polystyrene+ DVB (macroreticular)		Rh	Ligand association with $RhHCO(PPh_3)_3$	Gas phase hydroformylation of propene	L
Polystyrene+ 2% DVB		Rh	Ligand exchange with $[Rh_2Cl_2(cod)_2]$	Hydroformylation of 1- heptene	M
Polystyrene-chloromethylstyrene (CMS)- DVB		Rh	Ligand exchange with $[RhCl(CO)_2]_2$ or $RhCl(PPh_3)_3$	Hydrogenation of aromatic and aliphatic hydrocarbons	N, O
Polystyrene+ DVB		Os	Ligand association with $H_2Os_3(CO)_{10}$	Not specified	P
		Ir	*In situ* synthesis using Ir(CO)Cl(*p*-toluidine) as precursor	Not specified	
Polystyrene+ 1% DVB		Co	Ligand exchange with $Co_2(CO)_8$	2- pentene hydroformylation	Q
Polystyrene		Co	Ligand exchange with $Co_2(CO)_8$	Pauson- Khand reaction	31(*)
				Traceless linker	30(*)
Polystyrene		Co	Ligand exchange with $CoCl_2(PPh_3)_2$	Alcohol oxidation	33(*)
				Acid anhydride synthesis	
Polystyrene+ 2% DVB		Ru	Ligand exchange with $RuCl_3\cdot 3H_2O$	Not specified	O
Polystyrene+ 1% DVB		Ru	Ligand exchange with $Ru(CO)_3(PPh_3)_2$	Hydroformylation of 1-pentene	R
Polystyrene		Ru	Ligand exchange with $[Ru(p\text{-cymene})Cl_2]_2$	Enol formate synthesis	32(*)
				Olefin cyclopropanation	
Polystyrene		Ru	Ligand exchange with $RuCl_2(PPh_3)_3$	Alcohol and hydrocarbon oxidation	34(*)
Polystyrene		Cr	Ligand exchange with $Cr(CO)_3$(arene)	Traceless linker	43(*), 44(*)
Polystyrene		Cr	Ligand exchange with $Cr(CO)_5$(carbene)	Preparation of supported aminocarbenes	47(*)
Polystyrene		Cu and Li	Firstly ligand association with CuI and then lithiation with lithium naphtalide	Oxidative addition to organic halides	S
Polystyrene		Ru	Ligand exchange with $RuCl_2(PPh_3)_2Ru{=}CHPh$	Olefin metathesis	80(*)
Polystyrene		Ru	Ligand exchange with $RuCl_2(PPh_3)_2Ru{=}CHPh$	Olefin metathesis	80(*)
Polystyrene		Pd	Ligand exchange with $PdCl_2(PhCN)_2$	Ethoxy carbonylation of 4, 4'-dibromobiphenyl	T
Polystyrene		Pd	Ligand exchange with $PdCl_2(PhCN)_2$ or $Pd(C_5H_5N)_2Cl_2$	Not specified	U
Polystyrene+ (2-20)% DVB		Pd	Ligand association with $Pd(acac)_2$	Telomerization of isoprene with water to synthesize terpenols	I
Polystyrene		Cr	Ligand exchange with $Cr(CO)_3$(arene)	[6π + 2π] cycloaddition reactions	45(*)

Table 1 (Continued)[a]

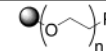
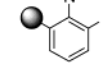
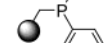
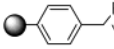
POLYMER SUPPORT	SUPPORTED PHOSPHINE	METAL	PREPARATION	USE IN CATALYSIS	REF
Polystyrene		Cr	*In-situ* synthesis using UV-photolysis to prepare the Cr precursor	Solid-phase synthesis of tertiary alcohols and esters	46(*)
Polystyrene		Ru	Ligand exchange with $RuCl_2(PPh_3)_2Ru{=}CHPh$	Olefin metathesis	80(*)
Polystyrene		Co	Ligand exchange with $PhCCo_3(CO)_9$	Hydroformylation of 1-heptene	X
Polystyrene+ 1% DVB		Co	Ligand exchange with $Co_2(CO)_8$	2- pentene hydroformylation	Q
Polystyrene+ DVB (macroreticular)		Rh	Ligand association with $RhHCO(PPh_3)_3$	Gas phase hydroformylation of propylene	L
Polystyrene+ DVB		Ir	Ligand exchange with $[Ir(cod)Ir(C_5H_5N)_2]^+$	Hydrogenation of olefins	V
Polystyrene		Ni	Ligand exchange with $Ni(cod)_2$	Ethylene oligomerization	E
Polystyrene		Pd	Ligand exchange with $Pd(OAc)_2$ or $Pd_2(dba)_3$	Aryl halide amination reactions	41(*)
				Suzuki coupling reactions	
Polystyrene+poly-vinylbenzyl chloride (VBC)		Pd	Ligand association using $Pd(OAc)_2$ as precursor	Vinylation of iodobenzene with methyl acrylate	W
Polystyrene/ poly (ethylene glycol)		Ru	Ligand exchange with $Ru_6C(CO)_{17}$	Hydrogenation of olefins	40(*)
Polystyrene+ 1% DVB		Co	Ligand exchange with $Co_2(CO)_8$	2-pentene hydroformylation	Q
Polystyrene+ 2% DVB		Rh	Not specified	Wittig reactions for chain homologation	Y
Polystyrene		Rh	Ligand exchange with $[RhCl(cod)]_2$	Hydrogenation reactions	Z
Polystyrene		Cr	Dichromate salt formation, reacting with CrO_3 in H_2O	Oxidizing agent	AA
Polystyrene		Ni	Ligand exchange from $Ni(cod)_2$	Ethylene oligomerization	E
Polystyrene-chloromethylstyrene (CMS)- DVB		Rh	Ligand exchange from $[RhCl(CO)_2]_2$	Hydrosilylation of 1- hexene by dimethylphenylsilane	BB
Polystyrene+ DVB		Rh	Ligand association / exchange using $RhCl_3{\cdot}3H_2O$ or $RhCl(CO)(PPh_3)_2$	Hydroformylation of propene and propylene	CC, DD
Polystyrene		Pd	Ligand association with $PdCl_2$	Synthesis of *ortho*- functional phenylacetylenes	EE
Polystyrene		Pt	Ligand exchange with $PtCl_2(PhCN)_2$	Characterization and study by ^{31}P NMR spectroscopy.	FF
Polystyrene		Ni	Ligand association with $NiCl_2$	Comparison with homogeneous analogue	54(*)
		Pd	Ligand exchange with $PdCl_2(PhCN)_2$	Comparison with homogeneous analogue	
		Pt	Ligand exchange with $PtCl_2(PhCN)_2$	Comparison with homogeneous analogue	
		Rh	Ligand exchange with $Rh(PPh_3)_3Cl$	Comparison with homogeneous analogue	
		Ru	Ligand exchange with $Ru(PPh_3)_3Cl_2$	Comparison with homogeneous analogue	
Polyvinylbenzyl		Pd	Ligand exchange with $PdCl_2(PhCN)_2$	Heck arylation	55(*)
Polystyrene+ DVB		Pd	Ligand exchange with $Pd(PPh_3)_4$	Carbonylative cyclization reactions (formation of keto lactones from esters)	51(*)

Table 1 (Continued)[a]

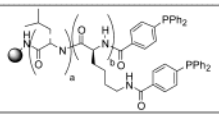
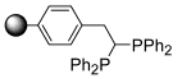
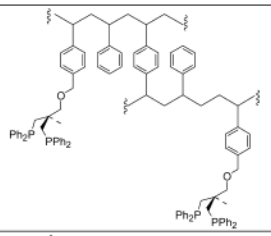
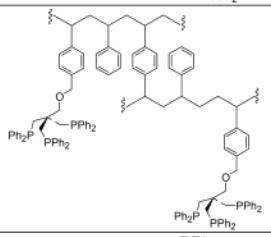
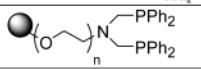
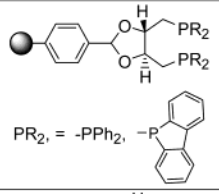
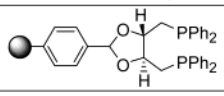
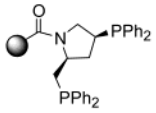
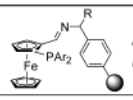
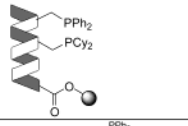
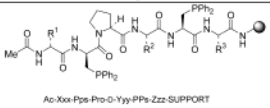
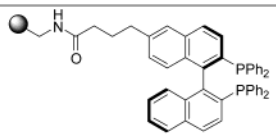
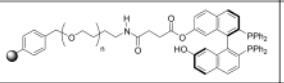
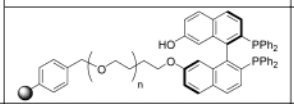
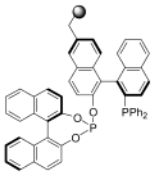
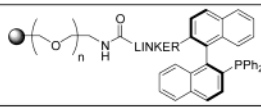
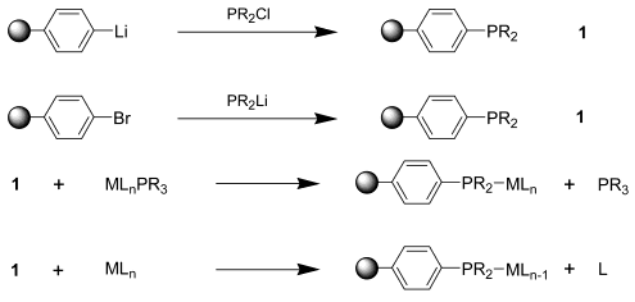
POLYMER SUPPORT	SUPPORTED PHOSPHINE	METAL	PREPARATION	USE IN CATALYSIS	REF
Polystyrene/poly (ethylene glycol)		Pd	*In-situ* synthesis using $[PdCl(CH_2CHCH_2)]_2$	Addition of dimethyl malonate to an allylic acetate	38(*)
Polystyrene+ DVB		Pd	Ligand association using $Pd(OAc)_2$ as precursor	1, 3- butadiene telomerization with methanol Hydrogenation of nitrobenzene and α, β- unsaturated aldehydes	49(*)
Polystyrene+ DVB		Rh	Ligand exchange with $[RhCl(cod)]_2$ followed by treatment with NBu_4PF_6	Hydrogenation of *N*-heterocycles	52(*)
Polystyrene+ DVB		Rh	Ligand exchange with $[RhCl(cod)]_2$ followed by treatment with NBu_4PF_6	Hydrogenation of benzo[*b*]thiophene	53(*)
Polystyrene/ poly (ethylene glycol)		Ru	Ligand exchange from $Ru_6C(CO)_{17}$	Hydrogenation of olefins	40(*)
Polystyrene+ DVB		Pt	Ligand exchange using $PtCl_2(PhCN)_2$ followed, by reaction with $SnCl_2$	Asymmetric hydroformylations	GG
Polystyrene+ DVB		Rh	Ligand exchange with $[RhCl(cod)]_2$	Hydrogenation reactions	66(*)
Polystyrene		Pt	Ligand exchange with $PtCl_2(PhCN)_2$ followed by reaction with $SnCl_2$	Asymmetric hydroformylation of prochiral olefins	HH, II
		Rh	Ligand exchange with $[RhCl(cod)]_2$ or $[Rh(\pi\text{-allyl})Cl]_2$	Hydroformylation of olefins	JJ
				Hydrogenation of dehydroamino acids	KK
Polystyrene		Pd	*In-situ* synthesis with $[(\eta^3\text{-}C_3H_5)PdCl]_2$	Asymmetric allylic alkylation	77(*)
Polystyrene		Rh	Ligand exchange with $[Rh(nbd)][ClO_4]$	Hydrogenation reactions	60(*), 61(*), 62(*)
Polystyrene		Pd	Ligand exchange with $[PdCl(h^3\text{-}C_3H_5)]_2$	Hydrogenation reactions	63(*)
Polystyrene		Ru	Ligand exchange with (cod)Ru(bis-methallyl)	Enantioselective hydrogenation	68(*)
		Pd	*In-situ* synthesis from $[Pd(MeCN)_2]^{2+}$ $(BF_2)^-_2$	Asymmetric aldol and Mannich type reactions	71(*)

Table 1 (Continued)[a]

POLYMER SUPPORT	SUPPORTED PHOSPHINE	METAL	PREPARATION	USE IN CATALYSIS	REF
Polystyrene / PEG		Rh	*In-situ* synthesis from $[Rh(cod)_2]^+[CF_3SO_3]^-$	Asymmetric isomerization of alkenes	69(*)
		Rh			
DVB + ethylstyrene		Rh	Ligand exchange with $Rh(acac)(CO)_2$	Asymmetric hydroformylation reactions	72, 73(*)
		Pd	Ligand exchange with PdMe(cod) followed by treatment with $NaBAr_4$ (Ar = 3,5-$(CF_3)_2$-C_6H_3)	Alternating copolymerisation of ω-perfluoroalkyl-1-alkenes with CO	74(*)
Polystyrene/ poly (ethylene glycol)		Pd	Ligand exchange from $[PdCl(\mu^3\text{-}C_3H_5)]_2$	Asymmetric allylic substitution	75(*)

[a] acac = pentane-2,5-dione; cod = 1,5-cyclooctadiene, dba = dibenzylideneacetone; nbd = norbornadiene. An asterisk in the reference column indicates the examples are discussed in the text. References: (A) O'Brien, R. A.; Gupta, A. K.; Riecke, R. D.; Shoemaker, R. K. *Magn. Resonan. Chem.* **1992**, *30*, 398. (B) Amaratunga, W.; Frechet, J. M. J. *Polym. Prepr. (Am. Chem. Soc., Div. Polym. Chem.)* **1981**, *22*, 151. (C) Muralidharan, S.; Freiser, H. *Inorg. Chem.* **1988**, *27*, 3251. (D) Cermak, J.; Soukupova', L.; Chualousky, V. *J. Mol. Catal.* **1983**, *80*, 181. (E) Peuckert, M.; Keim, W. *J. Mol. Catal.* **1984**, *22*, 289. (F) Li, G. Q.; Gorind, R. *Inorg. Chim. Acta* **1995**, *230*, 219. (G) Kandeda, K.; Kurasaki, H.; Tersawa, M.; Imannaka, T.; Teranishi, S. *J. Org. Chem.* **1981**, *46*, 2356. (H) Choudan, B. M.; Lakshmi, Kantam, M. *J. Mol. Catal.* **1986**, *36*, 343. (I) Bianchini, J. P.; Gaydou, E. M.; Waegell, B.; Eisenbeis, A.; Keim, W. *J. Mol. Catal.* **1985**, *30*, 197. (J) Kalck, P.; de Olivira, E. L.; Quean, R.; Peyrike, B.; Molinier, J. *J. Organomet. Chem.* **1992**, *433*, C4. (K) Park, S. C.; Ekerdt, J. G. *J. Mol. Catal.* **1984**, *24*, 33. (L) De Munck, N. A.; Verlaruggen, M. W.; Scholten, J. J. F. *J. Mol. Catal.* **1981**, *10*, 313. (M) Terreros, P.; Pastor, E.; Fierro, J. L. G. *J. Mol. Catal.* **1989**, *53*, 359. (N) Bartholin, M.; Graillat, C.; Guyot, A. *J. Mol. Catal.* **1981**, *10*, 361. (O) Torroni, S.; Innorta, G.; Foffani, A.; Scagnolari, F.; Modeli, A. *J. Mol. Catal.* **1985**, *33*, 37. (P) Lieto, J.; Milstein, D.; Albright, R. L.; Minkiewicz, J. V.; Gates, B. C. *CHEMTECH* **1983**, 46. (Q) De-an, C.; Pittman, C. U., Jr. *J. Mol. Catal.* **1983**, 405. (R) Pittman, C. U., Jr.; Wilemon, G. M. *J. Org. Chem.* **1981**, *46*, 1901. (S) O'Brien, R. A.; Rieke, R. D. *J. Org. Chem.* **1990**, *55*, 788. (T) Hanaoka, T.; Takenchi, K.; Sugi, Y.; Teranishi, K.; Okuno, M.; Sato, J. *Catal. Lett.* **1994**, *28*, 337. (U) Andersson, C.; Larsson, R. *J. Catal.* **1983**, *81*, 179. (V) Bartholin, M.;Graillat, C.; Guyot, A. *J. Mol. Catal.* **1981**, *10*, 377. (W) Hong, L.; Ruckenstein, E. *React. Polym.* **1991**, *16*, 181. (X) Wang. Y.; Lei, Z. *React. Polym.* **1991**, *15*, 85. (Y) Regen, S. L.; Kodomari, M. *J. Chem. Soc., Chem. Commun.* **1987**, 1428. (Z) Sybert, P. D.; Bertelo, C.; Brigelow, W. B.; Varaprath, S.; Stille, J. K. *Macromolecules* **1981**, *14*, 502. (AA) Hassanein, M. *Eur. Polym. J.* **1991**, *27*, 217. (BB) Michalska, Z. M., *J. Mol. Catal.* **1983**, *19*, 345. (CC) Ro, K. S.; Woo, S. I. *Appl. Catal.* **1991**, *69*, 169. (DD) Ro, K. S.; Woo, S. I. *J. Catal.* **1994**, *145*, 327. (EE) Villemin. D.; Goussu, D. *Heterocycles* **1989**, *29*, 1255. (FF) Clark, H. C.; Davies, J. A.; Fyfe, C. A.; Hayes, P. J.; Wasylishen, R. E. *Organometallics* **1983**, *2*, 177. (GG) Pittman, C. U., Jr.; Kawabata, Y.; Flowers, L. I. *J. Chem. Soc., Chem. Commun.* **1982**, 473. (HH) Parrinello, G.; Stille, J. K. *J. Am. Chem. Soc.* **1987**, *109*, 7122. (II) Stille, J. K. *React. Polym.* **1989**, *10*, 165. (JJ) Stille, J. K. *J. Macromol. Sci., Chem.* **1984**, *A21*, 1689. (KK) Baker, G. L.; Fritschel, S. J.; Stille, J. R.; Stille, J. K. *J. Org. Chem.* **1981**, *46*, 2954.

Scheme 1



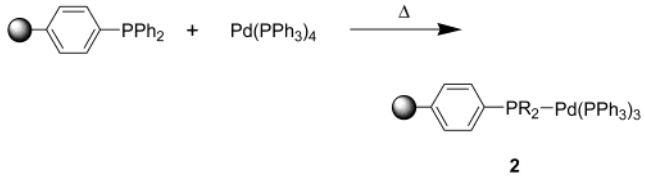
tallic precursor. These synthetic approaches are shown in Scheme 1.

2.2. Polymer-Supported Monodentate Phosphines and Their Metal Complexes

2.2.1. Polymer-Supported Triphenylphosphine

Polymer-supported triphenylphosphine (PS−PPh_2; PS = polystyrene) has attracted much attention as a ligand for immobilization of metal complexes as it

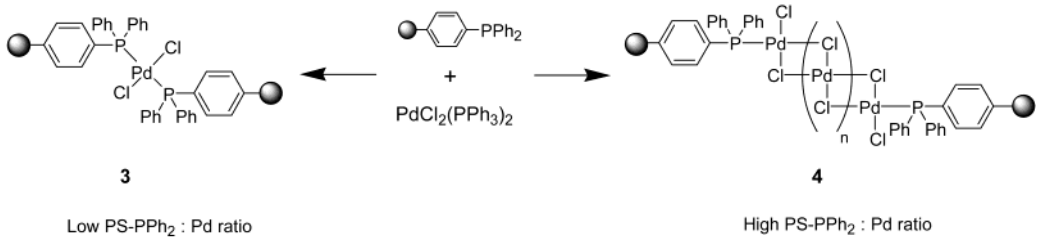
Scheme 2



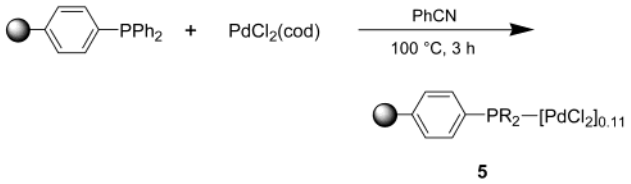
is the supported analogue of the ubiquitous simple tertiary phosphine ligand PPh_3. Also it is commercially available from a range of suppliers.

The attachment of palladium complexes to PS−PPh_2 and their subsequent use in catalysis has attracted much attention. Two of the first reports of the preparation and use of the supported analogue **2** of the well-known palladium complex $Pd(PPh_3)_4$ were in the 1970s by Pittman and co-workers[20] and by Keinan and Trost,[21] reporting that heating a solution of the parent metal complex with PS−PPh_2 leads to **2** containing between 1.5% and 2% Pd (Scheme 2). Since then, **2** has found numerous applications in catalysis, in many cases with differing selectivity to the homogeneous analogue.[22]

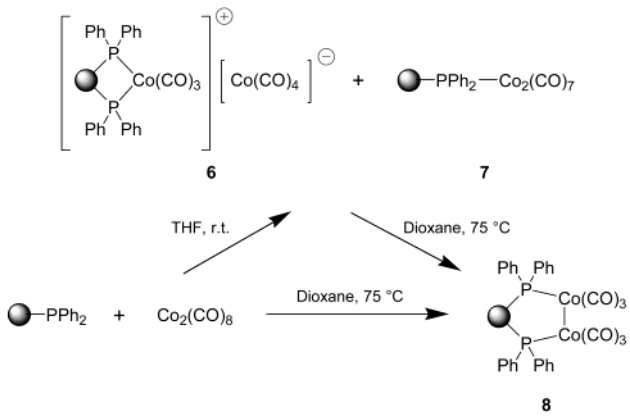
Scheme 3



Scheme 4



Scheme 5



Hallberg and co-workers[23] have prepared supported analogues of $PdCl_2(PPh_3)_2$ from PS−PPh_2 and $PdCl_2$-$(PhCN)_2$ again by simple mixing of the two components (Scheme 3). They prepared supported complexes with Pd:P ratios of 1:1, 1:2, 1:3, and 1:4 and found that the bonding of the metal to the support changes with metal loading, complex **3** being formed at low metal loading and **4** at higher metal loading.

A similar methodology was used by Miyaura and Inada in their preparation of **5**,[24] this complex being shown to be highly active in cross-coupling reactions involving chloropyridines and activated aryl chlorides (Scheme 4). The supported complex was prepared by stirring a mixture of PS−PPh_2 and $PdCl_2$(cod) [cod = 1,5-cyclooctadiene] in benzonitrile at 100 °C for 3 h. Elemental analysis showed a P:Pd ratio of 11:1.

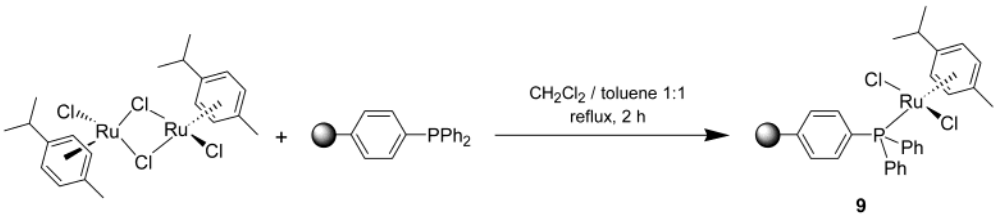
Other workers[25,26] have used mixtures of PS−PPh_2 and palladium salts to prepare supported palladium phosphine complexes for use in cross-coupling reactions, but these have been used directly as cross-coupling catalysts and the supported palladium complex has not been characterized. None of these show the activity of **5**, the reports only showing couplings with aryl bromides and iodides. One recent report was by Jang,[27,28] who prepared a polymer-supported palladium phosphine complex by modification of previous procedures. **3** was treated with PPh_3 and hydrazine hydrate to give a green polymer-supported complex which was uncharacterized but proved active as a catalyst in Suzuki reactions and also in the coupling of allylic alcohols with hypervalent iodonium salts. The supported complex has a P:Pd ratio of 3.9:1, and some later reports suggest that it is in fact **2**, but this should not be assumed, particularly as **2** is deep red in color. This highlights the fact that it is very important to determine the nature of a supported complex as this is essential to understanding its use in catalysis and for developing further synthetic applications. Pitter and co-workers[29] have studied the co-oligomerization of 1,3-butadiene and CO_2 using a supported palladium complex prepared in situ from PS−PPh_2 and Pd(η^5-C_5H_5)(η^3-C_3H_5) by reaction in acetonitrile.

The immobilized cobalt carbonyl complex $Co_2(CO)_6$-(PS−PPh_2)$_2$ (**8**) has been prepared by Gibson and co-workers using $Co_2(CO)_8$ as a starting material and has proven useful as an alkyne linker[30] and as a catalyst for the Pauson−Khand reaction[31] (Scheme 5). Reaction of PS−PPh_2 with $Co_2(CO)_8$ in THF at room temperature generates a mixture of phosphine-substituted cobalt carbonyl complexes **6** and **7**. Heating this mixture to 75 °C in dioxane leads cleanly to formation of **8**. This can be prepared directly from PS−PPh_2 (loading of 1.6 mmol/g) and $Co_2(CO)_8$ without isolation of **6** and **7** by performing the whole reaction in dioxane with a resultant metal of approximately 0.35 mmol/g.

Leadbeater and co-workers[32] have prepared a supported ruthenium arene complex for use as a catalyst for enol formate synthesis and olefin cyclopropanation. The immobilized complex **9** was prepared by thermolysis of the dimer [Ru(*p*-cymene)Cl_2]$_2$ with PS−PPh_2, a metal loading of 0.25 mmol/g being obtained (Scheme 6). The homogeneous analogue Ru(*p*-cymene)Cl_2PPh_3 is prepared in toluene, but the problem with this when using PS−PPh_2 is that the support does not swell well in toluene, and so a modified solvent mixture, 1:1 dichloromethane/toluene, was used. Unlike the homogeneous analogue, **9** is stable in air, no decomposition being noted over a period of three months at room temperature. This shows one of the advantages of immobilization of organometallic complexes—namely, increased stability.

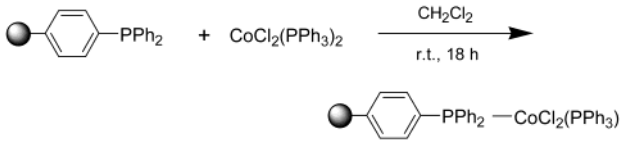
Leadbeater and co-workers[33] have prepared a supported cobalt phosphine complex for use in alcohol oxidation. Starting from PS−PPh_2, the immobilized complex **10** was prepared by stirring a dichloromethane solution of $CoCl_2(PPh_3)_2$ with the functionalized resin (Scheme 7). The polymer-bound complex formed is stable in air, no decomposition being noted over a period of four months at room temperature. In the presence of a catalytic amount

Scheme 6



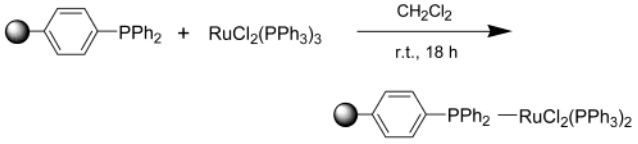
9

Scheme 7



10

Scheme 8



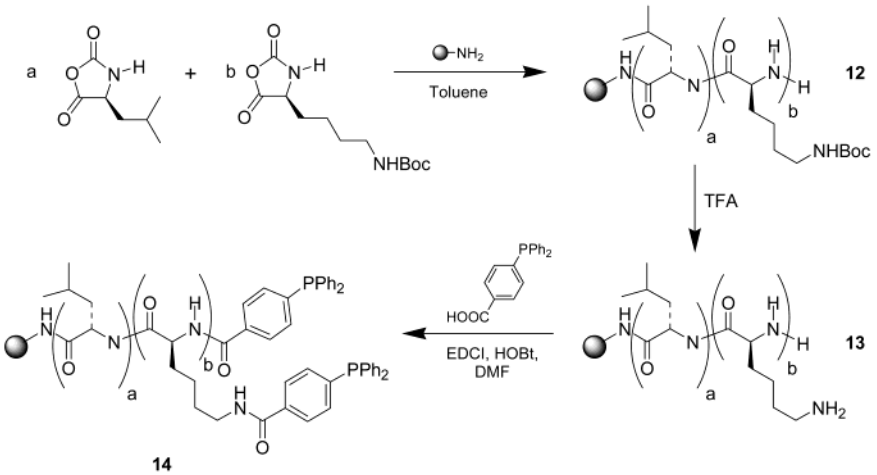
11

of **10**, the efficient oxidation of benzylic alcohols using *tert*-butyl hydroperoxide as oxidant can be effected. A point of interest is that, in the case of primary alcohol oxidation, while with $CoCl_2(PPh_3)_2$ equal yields of aldehyde and acid are observed, using the supported catalyst, formation of the acid is greatly reduced although not fully inhibited. This shows that the selectivity of a polymer-supported complex can be very different from that of its homogeneous analogue.

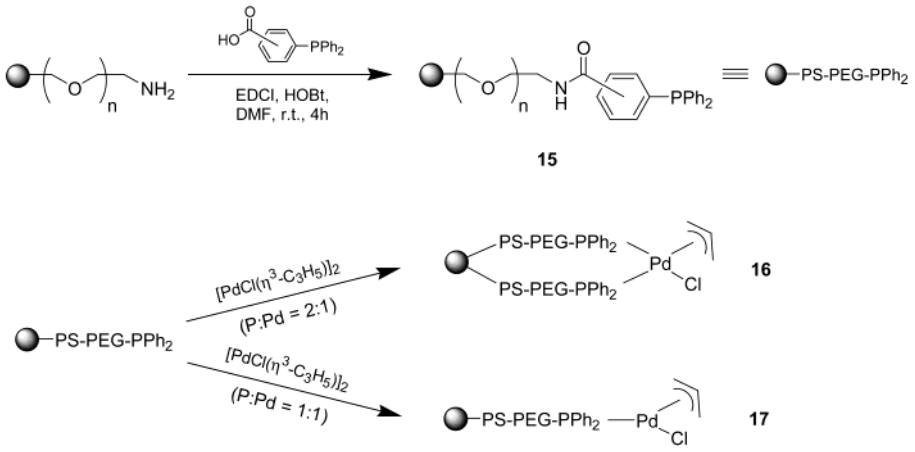
Using a similar methodology, Leadbeater[34] has prepared a supported ruthenium phosphine complex for use in hydrocarbon oxidation. The immobilized complex, **11**, was prepared by stirring $RuCl_2(PPh_3)_3$ with PS−PPh_2 in dichloromethane overnight, giving a metal loading of approximately 0.3 mmol/g of resin (Scheme 8). **11** has been used as a catalyst for oxidation of a range of alcohols and hydrocarbons. Of interest is that studies suggest that the metal comes off the support during the course of the reaction, returning at the end—very much like the "boomerang" catalysts reported by Barrett and co-workers for olefin metathesis[35,36] and discussed later in this review.

Building on a methodology for the preparation of resins containing poly(amino acid) chains first reported by Itsuno and co-workers,[37] Wills and co-workers[38] have developed a method for the multiplication of the level of phosphine functionalization on a solid support through the use of *N*-carboxyanhydride (NCA) derivatives of amino acids (Scheme 9). With an amine initiator, NCA derivatives of amino acids oligomerize in a stepwise manner. Using leucine−NCA, ϵ-^{t}Boc-protected lysine−NCA, and TentaGel−NH_2, an amine-derivatized poly(ethylene glycol) (PEG)−PS graft copolymer, peptide derivative **12** was formed. Although the exact degree of polymerization could not be determined, the authors suggest an approximate 4-fold increase in the number of amine functionalities. Deprotection of the ^{t}Boc-protected amine functionalities in **12** with TFA to form **13** followed by functionalization of all the amine groups with *p*-diphenylphosphinobenzoic acid (DPPBA) using EDCl and HOBt gives supported phosphine **14**. A combination of IR spectroscopic data on **12** and ^{31}P NMR data on **14** suggests that the composition of the copolymer is statistically distributed in a ratio corresponding to that of the NCAs used and that phosphine derivatization is almost quantitative. When only the leucine−NCA is used in the polymerization step, the phosphorus content of the resin after treatment with DPPBA is low due to the fact that only the terminal nitrogen is available for amide formation. The phosphine loading then increases with inclusion of lysine−NCA in the polymerization step, but when only lysine−NCA is used, not all of the

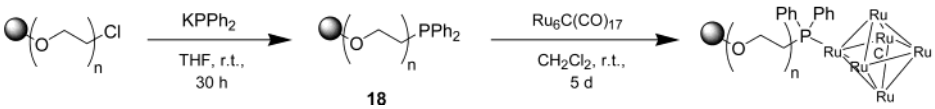
Scheme 9



Scheme 10



Scheme 11



amine groups of the resultant polymer are functionalized on treatment with DPPBA, this being attributed to steric hindrance around the active sites. The potential use of the phosphines as ligands for catalysis was assessed by screening palladium allyl complexes, prepared in situ by treatment of the supported ligand with $[PdCl(CH_2CHCH_2)]_2$, for the addition of dimethyl malonate to an allylic acetate. The homolysine polymer gave the best result in terms of reaction time and product yield, but it, and all the other polymers screened, did not show any notable asymmetric induction.

Amphiphilic derivatives of PS−PPh_2 have been prepared by Uozumi and co-workers[39] (Scheme 10). Using an amine-functionalized poly(ethylene glycol)−polystyrene resin, supported phosphines (PS−PEG−PPh_2) **15** have been prepared with total conversion using 2- or 4-(diphenylphosphino)benzoic acid under standard conditions for solid-phase amide synthesis. Allylpalladium complexes of the PS−PEG−PPh_2 supports have been prepared by treatment of the supported phosphine with 0.5 equiv of $[PdCl(\mu^3\text{-}C_3H_5)]_2$ in dichloromethane at room temperature for 10 min. Gel-phase ^{31}P NMR spectroscopy suggests the formation of the bisphosphine complex **16**. By varying the stoichiometry. it is also possible to prepare the monophosphine complex **17**.

Johnson, De Miguel, and co-workers[40] have immobilized the hexanuclear ruthenium cluster $Ru_6C(CO)_{17}$ on a PS−PEG−PPh_2 support, **18**. The supported phosphine was prepared by treatment of chloride-functionalized ArgoGel with $KPPh_2$, the metal cluster then being attached by agitating the support with an excess of $Ru_6C(CO)_{17}$ for 5 days (Scheme 11). Starting with a phosphine loading of 0.4 mmol/g, a metal loading of 0.24 mmol/g was obtained.

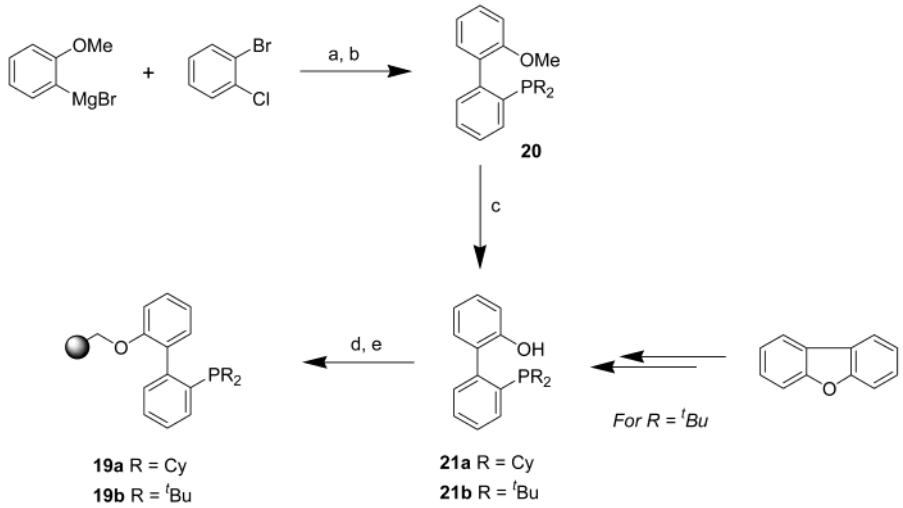
2.2.2. Polymer-Supported Dialkylphosphinobiphenylphosphines

Parrish and Buchwald[41] have prepared immobilized dialkylphosphinobiphenyl ligands **19a** and **19b**, the homogeneous analogues of which show high activity when used in palladium-catalyzed C−C- and C−N-bond-forming reactions (Scheme 12). The immobilized ligand **19a** is prepared starting from 2-methoxyphenylmagnesium bromide and benzyne (formed in situ from 2-bromochlorobenzene), these reacting to form **20**. This is then treated with $ClPR_2$ before deprotection of the methyl ether, forming **21a**. Deprotonation of **21a** using NaH in DMF followed by addition of Merrifield's resin leads to **19a** with approximately 80% of the chloromethylated sites being occupied by phosphine ligand. The di-*tert*-butylphosphinobiphenyl analogue **21b** is more difficult to prepare. The starting phosphine **21b** is prepared from dibenzofuran and then attached to the support in the same method as for **19a** but using a dilute solution of **21b**. Due to the easier preparation, chemistry using **19a** has received the most attention. Although not isolated, palladium complexes of **19a** have been prepared using $Pd(OAc)_2$ and $Pd_2(dba)_3$ and used successfully as catalysts for amination and Suzuki coupling reactions.

2.3. Polymer-Supported Chromium Phosphine Complexes

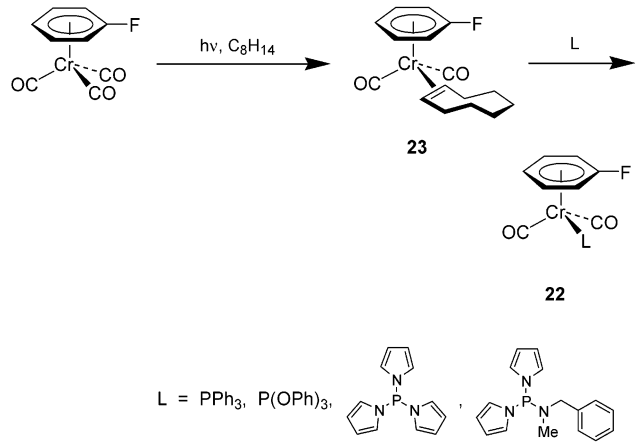
A number of reports of the synthesis of polymer-supported phosphine-linked chromium arene complexes have been prepared and their use both as linkers and as catalysts explored. Although not actually attaching the metal complex to a solid support, Semmelhack and co-workers[42] have undertaken an interesting study into the effects on the rate of nucleophilic substitution in fluoroarene−$Cr(CO)_2L$ complexes **22** of changing the ligand, L, with the specific aim of finding the best linker for formation of polymer-supported chromium arene complexes. In evaluating candidates for the linker, their attention focused on phosphorus-based ligands. They prepared substituted chromium fluorobenzene complexes shown in Scheme 13. The series of complexes were prepared by initial formation of the arene−$Cr(CO)_2(\eta^2$-cy-

Scheme 12[a]



[a] Reagents and conditions: (a) Mg, THF, 60 °C, 2.5 h; (b) CuCl, $ClPR_2$, THF, rt, 16 h; (c) BBr_3, CH_2Cl_2, −78 °C → rt, 16 h; (d) NaH, DMF, rt, 15 min; (e) Merrifield's resin (1.23 mmol of Cl/g), DMF, rt, 23 h.

Scheme 13

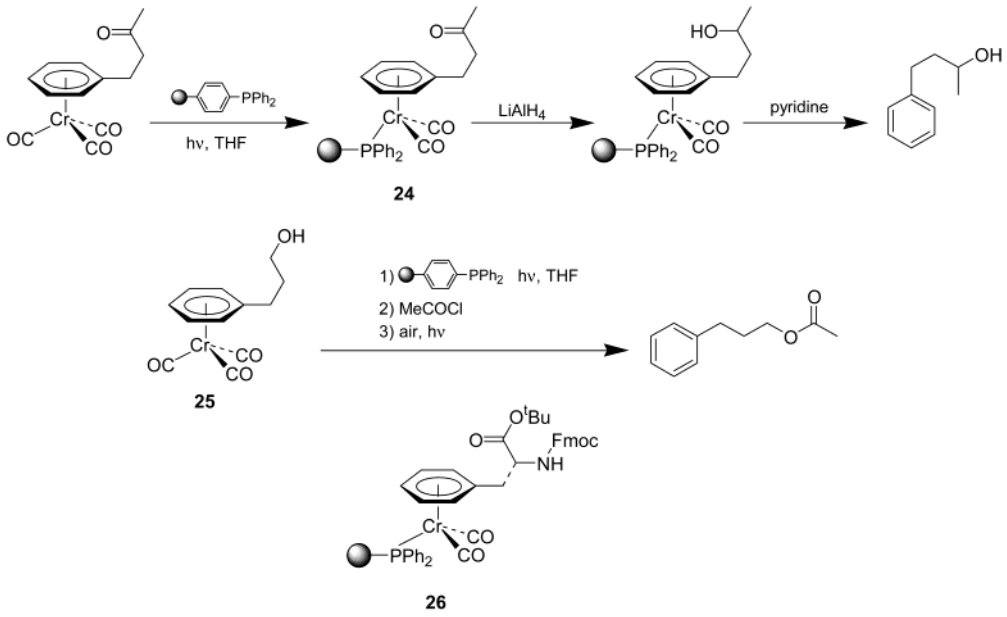


clooctene) derivative **23** by photolysis of the parent tricarbonyl complex with cyclooctene followed by thermal replacement of the very labile cyclooctene with the ligand of choice. The relative rates of nucleophilic substitution of the complexes with pyrrolidine have been determined by ^{19}F NMR studies. The results show that with triphenylphosphine as a ligand the substitution reaction is strongly inhibited. Even when using the amine as solvent, no reaction was observed at 50 °C. Triphenyl phosphite is a more suitable ligand, with the substitution reaction occurring at room temperature but still being 3600 times slower than with $Cr(CO)_3(C_6H_5F)$. The best results are reported with tris(pyrrolyl)phosphine, the substitution occurring only 1.4 times slower than with $Cr(CO)_3(C_6H_5F)$. As an extension to the work an aminophosphine bearing a benzylmethylamino substituent on phosphorus was prepared as this best represents the sort of ligand that could be easily immobilized on polystyrene starting from Merrifield's resin or an analogue. Using this ligand, the rate of the substitution reaction was not as close to that of the parent as the rate using tris(pyrrolyl)phosphine but still gave good results. These studies highlight how important it is to consider the effects of substituting groups on metal complexes to facilitate attachment to a polymer support. Clearly, for S_NAr reactions, attachment of the chromium arene complexes to a support such as PS−PPh_2 would be of no use due to the impedence of the reaction.

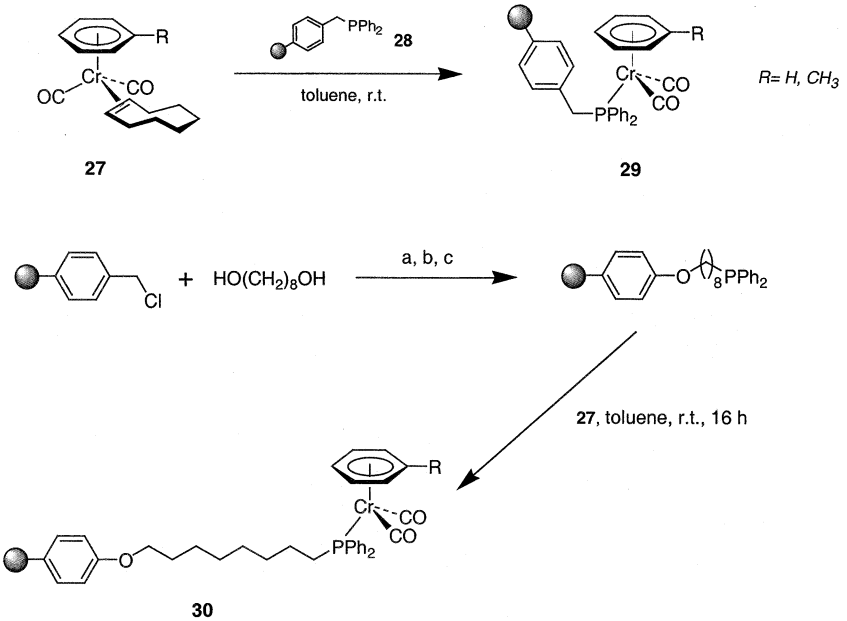
Gibson and co-workers[43] have prepared polymer-supported arene complex **24** by direct photolysis of a solution of PS−PPh_2 and $Cr(CO)_3$(arene) [arene = 4-(4-methoxyphenyl)butan-2-one] in THF (Scheme 14). The ^{31}P NMR analysis of the support after photolysis suggests that coverage with the $Cr(CO)_2$-(arene) complex is approximately 40%, with the remainder being PS−PPh_2–$Cr(CO)_5$ (20%), PS−PPh_2═O (10%), and unreacted PS−PPh_2 (30%). They also prepared **25**, the 4-(4-methoxyphenyl)propan-1-ol analogue of **24**, using the same methods and obtaining a coverage of the $Cr(CO)_2$(arene) complex of approximately 40%. The ketone and alcohol moieties of the supported complexes were chemically manipulated, and then the arene was released from the polymer, showing the use of arene−chromium complexes as traceless linkers. They have further demonstrated this[44] by immobilizing the phenylalanine derivative Fmoc-Phe-O^{t}Bu via its aromatic ring, and the resulting supported complex **26** was successfully subjected to standard amino acid deprotection and coupling procedures before cleavage of the linker to yield the derivatized amino acid product.

Rigby and co-workers[45] have presented a higher yielding route to phosphine-supported chromium arenes using the same methodology as applied by Semmelhack and co-workers[42] for the synthesis of their homogeneous phosphine-substituted complexes (Scheme 15), namely, by photolysis of the parent arene−tricarbonyl complex with cyclooctene to form **27** followed by thermal replacement of the cyclooctene with the ligand of choice, in this case polymer-supported benzyldiphenylphosphine (PS−*p*-CH_2PPh_2) (**28**) to form **29**. With simple arenes such as benzene and toluene the PS−*p*-CH_2PPh_2-supported chromium arene is formed easily, and the resulting complexes have been used as catalysts for effecting [$6\pi + 2\pi$] cyclooaddition reactions. To probe whether the chromium complex dissociates from the support during

Scheme 14



Scheme 15[a]

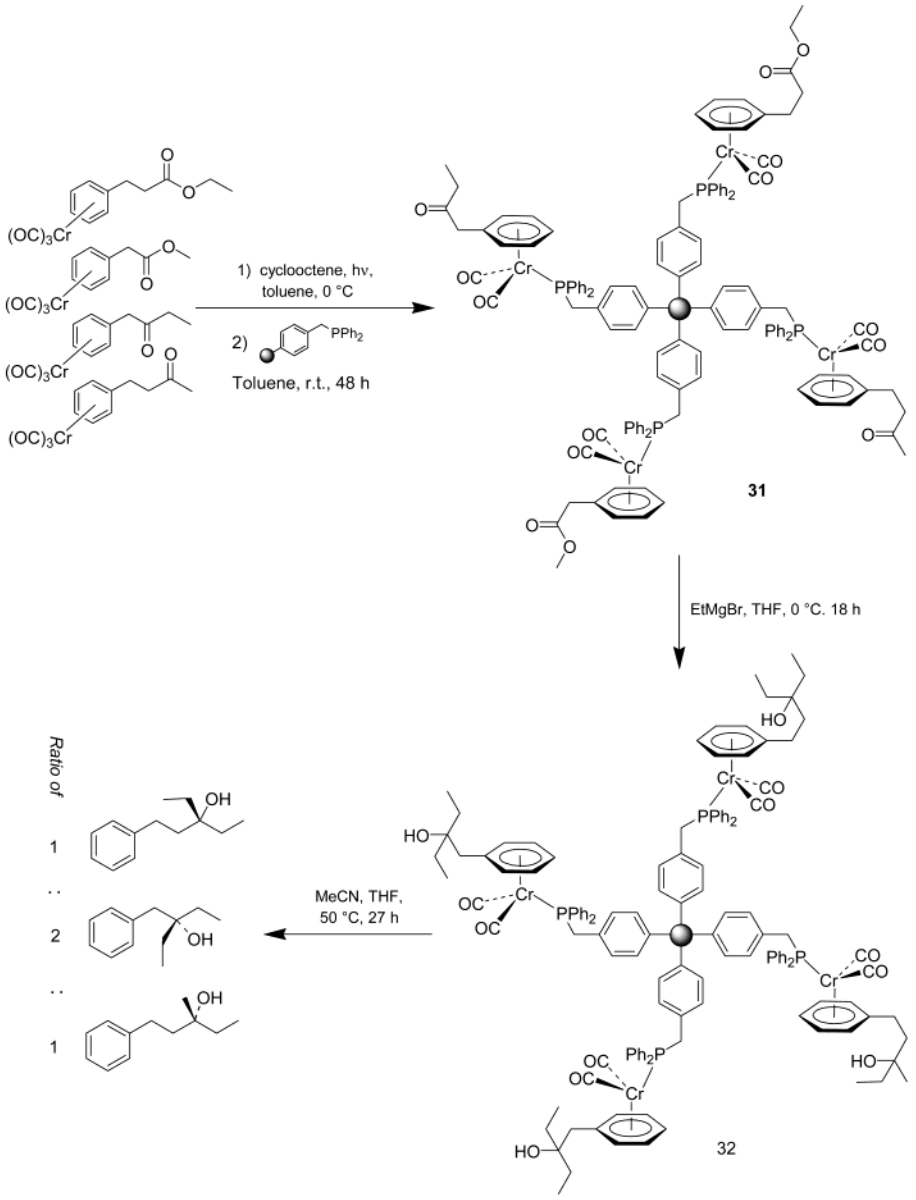


[a] Reagents and conditions: (a) NaH, Bu_4NI, DMF; (b) CBr_4, PPh_3; (c) $LiPPh_2$, THF.

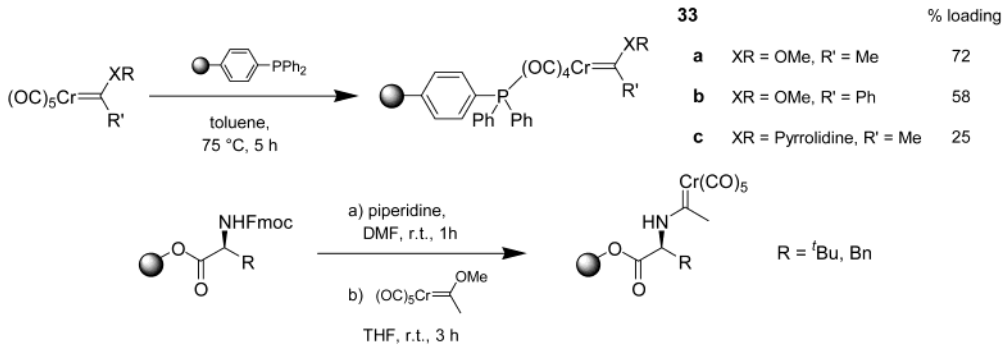
the course of the catalysis, they prepared supported phosphine complex **30** containing a much longer linker chain. Their reasoning was that, if the chromium complex does not dissociate off the support during the catalysis, then the yields of product should be greater using **30** than using the PS−*p*-CH_2PPh_2-supported analogue. This interestingly is the case providing some circumstantial evidence for the notion that the metal is retained on the support during the course of the reaction.

Rigby and Kondratenko[46] have extended their studies to the immobilization of arenes bearing oxygen atoms in the side chain. However, they find that partial decomposition of the organometallic complex is observed on photolysis with cyclooctene. This has been attributed to interaction of the chromium center with the oxygen substituent on the arene in the photogenerated fragment [$Cr(CO)_2$(arene)]. This is avoided by use of a large excess (70−80 equiv) of cyclooctene to trap out the [$Cr(CO)_2$(arene)] complex as its cyclooctene adduct, which can then be loaded onto PS−*p*-CH_2PPh_2 as before. As well as for the preparation of a range of homo-arene-supported complexes, the loading methodology was also used for simultaneous incorporation of a variety of starting materials onto the solid support. Irradiation of equimolar quantities of four different arenes with excess cyclooctene followed by treatment with PS−*p*-CH_2PPh_2 gave **31**, which contains all four substrates (Scheme 16). The range of supported arene complexes were subsequently used for the solid-phase synthesis of tertiary alcohol **32**. There is particular interest in this methodology because of the potential use in combinatorial or parallel synthesis, consider-

Scheme 16



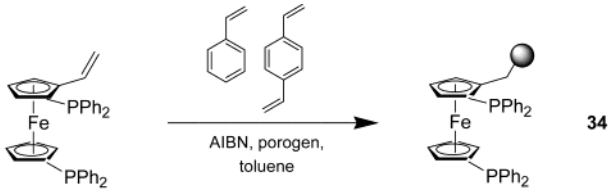
Scheme 17



able time being saved in preparing and testing diverse libraries.

Polymer-bound Fischer chromium alkoxy and aminocarbene complexes **33a**−**c** have been reported by Maiorana and co-workers (Scheme 17).[47] The supported alkoxycarbenes were prepared by heating the appropriate pentacarbonylchromium carbene complex with PS−PPh_2, variable loadings being reported. The supported alkoxycarbene complexes were converted to their aminocarbene analogues by reaction at room temperature in THF with a range of simple amines. Aminocarbenes were also prepared by reaction of alkoxycarbenes with leucine and phenylalanine grafted onto polystyrene and PS−PEG sup-

Scheme 18



34

ports (Scheme 17). After removal of the Fmoc group, a THF solution of the alkoxycarbene was added and the mixture stirred for 3 h at room temperature to give the supported aminocarbene, which was characterized by IR spectroscopy, but the loading was not determined.

2.4. Polymer-Supported Polydentate Phosphines and Their Metal Complexes

A number of polymer-supported polydentate phosphine ligands have been prepared as have their corresponding metal complexes. As polydentate phosphines show superior ligating properties over their monodentate analogues, attaching them to supports has a number of advantages such as possibly limiting leaching of the metal off the support during the course of a reaction when used as a catalyst.

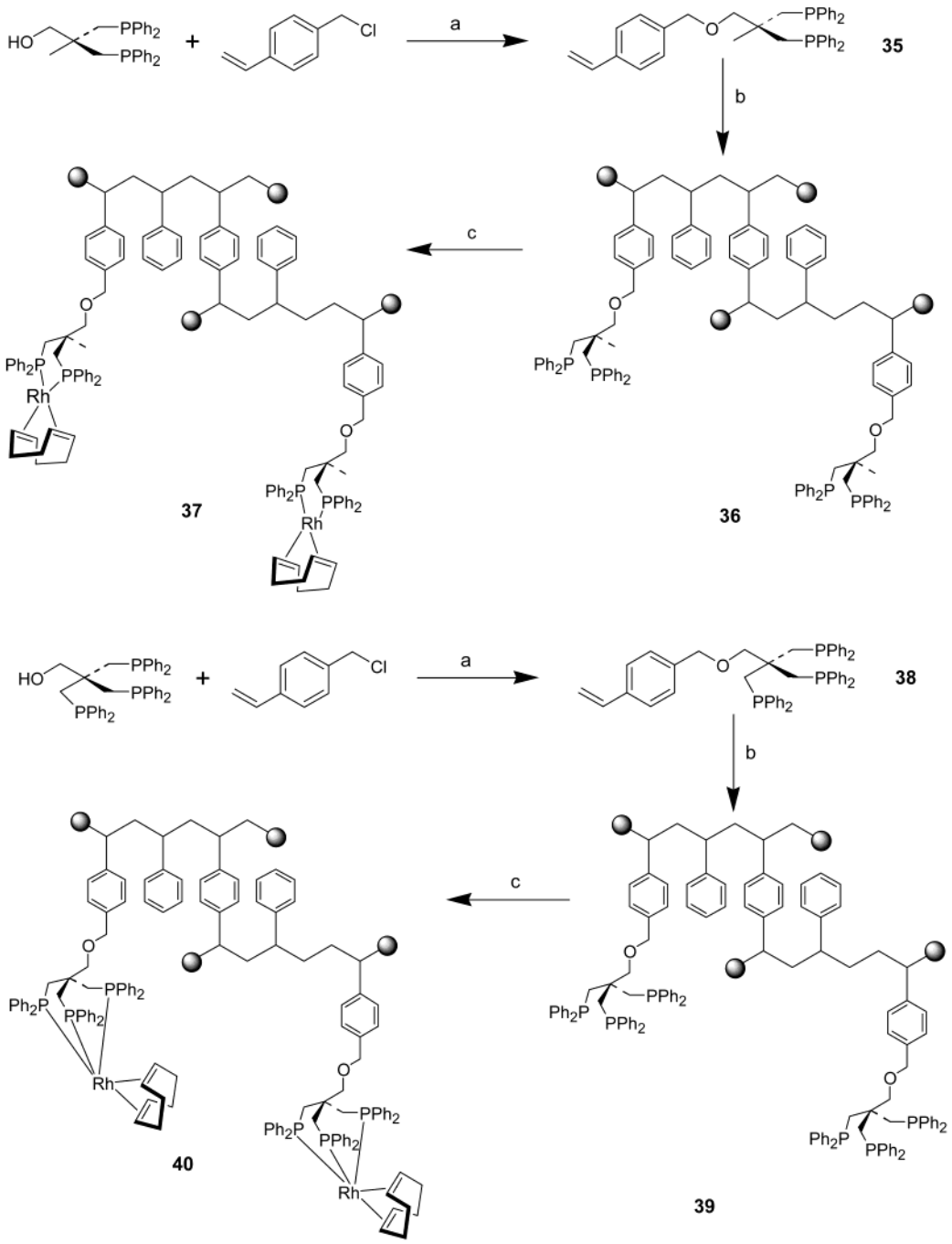
Polymer-supported bis(diphenylphosphino)methane (DPPM) has been prepared by Carlini and co-workers by treatment of Merrifield's resin with lithiated DPPM and subsequent reduction of the phosphine oxide.[48] A palladium complex of the supported DPPM has been prepared by treatment with $Pd(OAc)_2$ and screened in a range of catalytic transformations including the selective hydrogenation of cinnamaldehyde to hydrocinnamaldehyde.[49,50]

Polymer-immobilized bis(diphenylphosphino)ferrocene (DPPF) **34** and palladium complexes of this have been prepared by Hegedus and co-workers.[51] The immobilized ligand was prepared by AIBN-initiated suspension polymerization of vinyl-DPPF, styrene, and divinylbenzene (Scheme 18). This procedure gave macromolecular beads having a ligand loading of 0.22 mmol/g. The ratio of vinyl-DPPF to styrene to divinylbenzene of 0.02:0.48:0.50 used leads to a highly cross-linked polymer and ensures site isolation of the ligand moieties. A Pd(0) complex of **34** was prepared by refluxing a 1:1 mixture of immobilized ligand and $Pd(PPh_3)_4$ in toluene for 2 h, with almost quantitative palladium attachment being observed. This palladium complex was subsequently used for the synthesis of large-ring ketolactones by intramolecular carbonylative coupling reactions.

Bianchini and co-workers have prepared polymer-supported bidentate **36**[52] and tridentate **39**[53] ligands via copolymerization of styrene and divinylbenzene with styrene-derivatized monomeric phosphines (Scheme 19). Using NaH, 2,2-bis(diphenylphosphinomethyl)propanol was coupled to 4-vinylbenzyl chloride to yield the desired styrene-substituted phosphine **35**, which was copolymerized (0.5 equiv of phosphine) with styrene (1 equiv) and divinylbenzene (36 equiv) using AIBN as an initiator to give **36**. The tridentate analogue **39** is prepared in an analogous method but using 3,3-bis(diphenylphosphinomethyl)-oxacyclobutane as a starting material. Nucleophilic attack with $LiPPh_2$ followed by coupling with 4-vinylbenzyl chloride gives **38**, and then polymerization of this with either DVB on its own or styrene and DVB yields **39**. Rhodium complexes **37** and **40** have been prepared by stirring $[RhCl(COD)]_2$, Bu_4NPF_6, and the respective supported phosphine in dichloromethane. The key advantage of preparing the chelating phosphines by copolymerization rather than by grafting is that the synthesis is easier, it not being necessary to reduce the phosphine oxide back to the phosphine as is the case when chlorinated supports are treated with metalated phosphines. Also there is not the problem of removing trapped metal salts (such as LiCl) from the pores of the support.

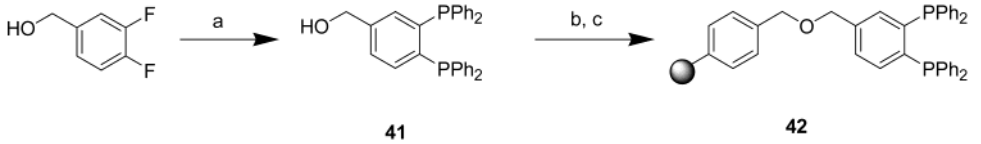
In their synthesis of polymer-supported *o*-phenylenediphenylphosphine, PS−PP (**42**), Levason and co-workers[54] used 3,4-difluorobenzyl alcohol as their starting material, forming the diphosphine **41** by reaction with $NaPPh_2$ (Scheme 20). The mode of attachment of the diphosphine to the support is through an ether linkage, **41** being readily deprotonated using NaH and treatment with Merrifield's resin, giving **42** with replacement of approximately one-third of the chlorines by diphosphine units. This offers significant advantages over previous routes involving the preparation of mixed chloro/alkyl-substituted bidentate phosphines and subsequent lithiation and reaction with a suitable support in that such phosphines are difficult to prepare in good yield and are very air and moisture sensitive.[55] The authors prepared a range of metal complexes using **42** as a ligand, treating this with a THF solution of metal salts and using a range of techniques to characterize the supported species, including EXAFS and diffuse reflectance UV−vis spectroscopy, comparing data recorded for the supported complexes with those for homogeneous model compounds containing the *o*-phenylenediphenylphosphine ligand. The reaction of **42** with Wilkinson's complex, $Rh(PPh_3)_3Cl$, gave what was proposed as PS−PP−$Rh(PPh_3)Cl$ on the basis of elemental analysis and solid-phase NMR, diffuse reflectance UV−vis, and EXAFS spectroscopy. Treatment of **42** with $PtCl_2(PPh_3)_2$ leads to the formation of a complex with a Pt:Cl:P ratio of 0.8:4:2 consistent with the formation of PS−PP−$PtCl_2$. This was confirmed by comparison of EXAFS data from PS−PP−$PtCl_2$ and the homogeneous *o*-phenylenediphenylphosphine (PP) analogue PP−$PtCl_2$, which show close correlation. Reaction of **42** with $NiCl_2$ or with $PdCl_2(PPh_3)_2$ does not lead in either case to simple PS−PP−MCl_2 complexes. In the case of $PdCl_2(PPh_3)_2$, EXAFS data suggest formation of more than one Pd complex on the support, Pd−C, Pd−P, Pd−Cl, and Pd−Pd bonding being observed. In the case of $NiCl_2$, EXAFS data suggest formation of a 5-coordinate metal complex with an oxygen in the coordination sphere, proposed as PS−PP−$NiCl_2$·THF or PS−PP−$NiCl_2$·H_2O. In the solution-phase analogue PP−$NiCl_2$, solvent coordination is not observed, and so this is unique to the supported complex, promoted by the environment within the polymer. With $Ru(PPh_3)_3Cl_2$ the product from the reaction with **42** is characterized as PS−PP−Ru-

Scheme 19[a]



[a] Reagents and conditions: (a) NaH, DMF; (b) styrene, DVB, AlBN, THF/MeOH (1:2), 85 °C; (c) $[RhCl(cod)]_2$, Bu_4NPF_6, CH_2Cl_2.

Scheme 20[a]

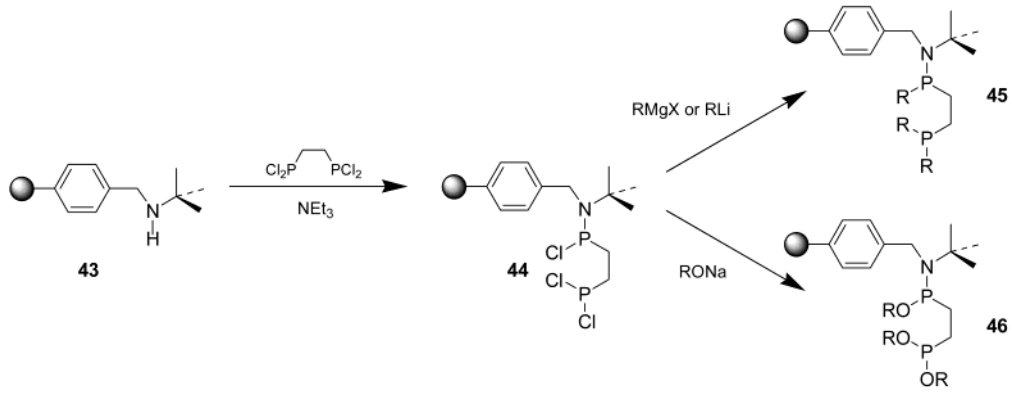


[a] Reagents and conditions: (a) 3 equiv of $NaPPh_2$, dioxane, reflux, 3 h, then 1 M HCl; (b) NaH, THF; (c) Merrifield's resin (1.7 mmol of Cl/g), rt, o/n.

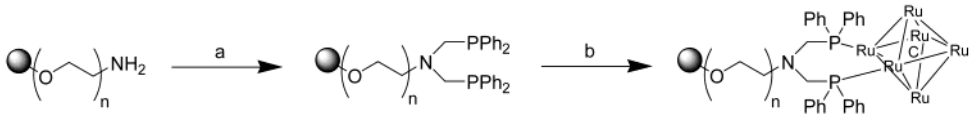
$(PPh_3)Cl_2$, again this differing from the bis-chelate product formed homogeneously from $Ru(PPh_3)_3Cl_2$ and PP, which is $Ru(PP)_2Cl_2$. The reason for this is most likely because of the large distances between neighboring diphosphine units on the support, the relative rigidity of the polymeric backbone, and the inflexibility of the strong chelating diphosphine ligand.

Li and co-workers[56] have recently reported a new approach to the synthesis of polymer-supported bidentate phosphorus-containing ligands (Scheme 21). The polymer-supported phosphine complexes are

Scheme 21



Scheme 22[a]



[a] Reagents and conditions: (a) $HPPh_2$/HCHO, MeOH/toluene, 60 °C, 3 h, then rt, 15 h; (b) $Ru_6C(CO)_{17}$, CH_2Cl_2, rt, 5 d.

prepared from polymer-supported secondary amine **43** by reaction with 1,2-bis(dichlorophosphino)ethane in the presence of NEt_3 to give intermediate **44**. This can then be reacted with a variety of organomagnesium or organolithium reagents to give supported phosphines **45** or with the sodium salts of alcohols to yield supported phosphites **46**. Of interest is that only one phosphorus atom of the bis(dichlorophosphino)ethane is linked to the resin. This has been attributed to the steric constraints of the *tert*-butyl groups on the resin and the excess of diphosphine used. Although the work was directed at the generation of libraries of C_1-symmetric ligands for use in homogeneous catalysis, the polymer-supported phosphines and phosphites being cleaved from the support using PCl_3, the immobilized ligands themselves show significant scope for use in supported catalysis.

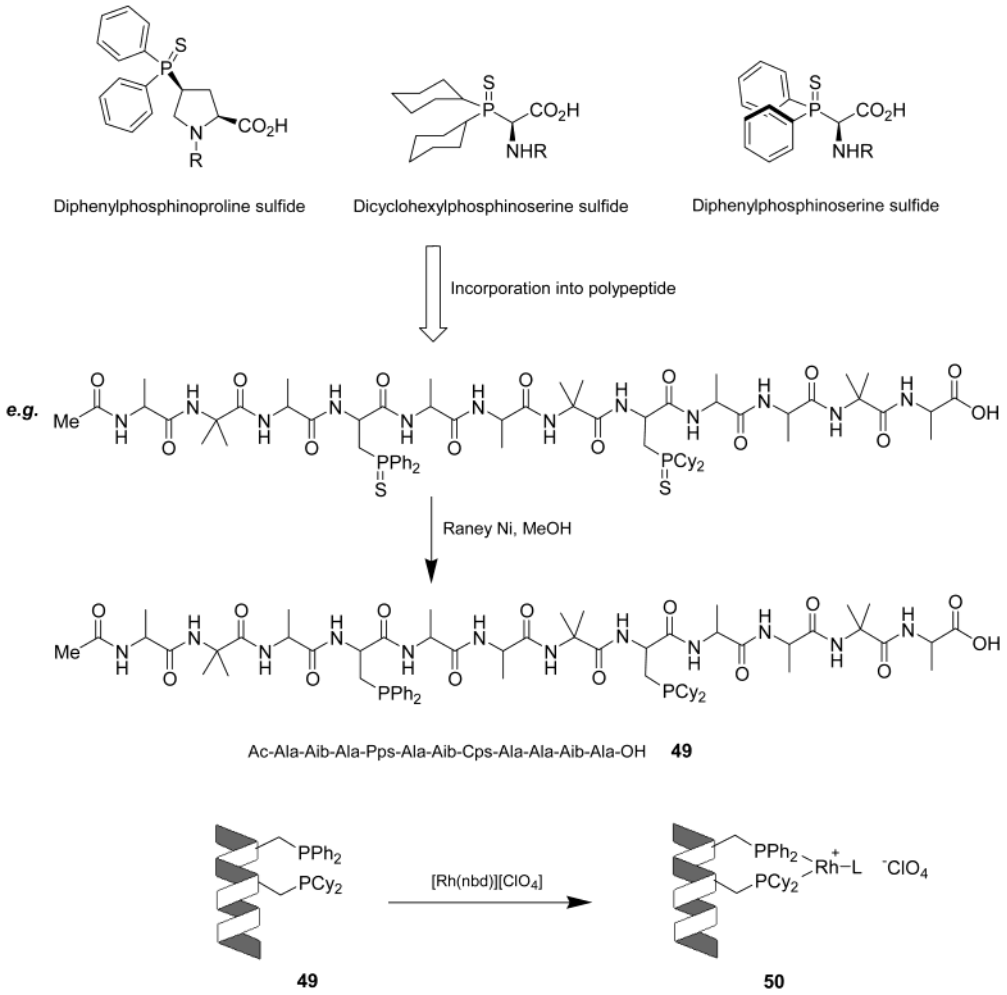
As a continuation of their studies into the immobilization of $Ru_6C(CO)_{17}$ for use in hydrogenation, Johnson, De Miguel, and co-workers[40] have prepared a bidentate phosphine ligand based on a PS−PEG support and immobilized the hexanuclear ruthenium cluster on it. The supported bidentate phosphine **47** was prepared by treatment of amine-functionalized ArgoGel with the phosphido-Mannich intermediate formed from the reaction of $HPPh_2$ with paraformaldehyde, the metal cluster then being attached by agitating the support with an excess of $Ru_6C(CO)_{17}$ for 5 days, giving **48** (Scheme 22). Starting with a phosphine loading of 0.68 mmol/g, a metal loading of 0.12 mmol/g was obtained, indicating that only 18% of the phosphine sites were metalated.

2.5. Phosphines Attached to Polymer-Supported Peptides

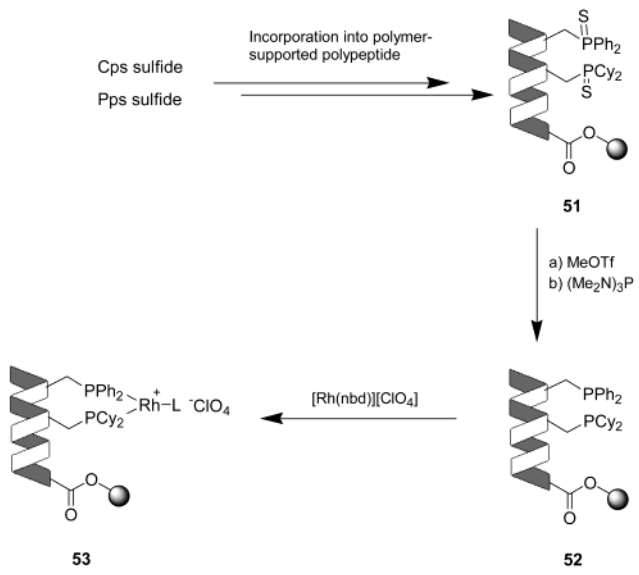
A range of variants of $PS-PR_2$ have been reported based on standard peptide synthesis resins. Gilbertson and co-workers first reported solution-phase routes to incorporation of phosphines into peptides in 1994.[57] They achieved this by initial protection of the phosphine of choice as its sulfide to stop oxidation to its phosphine oxide during subsequent peptide synthesis steps. The phosphine sulfide is then incorporated into an amino acid building block such as serine[57,58] or proline[59] to give the thiophosphine-substituted analogue (Scheme 23). This can then be incorporated into polypeptides using traditional peptide synthesis methods before the sulfur protecting group is then removed from the phosphine groups using Raney nickel to give the free phosphine-substituted peptide. This method has been used to prepare the 12-residue peptide Ac-Ala-Aib-Ala-Pps-Ala-Aib-Cps-Ala-Ala-Aib-Ala-OH (**49**) [Pps = diphenylphosphinylserine, Cps = dicyclohexylphosphinylserine]. Assuming the peptide has an α-helical secondary structure, the phosphine-containing amino acids are placed in positions such that they are on the same side of the helix. Rhodium complex **50** was prepared by treatment of **49** with $[Rh(nbd)][ClO_4]$, prepared from $[Rh(nbd)Cl]_2$ and $AgClO_4$. Less than 1 equiv of metal complex was used in the preparation to prevent coordination to other functional groups in the peptide.

Gilbertson and co-workers have developed this methodology for the synthesis of phosphine-substituted peptides immobilized on polystyrene supports, preparing **52**, the immobilized analogue of **49** (Scheme 24).[60] The synthesis is analogous to the solution-phase case with one notable change. Although suitable for solution-phase synthesis, the use of Raney nickel as a reagent for reducing supported thiophospine-substituted polypeptides to their corresponding free phosphines is not a viable option. Instead, the phosphine sulfide **51** is methylated with methyl trifluoromethanesulfonate to give a phosphonium salt, treatment of which with tris(dimethylamino)-phosphine gives the free phosphine-substituted peptide **52**. The metalated supported peptide **53** has been screened for catalytic activity in hydrogenation reac-

Scheme 23



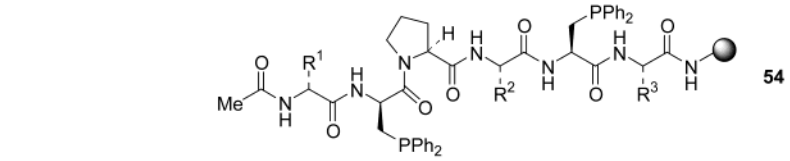
Scheme 24



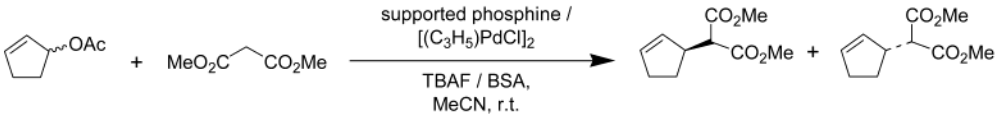
tions and found to be very efficient, 100% conversion being obtained in the hydrogenation of a prochiral enamide, with an enantiomeric excess of 4−9% being observed. This is perhaps rather surprising on two counts. First, the peptide backbone puts the metal in **53** in close proximity to amide and carbonyl functionalities, either of which could potentially coordinate and stop catalysis, but this does not seem to occur. Second, the peptide backbone in **53** contains nine chiral centers, and so the degree of asymmetric induction in the hydrogenation is remarkably low. The low ee observed is not as a result of the immobilization of the peptide since the same result is obtained with **50**.[58]

Gilbertson and co-workers have developed libraries of peptide-based phosphine ligands using a chiron multipin multiple peptide synthesis system, formed metal complexes from them, and screened them for catalytic activity.[61,62] The synthesis of peptides on pins allows the identity of each peptide attached to a given pin to be monitored and kept separate so screening of individual ligand−metal complexes can be performed. In their first-generation library, they prepared supported peptides of general form Ac-Ala-Aib-Ala-[variable peptide sequence]-Ala-Aib-Ala-support where, in the variable sequence, two phosphine-containing peptides are placed in either the *i* and *i* + 1 or *i* and *i* + 4 positions. The two phosphine-containing peptides were either both Pps, both Cps, or one of each. Rhodium complexes of each of the library members were prepared and screened in the hydrogenation of methyl 2-acetamidoacrylate. Only 10 of the 63 library members gave the product in greater than 10% ee. Building on the results from the first library, a second series of peptides were

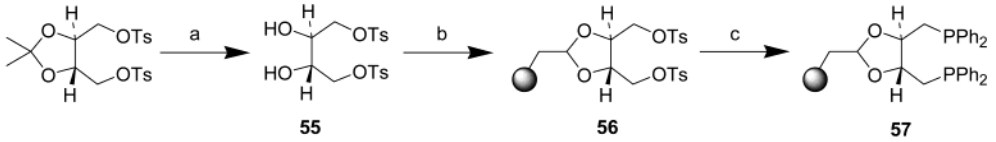
Scheme 25



Ac-Xxx-Pps-Pro-D-Yyy-PPs-Zzz-SUPPORT



Scheme 26[a]



[a] Reagents and conditions: (a) *p*-toluenesulfonic acid, ethanol, reflux, 24 h; (b) benzaldehyde-derivitized polystyrene, *p*-toluenesulfonic acid, benzene, reflux using a Dean−Stark apparatus, 24 h; (c) PPh_2Li, THF, 20 °C, 20 h.

designed where the positioning of the phosphines was such that they would be on the same side of the α-helix. Both 12- and 13-residue peptides containing a *d*-phosphine-containing peptide in the *i* position and a phosphine-containing peptide in either the *i* + 3 or *i* + 4 position were prepared as they were thought to fulfill this criterion. They were metalated and screened in the hydrogenation reaction, but again only a few of the library members led to the product in higher than 10% ee (8 out of 48 members), the highest being 38% ee. When test reactions were performed on solution analogues of three of the best peptides found in the screen of the supported complexes, the selectivities in a range of solvents were found to be very different from those found on the pins. Indeed the catalysis of the soluble peptides in THF gave results that not only did not correlate with those obtained when using the pins but in some cases yielded product of the opposite topicity (handedness). Similar results were obtained in dichloromethane, but in water results similar to those on the pins were obtained. Bearing in mind that the peptides studied are highly hydrophobic, they may well have some tertiary structure when aggregated in water. It has therefore been suggested that these aggregates are similar to the structures formed when the peptides are attached to the pins.

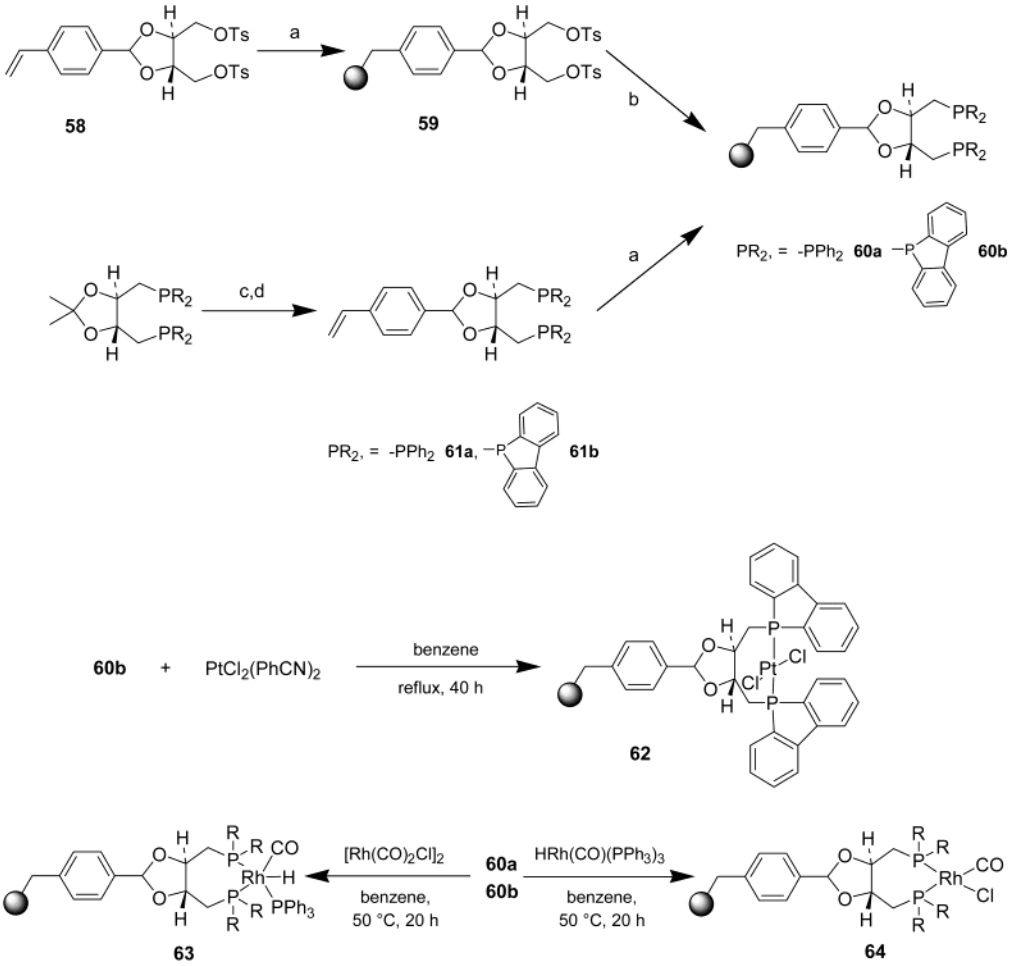
More recently Gilbertson and co-workers have presented a further library synthesis of phosphines which show properties in catalysis very different from those above. They have prepared on pins a library of phosphines (**54**) based on the well-known *β*-turn-forming motif -Pro-D-Yyy- (where Yyy is a D-amino acid), with the phosphine-containing amino acids flanking this element (Scheme 25).[63] The structural features that were varied in the initial library prepared were the amino acids at the N- and C-termini and substitutions of D-amino acids next to the proline of the -Pro-D-Yyy- fragment, the basic structure being shown in Scheme 22. Palladium complexes of the library members were formed on the pins from $[PdCl(\eta^3\text{-}C_3H_5)]_2$ and screened for catalytic activity in the asymmetric addition of dimethyl malonate to cyclopentenyl acetate. The selectivities obtained ranged from 34% ee for the lowest to 80% ee for the highest. To probe whether it was possible in this case to screen the library members accurately without having to remove them from the pins, one of the best ligands found from the investigations was prepared and then removed from the support before treating with the palladium source and screening in the test reaction. The selectivity obtained was identical to that of the supported complex, showing that, in this case, it is possible to undertake screening of libraries while they are attached to the supports they are synthesized on.

2.6. Polymer-Supported Asymmetric Phosphines and Their Metal Complexes

One of the key contributions to early polymer-supported asymmetric phosphine development was made by Kagan and co-workers with their report in 1973 of polymer-supported DIOP **57** [DIOP = 2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane] (Scheme 26).[64] Diol **55**, prepared by ethanolysis of the corresponding acetonide, was attached to polymer-supported benzaldehyde to give the ditosylate **56**, with the acetalyzation taking place in approximately 70% yield. This was then treated with $LiPPh_2$ to give **57**. This was treated with $[RhCl(C_2H_4)_2]_2$ at room temperature in benzene to give a supported Rh−DIOP complex with a metal loading of 0.12 mmol/g. Although not fully characterized, this complex was shown to contain **57**, Rh, Cl, and C_6H_6 and was used successfully as a catalyst in asymmetric hydrogenation and hydrosilylation reactions.

For completeness it should be mentioned here that Stille and co-workers[65−67] have presented two routes to immobilized DIOP ligands **60a** and **60b** by polymerization of suitably derivatized DIOP monomers with styrene and DVB (Scheme 27). In the first approach, the optically active styryl monomer **58**, prepared from **55** and 4-styrylbenzaldehyde, was suspension polymerized with styrene and divinyl-

Scheme 27[a]



[a] Reagents and conditions: (a) styrene, DVB, AIBN, benzene, 60 °C, 10 h; (b) PR_2Li, THF, rt, 5 d; (c) concentrated HCl, ethanol, reflux, 2 h; (d) *p*-toluenesulfonic acid, 4-vinylbenzaldehyde, benzene, reflux, 13 h.

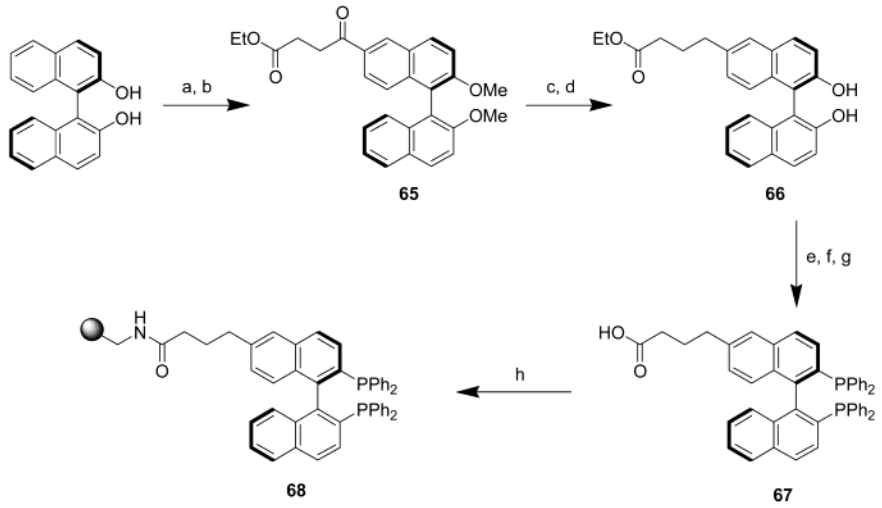
benzene using AIBN as inititator. The resulting polymer **59** was then treated with $LiPR_2$ to give **60a** or **60b**. In the other method, diphenylphosphine styryl monomer **61a** or diphenylphosphole styryl monomer **61b** was prepared from the corresponding enantiomerically pure DIOP by ethanolysis followed by treatment with 4-styrylbenzaldehyde. They were then suspension polymerized with styrene and divinylbenzene, giving **60a** or **60b** respectively. Using both methods, an inclusion of approximately 10 mol % DIOP ligand was obtained. Platinum complex **62** was formed by heating a benzene solution of **60b** and $PtCl_2(PhCN)_2$ for 30 h and subsequently used in the presence of $SnCl_2$ to catalyze the hydroformylation of olefins. Rhodium complexes **63** and **64**, prepared by ligand exchange reactions with $[Rh(CO)_2Cl]_2$ and $HRh(CO)(PPh_3)_3$, respectively, were used in asymmetric hydroformylation reactions. Comparable chemical and optical yields were obtained with the supported complexes and the homogeneous analogues.

Polymer-supported 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP) **68** was first prepared by Bayston and co-workers (Scheme 28).[68] Their methodology involves the preparation of a suitably functionalized BINAP monomer derivative in solution and its attachment to a commercially available polymer support. Starting from enantiomerically pure (*R*)-BINOL, the enantiomerically pure acylated compound **65** was formed in two steps, building in an ester moiety offering the link between the ligand and a support. Reduction of the ketone functionality followed by deprotection of the phenol moieties yielded **66**, formed in good yield and leaving the ethyl ester intact. The phosphine groups were attached to the ligand by formation of the ditriflate and then nickel-mediated double phosphination with $HPPh_2$, giving **67**. The ligand was then attached to aminopolystyrene (0.21 mmol of NH_2/g) under standard conditions for solid-phase amide synthesis to give **68** (ligand loading of 0.18 mmol/g). Aminopolystyrene was chosen as the support of choice since the amide functionality of **68** was considered to be robust to any hydrogenation conditions employed when using the supported ligand.

Chapuis and co-workers[69] have prepared two PEG–PS-supported BINAP ligands from derivatized TentaGel resins and dihydroxy-functionalized BINAP **71** (Scheme 29). Starting from acid-derivatized TentaGel **69**, they attached **70** using DCC and DMAP as coupling agents to form **71**. A ligand loading of 0.1 mmol/g was obtained. Starting from TentaGel–(*S*)-Br, **72**, they formed **73** by first treating **70** with BuLi before adding the resin.

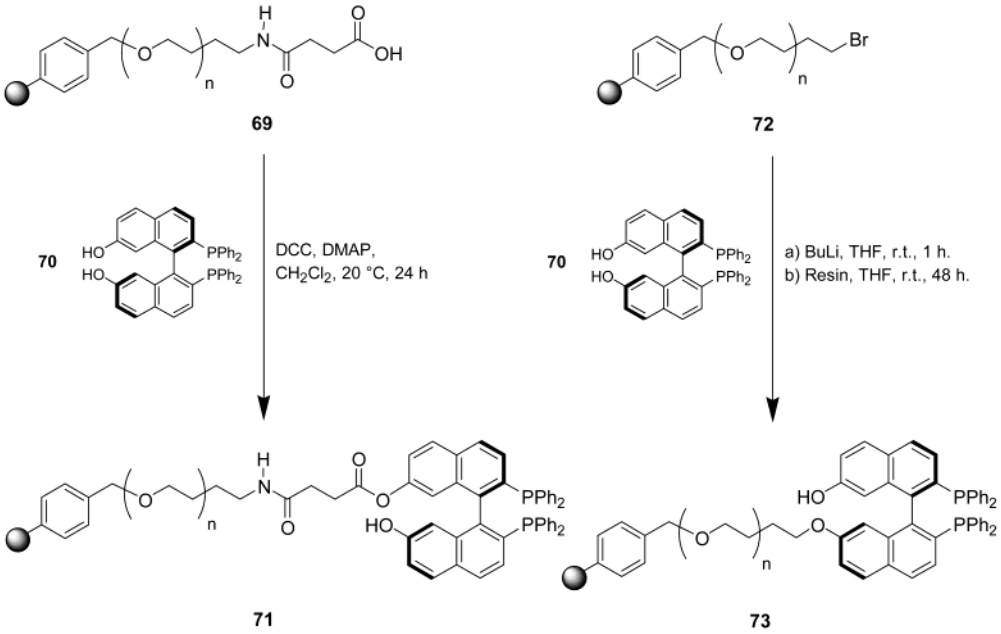
Attempts to form metal complexes of **68** and screen them in catalysis have been limited to date but show the usefulness and versatility of the ligand, which is

Scheme 28[a]



[a] Reagents and conditions: (a) MeI, K_2CO_3, acetone, reflux, 18 h; (b) ethylsuccinyl chloride, $AlCl_3$, CH_2Cl_2, 0 °C → rt, 18 h; (c) Pd on C, H_2, AcOH/EtOH/EtOAc, rt, 18 h; (d) BBr_4, CH_2Cl_2, −78 °C → rt, 3.5 h; (e) Tf_2O, 2,6-lutidine, CH_2Cl_2, 0 °C → rt, 20 h; (f) 2 equiv + 2 equiv of $HPPh_2$, 1.2 equiv of $NiCl_2$(dppe), DABCO, DMF, 100 °C, 24 h; (g) LiOH, THF, reflux, 20 h; (h) polystyrene−NH_2 (loading 0.21 mmol of NH_2/g), DIC, HOBt, Net^{i}Pr$_2$, DMF, rt, 24 h.

Scheme 29

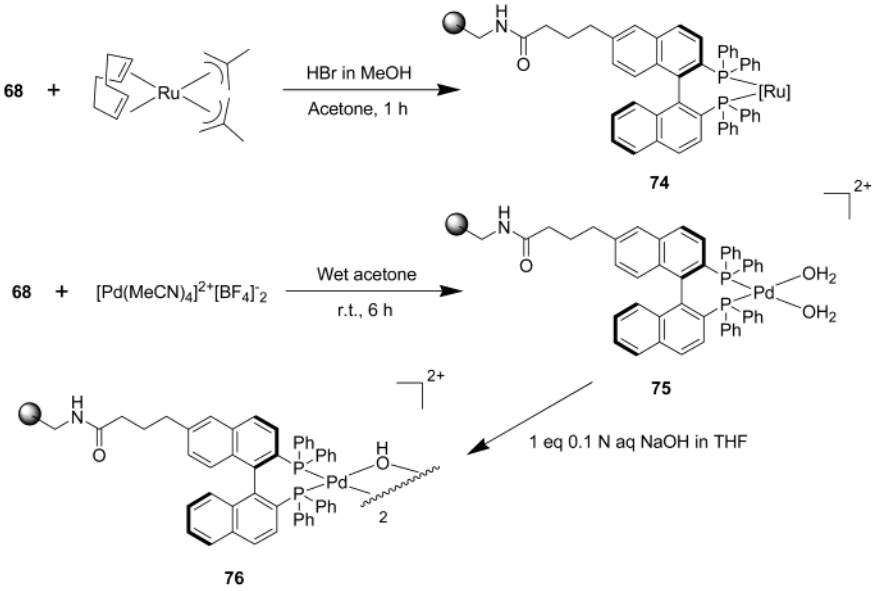


now commercially available[70] (Scheme 30). Bayston and co-workers[68] have formed what they propose to be **74**, a ruthenium diallyl complex of **68**, by mixing (cod)Ru(bismethallyl), HBr, and supported ligand and have found it to be an efficient and enantioselective hydrogenation catalyst. The results show that the perturbation of the ligand from C_2 symmetry to pseudo-C_2 symmetry and the act of immobilization is not detrimental to enantioselectivity or chemical yield, a drop of only 2% in ee being observed in going from a heterogeneous catalyst to the homogeneous analogue (97% vs 99% ee). The catalyst is recyclable with only slight decreases in chemical and optical yields although reaction times need to be extended.

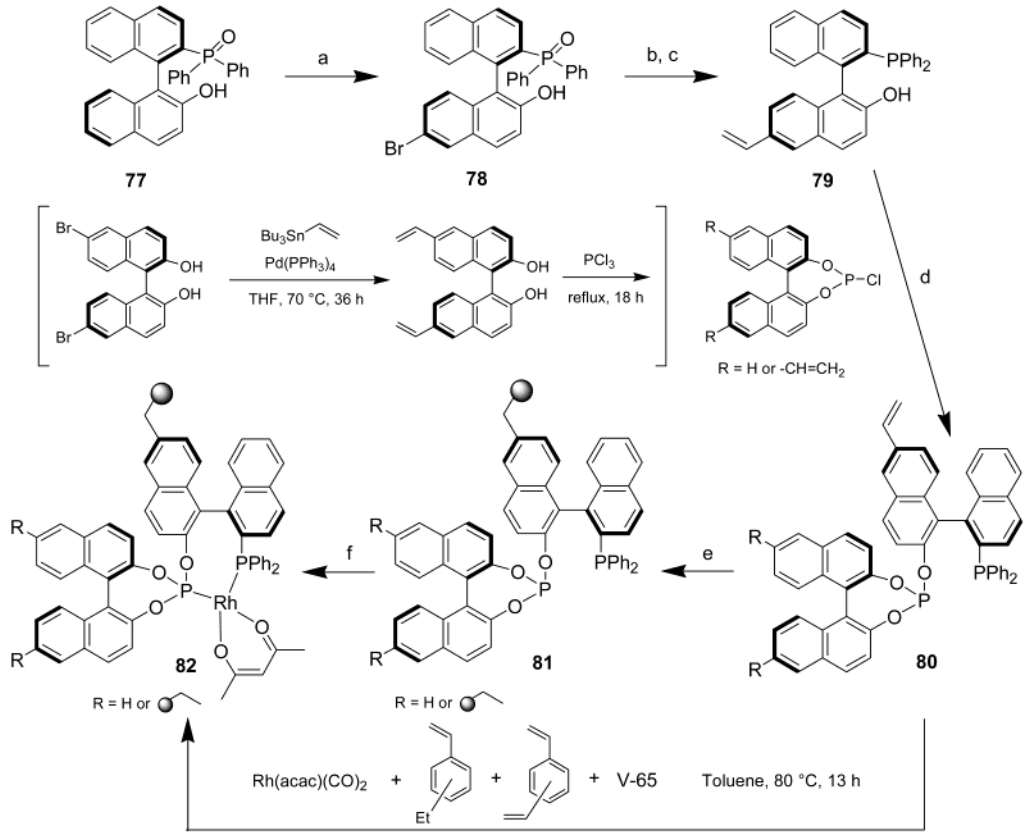
Sodeoka and Fujii have prepared two palladium complexes of **68**.[71] Reaction at room temperature of $[Pd(MeCN)_2]^{2+}(BF_2)^{-}_2$ with **68** in wet acetone yields the diaqua complex **75** with a palladium loading of 0.38 mmol/g. If instead the reaction of $[Pd(MeCN)_2]^{2+}(BF_2)^{-}_2$ and **68** is followed by heating with 0.1 N NaOH in THF, polymer-supported hydroxo complex **76** is formed. Both complexes were used in asymmetric aldol and Mannich-type reactions. In the aldol reactions the addition of a small quantity of water to the reaction mixture containing **75** was found to be essential to obtaining good chemical yields of product, 0.2 equiv being found to give both chemical and optical yields comparable with those of the homogeneous analogue. **76** was found to be active in asymmetric Mannich-type reactions although with slightly lower ee as compared to its homogeneous analogue (81% vs 89% ee). Both the catalysts are recyclable although again longer reaction times are needed on subsequent uses.

The TentaGel-supported BINAPs **71** and **73** were used as ligands for Rh-catalyzed asymmetric isomer-

Scheme 30



Scheme 31[a]

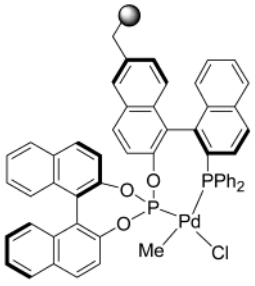


[a] Reagents and conditions: (a) Br_2, dioxane, 5 °C, 2 h; (b) $HSiCl_3$, NEt_3, xylene, 0 °C → 110 °C, 22 h; (c) 2-vinyl-5,5-dimethyl-1,3,2-dioxaborane, $Pd(PPh_3)_4$, DMF, 80 °C, 16 h; (d) NEt_3, Et_2O, 0 °C → rt, 24 h; (e) DVB, ethylstyrene, V-65, toluene, 70 °C, 5 h; (f) $Rh(acac)(CO)_2$, benzene, 0 °C, 1 d.

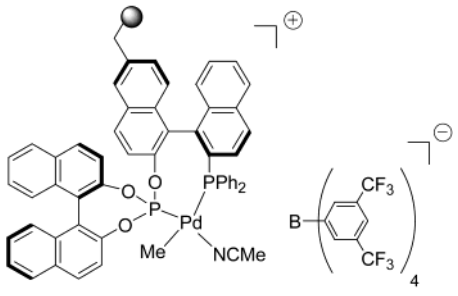
izations, the metal complexes being formed in situ by reaction of the supported ligands with $[Rh(cod)_2]^+[CF_3SO_3]^-$. Both these and their silica-immobilized counterparts were found to be less reactive than their homogeneous analogues although the selectivity was found to be the same.

Nozaki and co-workers[72,73] have prepared an immobilized analogue of BINAPHOS, **81** (Scheme 31). The synthesis starts from the phosphine oxide−hydroxybinaphthyl complex **77**, bromination of which gives **78** with the bromo substituent in the 6-position of the naphthol ring. Reduction to the corresponding phosphine and Suzuki coupling with a vinyl boronic ester then gives monovinylphosphine **79**. This is coupled with either an unsubstituted or a divinyl-substituted chlorophosphite to give derivatized BINAPHOSs **80**, which are copolymerized with DVB and ethylstyrene using 2,2′-azobis(2,4-dimethylpen-

tanenitrile), V-65, as the initiator to give the corresponding immobilized BINAPHOS analogues **81**. The resulting polymers contained a high degree of cross-linking. The supported Rh−BINAPHOS complexes **82** were prepared by reacting **81** with $Rh(acac)(CO)_2$ and used in asymmetric hydroformylation reactions. An alternative synthesis of **82** from **80** is also reported. First, **80** was treated with $Rh(acac)(CO)_2$ to form the metal-coordinated BINAPHOS complex, which was copolymerized with DVB and ethylstyrene again using V-65 as initiator. The **82** prepared in this way showed higher catalytic activity and enantioselectivity than that prepared by immobilization of the ligand followed by metal attachment. This is not that unexpected because this second route leads to a polymer with higher metal loadings as all the BINAPHOS ligand centers are coordinated to Rh and also the environment around the metal centers will be more accessible. In the route where the ligand is first incorporated into the polymer (**81**) and then loaded with metal (**82**), the ligand is frozen as a matrix of different conformations, only some of which are accessible to Rh. The authors report no difference in activity or selectivity on variation of the degree of cross-linking. Also they find that any remaining vinyl groups in the supported catalysts, left from the polymerization step, are hydroformylated under the reaction conditions but report that this does not cause any change in activity of the catalyst as evidenced by the reusability of the supported complex a number of times with similar activity. The workers have subsequently prepared **83**, a palladium complex of **81**, by treatment of the supported ligand with PdMeCl(cod).[74] A cationic derivative of this, **84**, was prepared by treatment of **83** with $NaBAr_4$ ($Ar = 3,5\text{-}(CF_3)_2C_6H_3$) and used as a catalyst in alternating copolymerization of ω-perfluoroalkyl-1-alkenes with CO.



83



84

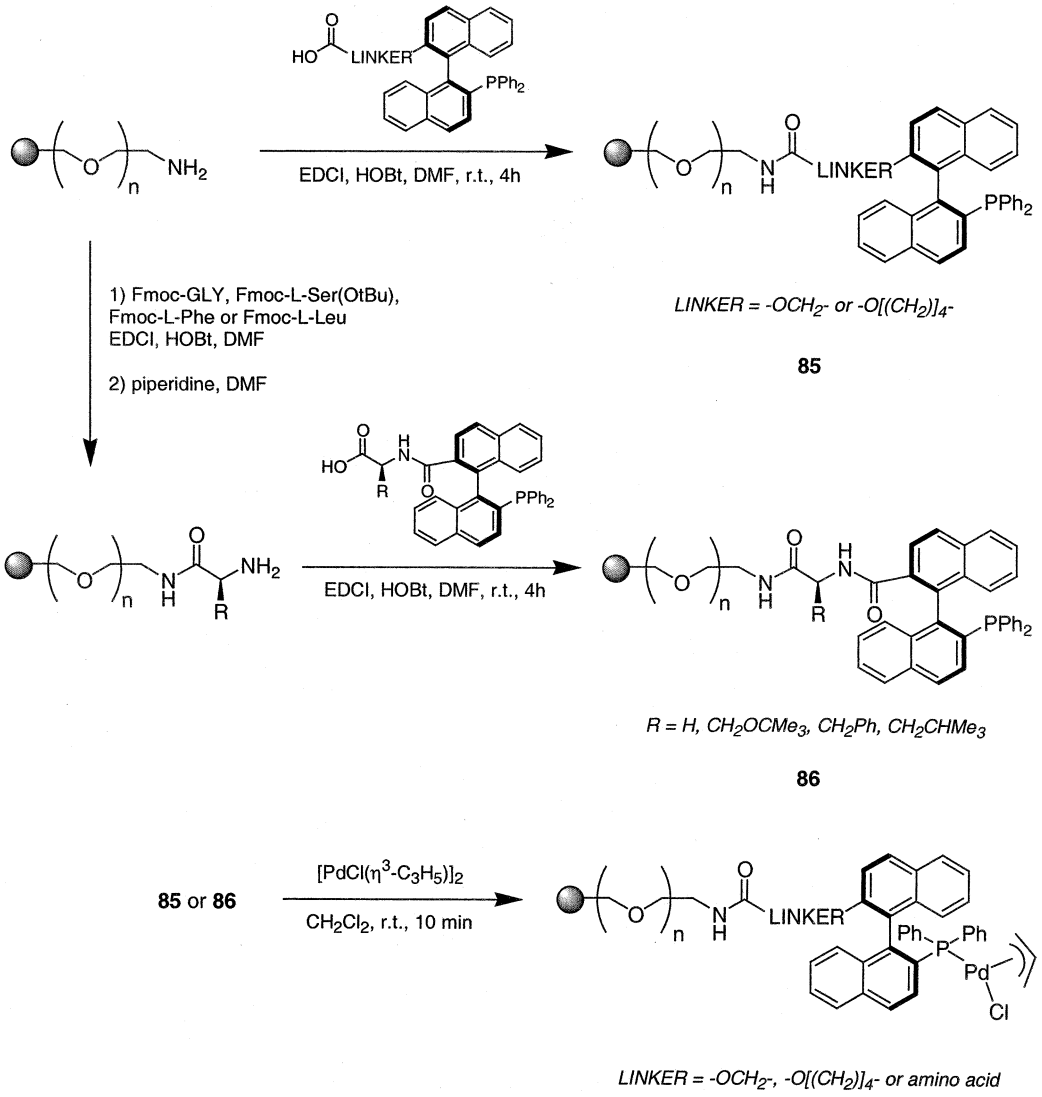
With a similar methodology to that for the preparation of **15**, Uozumi and co-workers[75] have prepared amphiphilic supported 2-diarylphosphino-1,1′-binaphthyls **85** (so-called MOP ligands) and corresponding coordinated palladium complexes (Scheme 32). Starting from an amine-functionalized PS−PEG support, ligands have been prepared with total conversion using acid-functionalized 2-diarylphosphino-1,1′-binaphthyls under standard conditions for solid-phase amide synthesis. Using an analogous methodology, a library of supported MOP ligands (**86**) bearing an α-amino acid unit between the resin and the phosphine have also been prepared. Allylpalladium complexes of the PEG−PS−MOP supports have been prepared by treatment of the supported phosphine with $[PdCl(\mu^3\text{-}C_3H_5)]_2$ in dichloromethane at room temperature for 10 min. Analysis of the Pd-bound phosphines showed that all P sites are occupied, the ratio of P to Pd being 1:1.

2.7. Polymer-Supported Amino- and Iminophosphines

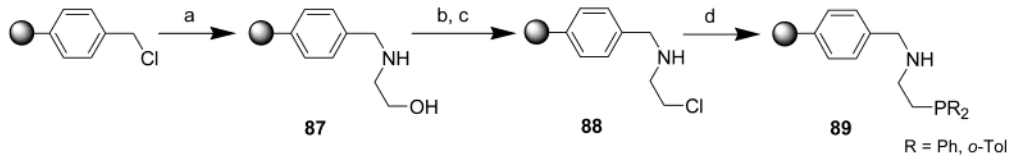
A range of polymer-supported β-aminophosphines have been prepared by Mansour and Portnoy (Scheme 33).[76] The point of attachment chosen was the nitrogen as this offered the most synthetic simplicity together with the greatest diversity of possible building blocks that can be used. Starting from Merrifield's resin, the polymer-supported amino alcohol **87** was formed by reaction with ethanolamine. Chlorodehydroxylation with $SOCl_2$ followed by deprotonation of the chloroethylammonium salt formed gave chloroamine **88**. Reaction of this with $LiPR_2$ (R = Ph, *o*-Tol) gave the desired supported β-aminophosphine **89**. A number of derivatives have been prepared varying the substituents at nitrogen, the α-carbon, and phosphorus. Each step of the reactions was thoroughly monitored spectroscopically by a combination of gel-phase ^{13}C and ^{31}P NMR techniques. Of particular interest is that a number of the steps in the preparation of **89** and its analogues proceed much better than their solution counterparts. The chlorodehydroxylation of **87** occurs almost quantitatively compared to 35% for its solution analogue, similar observations being made in the deprotonation step to give **88**. These differences have been attributed to the site isolation on the solid support, thus preventing oligomerization of intermediates or products formed in the reactions, this being known to be a problem in solution.

Chung and co-workers[77] have prepared some supported chiral ferrocenylphosphinimines **90** by condensation of ferrocenylphosphinecarboxaldehydes with amine-derivatized supports (Scheme 34). Both aminomethylated polystyrene and 4-methylbenzhydrylamine polystyrene were used, but not surprisingly on steric grounds, loadings with the former were significantly greater than those with the latter. Palladium complexes of the supported ferrocenylphosphinimines were prepared in situ by treating the ligands with $[(\eta^3\text{-}C_3H_5)PdCl]_2$ and used for asymmetric allylic alkylation.

Scheme 32



Scheme 33[a]



[a] Reagents and conditions: (a) ethanolamine, DMF, 50 °C, 17 h; (b) $SOCl_2$, $CHCl_3$, 60 °C, 2 h; (c) N^iPr_2Et, THF, rt, 2 h; (d) $LiPR_2$, THF, rt, 24 h.

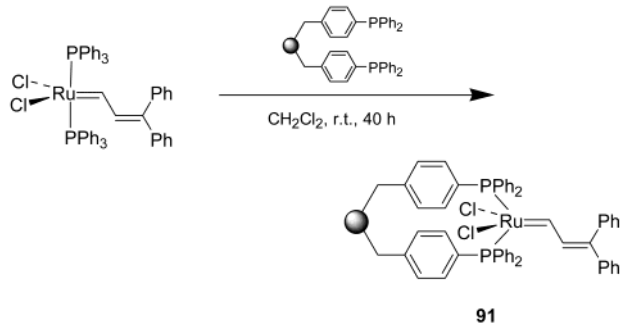
Scheme 34

90

3. Olefin Metathesis

In the past decade, olefin metathesis catalysis using transition-metal alkylidene complexes has become a very powerful tool for carbon−carbon-bond-forming reactions.[78,79] As research effort has increased in the area, a number of approaches to immobilization of olefin metathesis catalysts have appeared in the literature. The first, in 1995, was by Grubbs and Nguyen[80] using PS−PPh_2, treating it with a solution of carbene $Cl_2(PPh_3)_2Ru{=}CHCH{=}CPh_2$, giving **91** (Scheme 35). They have also prepared the PS−PCy_2 and PS−*p*-CH_2PCy_2 (Cy = cy-

Scheme 35



clohexyl) analogues of **91**. Loadings of metal of between 0.1 and 0.56 mmol/g of resin were obtained.

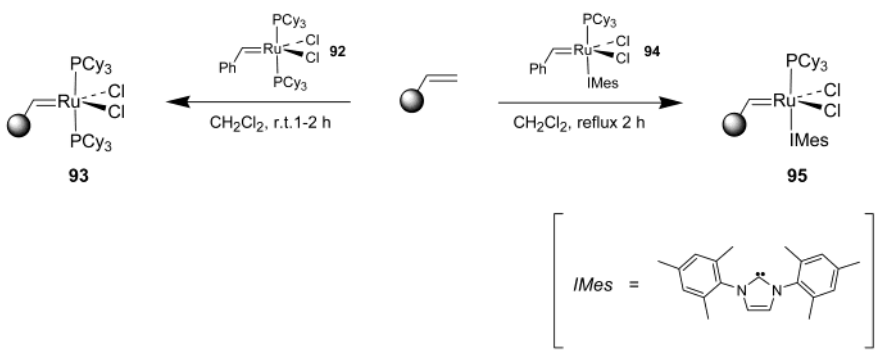
Barrett and co-workers have prepared a polymer-supported version, **93**, of Grubbs' carbene, $RuCl_2(PCy_3)_2Ru{=}CHPh$ (**92**), by attachment through the alkene functionality (Scheme 36).[35] Simply shaking vinylpolystyrene with **92** (approximately 10 mol % based on calculated vinyl resin sites) leads to the formation of **93** with complete incorporation of the metal. More recently they have prepared an analogous supported complex, **95**, but containing an *N*-heterocyclic carbene (NHC) ligand in the place of a phosphine, ruthenium−NHC complexes such as **94** having increased metathesis activity and air and moisture stability over their phosphine analogues (Scheme 36).[36] Complexes **93** and **95** are termed "boomerang" catalysts since the active alkylidene is released from the support into solution during the course of the reaction and then recaptured on completion.

Nolan and co-workers have also reported the preparation of boomerang-type supported catalysts for use in metathesis.[81,82] They have focused attention on immobilization of the metal complex on a macroporous polymer rather than lightly cross-linked supports such as those derived from Merrifield's resin, the advantage being that swelling is not necessary to ensure accessibility of pore sites. The resin used was prepared from divinylbenzene using toluene as a porogen, the bulk polymer having a high degree of cross-linking (55%) (Scheme 37). Metal complexes **92**, **94**, **96**, **97**, and **98** were immobilized on the support using a simple impregnation protocol involving heating the metal complex with the support in toluene for 1 h followed by filtration, washing, and then drying to give the supported complexes with metal loadings of 0.5, 0.35, 1.2, 0.12, and 0.46 mmol/g for **92**, **94**, **96**, **97**, and **98**, respectively. The increased loading of **96** onto the support has been attributed to the increased cross-metathesis activity of the parent metal complex. Likewise, the low loading of **97** has been attributed to the low activity of the parent complex. In ring closing metathesis reactions they find that in many cases the supported complexes containing **92**, **94**, and **96** show activity similar to that of their homogeneous analogues. In the case of **97** and **98** the activity of the metal complex is often increased by immobilization. Although all the immobilized complexes can be recycled, that inorporating **96** exhibits particularly effective recylability while that incorporating **98** displays significant loss of activity after initial use. The supported complexes however perform poorly with substrates such as oxygen-containing dienes, where a stable oxygen-ligated ruthenium carbene complex can be formed. This complex proves to be more stable and less reactive than the supported ruthenium carbene complex, and as a result, the metal stays in solution rather than being attached back onto the polymer support. Consequently the active sites on the polymer support are depleated, leading to a loss of activity in subsequent cycles.

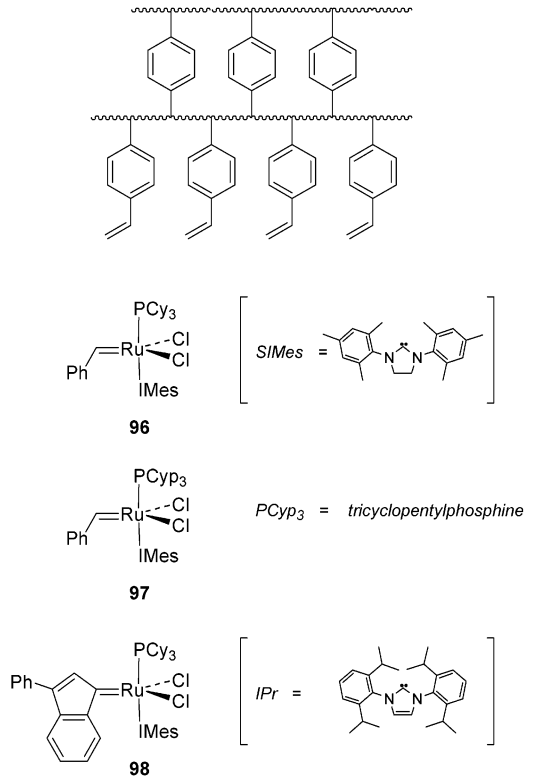
Blechert and co-workers have prepared an immobilized metathesis catalyst bearing an NHC ligand, **103** (Scheme 38).[83] Their methodology employed for the preparation of **103** revolves around construction of the NHC ligand on the support and then appending the metal. Attachment of amine **99**, prepared from 2,3-dibromo-1-propanol and 2,4,6-trimethylaniline, to Merrifield's resin gives **100**, cyclization of which followed by anion exchange yields the supported dihydridoimidazolium chloride **101**. This is then converted to the corresponding dihydroimidazoline **102**, which is, in essence, a protected carbene. Treatment of this with **92** yields **103**. Loadings of metal complex of between 0.14 and 0.40 mmol/g are reported based on a loading of Cl on the parent Merrifield's resin of 0.50−0.90 mmol/g.

Dowden and Savovic[84] have developed a polymer-supported version, **107**, of Hoveyda's robust olefin metathesis catalyst **104** (Scheme 39). This was achieved starting from δ-hexanolactone, opening the ring with NaOMe followed by Mitsunobu reaction with 2-vinylphenol and saponification to give derivatized styrene **105**, which was attached to aminomethylpolystyrene to give the supported ligand **106**. Attachment of the metal was by olefin metathesis

Scheme 36



Scheme 37

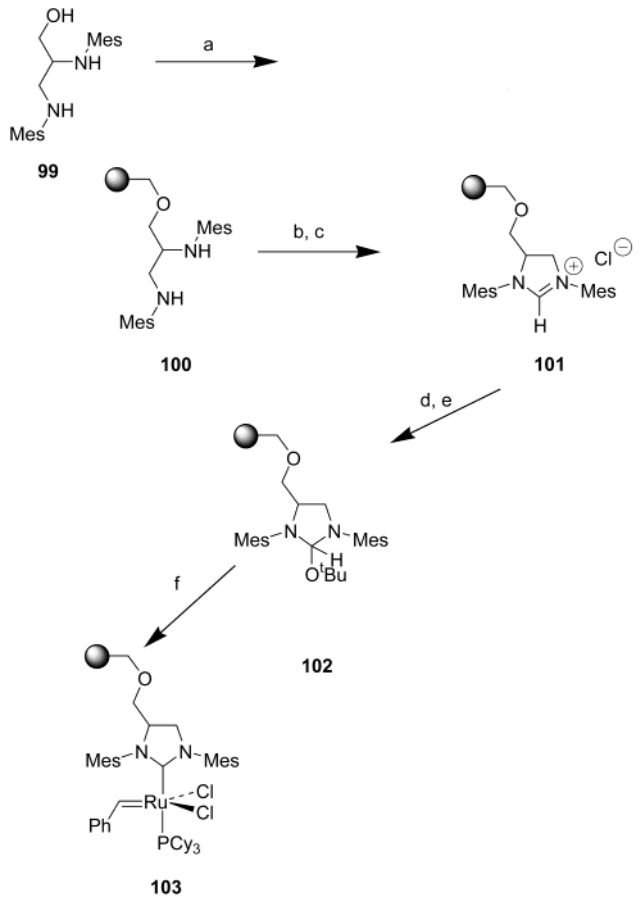


reaction of **106** with **92** to give **107**, with maximum loadings of 0.2 mmol of Ru/g of resin being obtained after five successive treatments of ligand with the metal complex. The low loading and need for the arduous synthesis is attributed to the accumulation of free phosphine during the course of the reaction, something that is known to inhibit olefin metathesis.[85]

Blechert and co-workers extended their methodology for immobilization of NHC complexes to the preparation of a supported NHC analogue (**108**) of the Hoveyda catalyst **104** (Scheme 40).[86] The supported NHC ligand was prepared in the same manner as for **103**, the metal complex then being attached to the support via a ligand exchange reaction. Metal loadings of 0.7 mmol/g of resin were obtained. The authors also report a metal complex (**110**) bound to the support via the styrene ligand **109**. The supported ligand was prepared by coupling of 2-isopropoxy-5-hydroxystyrene to Wang resin (loading 0.72 mmol/g), used in place of Merrifield's resin to maximize accessibility of the metal sites. Attachment of the metal to form **110** was again by ligand exchange but using CuCl as a phosphine scavenger. Using this method, it was possible to obtain a metal loading of 0.35 mmol/g in one treatment of ligand with the metal complex.

Hoveyda, Shrock, and co-workers have very recently reported the preparation of **118**, the first polymer-supported chiral catalyst for enantioselective olefin metathesis.[87] **118** is based on **111**, an enantioselective catalyst prepared and screened by the same workers. The route to the preparation of **118** is shown in Scheme 41. The strategy taken was to prepare a system where the chiral ligand was attached to the polymer by a nonlabile tether that imposes little or

Scheme 38[a]



[a] Reagents and conditions: (a) 1.0 equiv of KO^{t}Bu, DMF, rt, 20 min, then 0.5 equiv of Merrifield's resin (1% DVB), ^{t}Bu$_4$NI, DMF, 60 °C, 12 h; (b) NC(OMe)$_3$, HCOOH, toluene, 100 °C, 100 mbar, 15 h; (c) 0.1 M HCl in THF, rt, 5 min; (d) TMSOTf, 2,6-lutidine, CH_2Cl_2, rt, 30 min; (e) KO^{t}Bu, THF, rt, 1 h; (f) 1.5 equiv of **92**, toluene, 70−80 °C, 1 h.

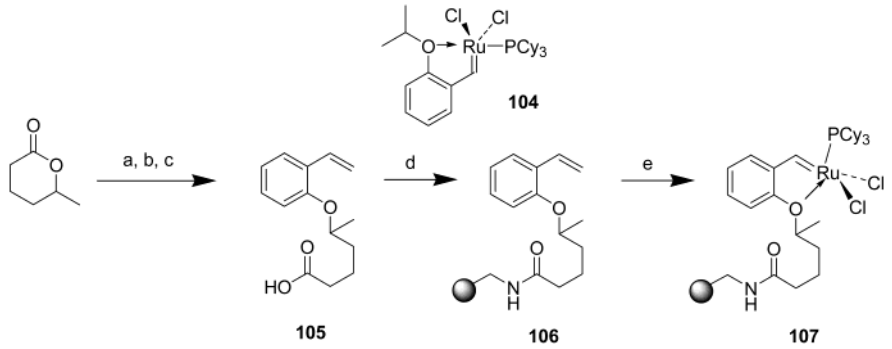
no steric influence on the metal center. Treatment of biphenol **112** with bromine and sodium acetate in acetic acid yields the nonaromatic bromide **113**, which, after 5 days in the solid state, rearranges to give **114**. Reaction of this with 4 equiv of *p*-vinylbenzylmagnesium chloride and subsequent protection of the phenol groups as methoxymethyl (MOM) ethers leads to the formation of **115**. This was then copolymerized with styrene before removal of the MOM protecting groups to give the supported chiral ligand **116**. The supported metal complex **118** was prepared by deprotonation of **116** with KN(TMS)$_2$ followed by treatment with **117**. A metal loading of 0.23 mmol/g was obtained. The supported complex proves active in asymmetric ring closing metathesis reactions, showing lower activity than the homogeneous analogue but as good an enantioselectivity. **118** can be recycled, but increasing degrees of leaching occur on each use.

4. Polymer-Supported BINOL and TADDOL Ligands and Metal Complexes

4.1. Polymer-Supported BINOL Complexes

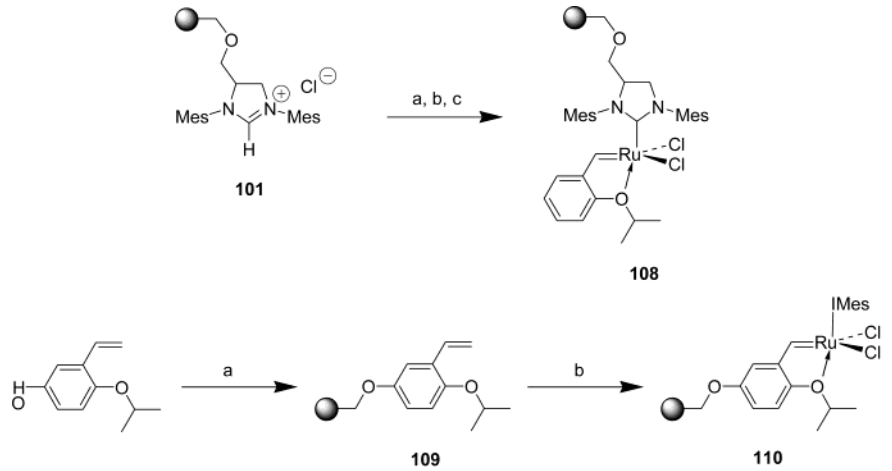
Ligands based on the 1,1′-bi-2-naphthol (BINOL) structural motif have been used with success in a

Scheme 39[a]



[a] Reagents and conditions: (a) NaOMe, MeOH, 0 °C → rt, 6 h; (b) 2-vinylphenol, *d*-isopropyl azodicarboxylate, PPh_3, THF, 0 °C → rt, 14 h; (c) 1 M NaOH in dioxane, rt, 12 h; (d) polystyrene−NH_2, DIC, HOBt, CH_2Cl_2/DMF (1:1), rt, 12 h; (e) **92**, dichloroethane, rt, 12 h.

Scheme 40[a]



[a] Reagents and conditions for the top reaction: (a) TMSOTf, 2,6-lutidine, CH_2Cl_2, rt, 30 min; (b) KO^{t}Bu, THF, rt, 1 h; (c) 2 equiv of **104**, toluene, 70−80 °C, 1 h. Reagents and conditions for the bottom reaction: (a) Wang resin, Misunobu coupling; (b) 1.1 equiv of **94**, 1.1 equiv of CuCl, CH_2Cl_2, reflux, 3 h.

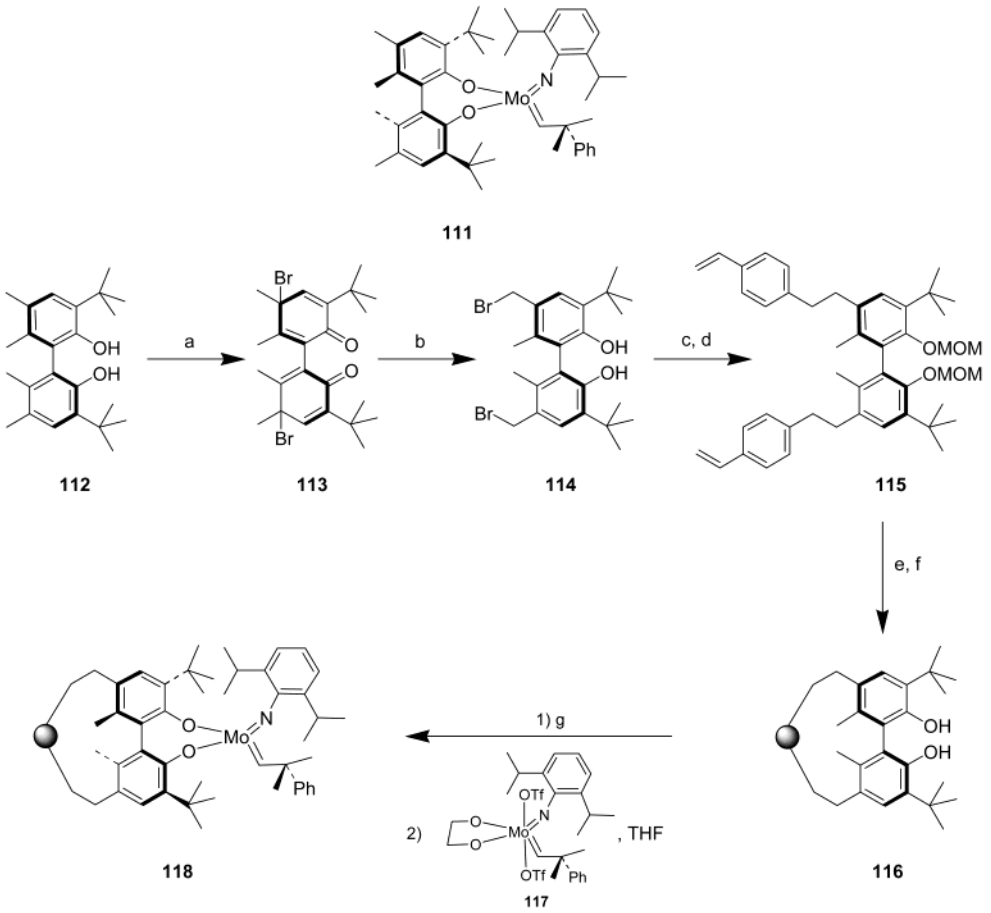
wide range of stereoselective metal-mediated transformations.[88] Polymer-supported BINOLs have been prepared in a variety of ways, most using BINOL as a starting material. Attachment can be at either the 3 or 6 positions of the biaryl rings, both having their potential merits. The advantage of attaching at the 6 position is that the point of immobilization is far from the active center, therefore minimizing adverse effects on moving from homogeneous to heterogeneous catalysis. The introduction of bulky substituents at the 3 and 3′ positions of BINOL is known to increase steric control and hence enantioselectivity, so it follows that a polymer backbone attached here would behave as a very bulky group and thus may have an advantageous effect on activity. In terms of catalytic activity, results from ligands attached at either of these points compare well with homogeneous analogues, and in some cases enantioselectivities are improved. The polymer-supported BINOLs discussed here are complimented by the classes of soluble polymeric BINOLS that have been prepared by Pu and co-workers.[89]

Kobayashi and co-workers[90] have prepared a number of 3,3′-diaryl-substituted BINOLs **122** (Scheme 42) by using the initial steps of the Moses BINAP synthesis[68] followed by MOM protection of the phenolic moieties and reduction of the ester group using $LiAlH_4$ to generate **119**. Bromination of the 3,3′ positions of the biaryl rings was achieved using BuLi/BrF_2CCF_2Br treatment after protection of the hydroxyl group as its TBS ether. Following deprotection of the hydroxy functionality, the substituted BINAP **120** was attached to Merrifield's resin to give **121** before aryl substituents were introduced using a Suzuki coupling reaction, and finally the deprotection of the MOM groups yielded **122**. The polymer-supported BINOLs were treated with $Zr(O^tBu)_4$ to generate metal-substituted analogues **123**.

Chan and co-workers have reported the synthesis of two polymer-supported BINOLs, **125** and **127**. In both cases the ligand is anchored to the support through the 3 or the 3 and 3′ positions of the biaryl rings (Scheme 43).[91] Starting from bis-MOM-protected BINOL, they prepared acid-derivatized BINOLs **124** and **126** by lithiation, carboxylation, and then quenching with HCl in isopropyl alcohol. These were reacted with aminomethylated polystyrene using standard peptide coupling procedures. Loadings of BINOL of approximately 0.36 mmol/g were obtained. Titanium complexes of **125** and **127** were prepared using $Ti(O^iPr)_4$ as the metal source and the resulting complexes used for enantioselective diethylzinc addition to aldehydes.

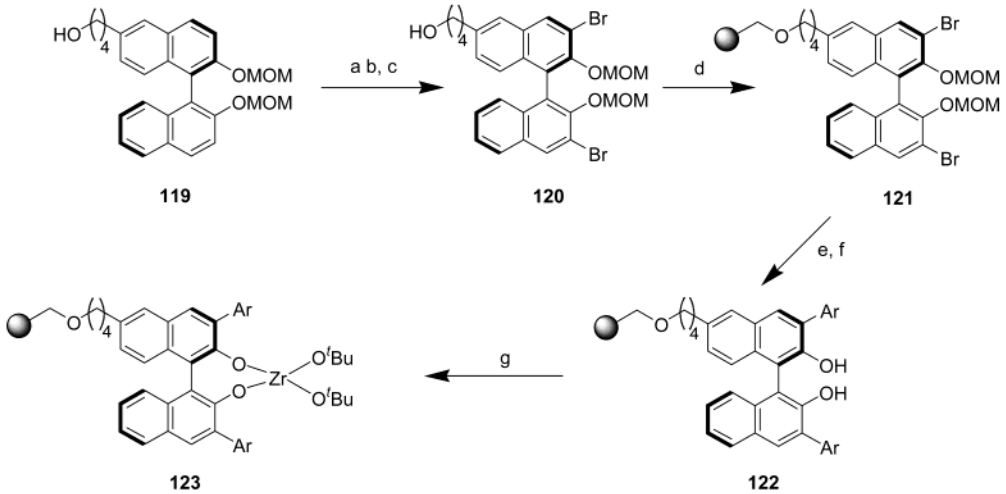
Shibasaki and co-workers[92] have immobilized a linked BINOL ligand to give **131**, choosing as their

Scheme 41[a]



[a] Reagents and conditions: (a) Br_2, 2 equiv, NaOAc, AcOH, rt, 30 min; (b) 5 d in the solid state; (c) *p*-vinylphenylmagnesium chloride, THF, −20 °C, MeOH, 1 h; (d) KH, MOMCl; (e) benzoyl peroxide, styrene, poly(vinyl alcohol), H_2O, toluene, 90 °C, 24 h; (f) MeOH, HCl, THF, rt, 48 h; (g) $KN(TMS)_2$, THF, rt, 24 h.

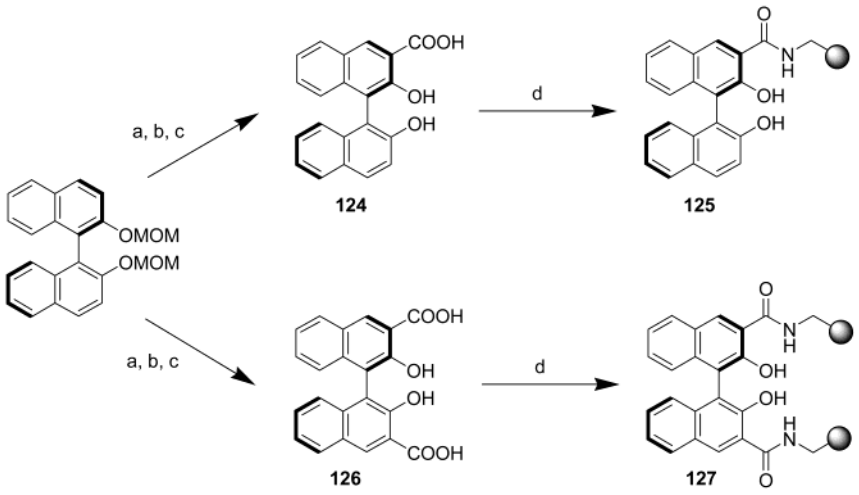
Scheme 42[a]



[a] Reagents and conditions: (a) TBSCl, imidazole, DMF, rt, 2 h; (b) (i) BuLi Et_2O, rt, 3 h; (ii) BrF_2CCF_2Br, THF, 0 °C → rt, 4 h; (c) Bu_4NF, THF, rt, 4 h; (d) Merrifield's resin, NaH, Bu_4NI, DMF, rt, 24 h; (e) $Pd(PPh_3)_4$, $ArB(OH)_2$, Na_2CO_3, DMF, reflux, 24 h; (f) concentrated HCl, MeOH, 60 °C, 6 h; (g) $Zr(O^tBu)_4$, benzene.

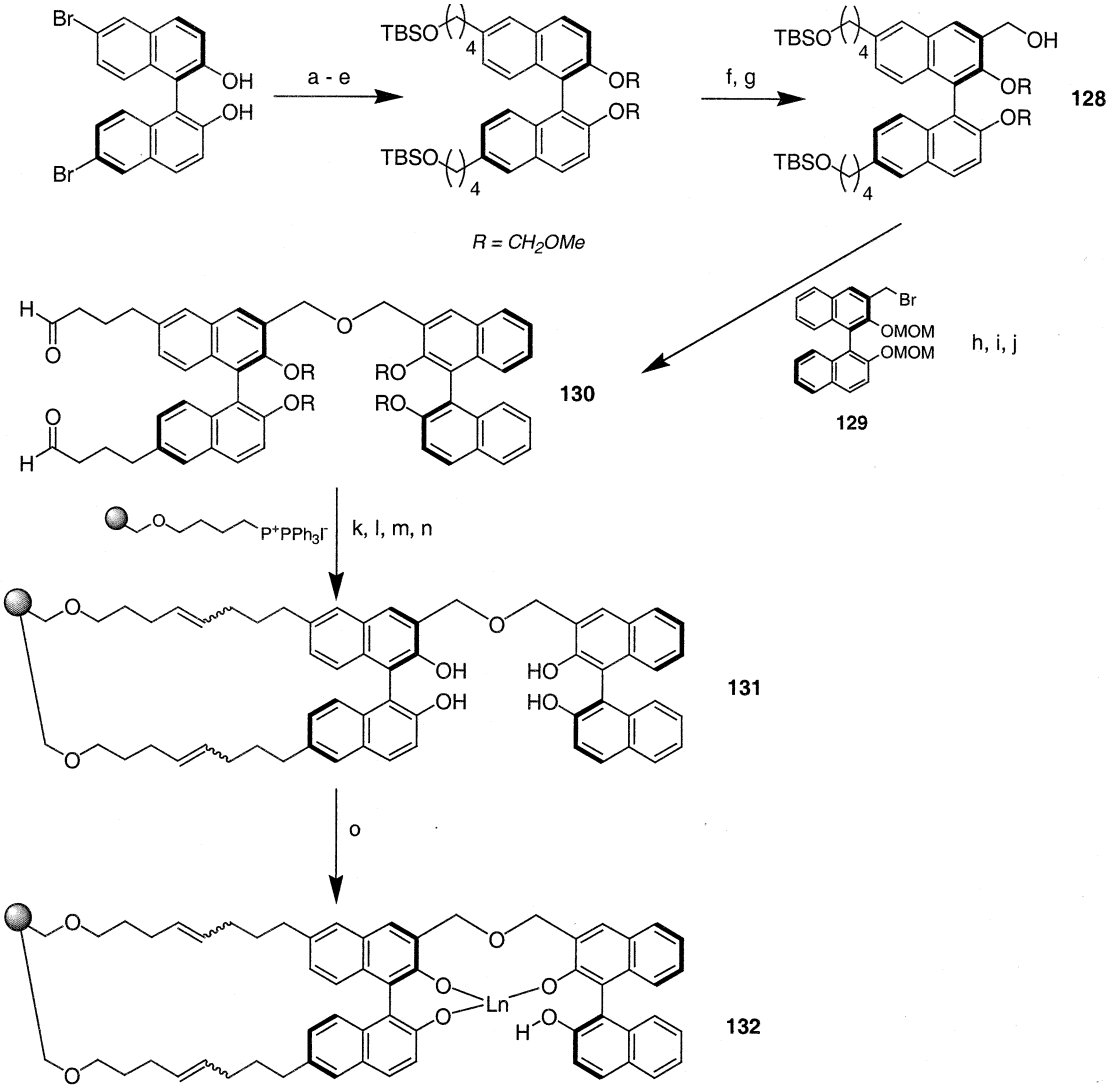
point of immobilization the 6 and 6′ positions (Scheme 44). Starting from 6,6′-dibromo-BINOL, **128** is formed in seven steps and the linked BINOL complex formed from this by treatment with 3-bromomethyl-functionalized BINOL **129**. In the immobilization steps of the synthesis, aldehyde-derivatized linked BINOL **130** is attached to a triphenylphosphonium iodide-derivatized polymer support via a Wittig reaction and the BINOL hydroxy groups are deprotected. A long (C_8) spacer is built into the BINOL complex to maximize accessibility when attached to the polymer support. Lanthanum complex **132** and mixed lanthanum−zinc complexes of **131** have been prepared and used in asymmetric Michael reactions.

Scheme 43[a]



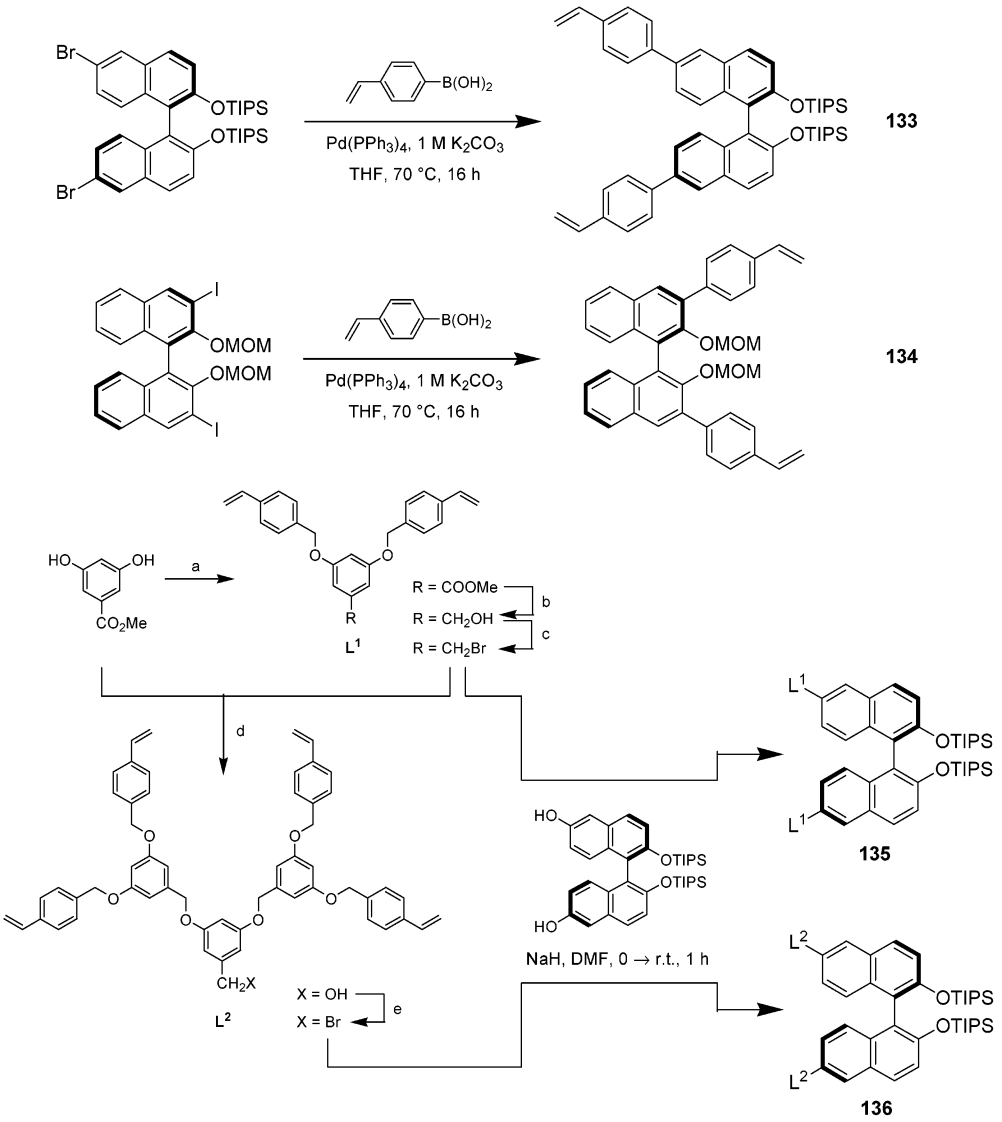
[a] Reagents and conditions: (a) BuLi, THF, 0 °C, 2 h; (b) dry CO_2, THF; (c) saturated HCl/^{i}PrOH, rt, 2 h; (d) aminomethylated polystyrene (1 mmol of NH_2/g), DCC, HOBt, CH_2Cl_2, rt, 24 h.

Scheme 44[a]



[a] Reagents and conditions: (a) MOMCl, NEt^iPr_2, CH_2Cl_2, rt; (b) CH_2═$CHCH_2CH_2MgBr$, 4 mol % $PdCl_2$(dppf), THF, 50 °C; (c) 9-BBN, THF, rt; (d) aqueous NAOH, 30% H_2O_2, rt; (e) TBSCl, imidazole, DMF, rt; (f) BuLi, THF, −78 °C, then DMF, rt; (g) $NaBH_4$, THF/MeOH, 0 °C; (h) 3-bromomethyl-BINOL, NaH, THF/DM, rt; (i) Bu_4NF, THF, rt; (j) PCC, 4 Å molecular sieves, CH_2Cl_2, rt; (k) LHMDS, THF, rt; (l) 4 equiv of supported phosphonium salt, THF, −10 °C → rt; (m) acetaldehyde; (n) TsOH, CH_2Cl_2, 40 °C; (o) Ln(O^iPr)$_3$, THF, rt, 12 h.

Scheme 45[a]



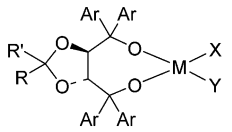
[a] Reagents and conditions: (a) 4-vinylbenzyl chloride, K_2CO_3, 18-crown-6, acetone, 70 °C, 48 h; (b) $LiAlH_4$, THF, 70 °C, 4 h; (c) CBr_4, PPh_3, THF, rt, 20 h; (d) K_2CO_3, 18-crown-6, acetone, 70 °C, 48 h; (e) CBr_4, PPh_3, THF, rt, 48 h.

Seebach and co-workers[93] have prepared a range of polystyrene-immobilized BINOLs by suspension polymerization of suitably functionalized BINOL derivatives with styrene (Scheme 45). The functionalized BINOLs were formed in one of two ways. BINOL **133** was prepared from 6,6′-dibromo-BINOL with the OH groups protected as their TIPS ethers by $Pd(PPh_3)_4$-catalyzed Suzuki coupling with 4-styreneboronic acid. Similarly, **134** was prepared by Suzuki coupling of 4-styreneboronic acid with bis-MOM-protected 3,3′-diiodo-BINOL. As well as simple BINOLs, the dedrimeric compounds **135** and **136** were prepared. This was achieved by coupling styryl-substituted first- and second-generation branches, prepared from the methyl ester of 3,5-dihydroxybenzoic acid and 4-vinylbenzyl chloride, to 6,6′-dihydroxy-BINOL using NaH in DMF. The yields of the coupling reactions were low (40−50%), this being attributed to migration of the silyl protecting groups under the coupling conditions used. The styrene-derivatized BINOLs were polymerized with styrene using AIBN as initiator, the TIPS- or MOM-protected BINOLs being used to prevent racemization of the BINOL core unit during the copolymerization process. Ti complexes of the immobilized BINOLS were prepared using $Ti(O^iPr)_4$ and were used for enantioselective diethylzinc addition to aldehydes. The supported BINOLs were found, with a notable exception of **136**, to be as active and selective as the homogeneous analogues. This is interesting bearing in mind that the BINOL moieties are located in the cross-links, which would be expected to impair local mobility and accessibility. This being said, they report that the activity of the metal-coordinated polymers, especially those formed from **135**, show slightly increased catalytic performance with decreased loading, lower loading meaning lower cross-linking and hence better accessibility for reaction substrates.

4.2. Polymer-Supported TADDOL Complexes

In the solution phase, α,α,α′,α′-tetraaryl-1,3-dioxolane-4,5-dimethanols (TADDOLs), prepared from tartrate esters, have been used extensively for the preparation of enatioselective catalysts.[94] Their general structure, **137**, has great potential for molecular diversity through changes to R, R′, Ar, M, X, and Y

groups. Both these factors mean that, like BINOLs, the immobilization of TADDOL ligands has received much attention over recent years.[95]

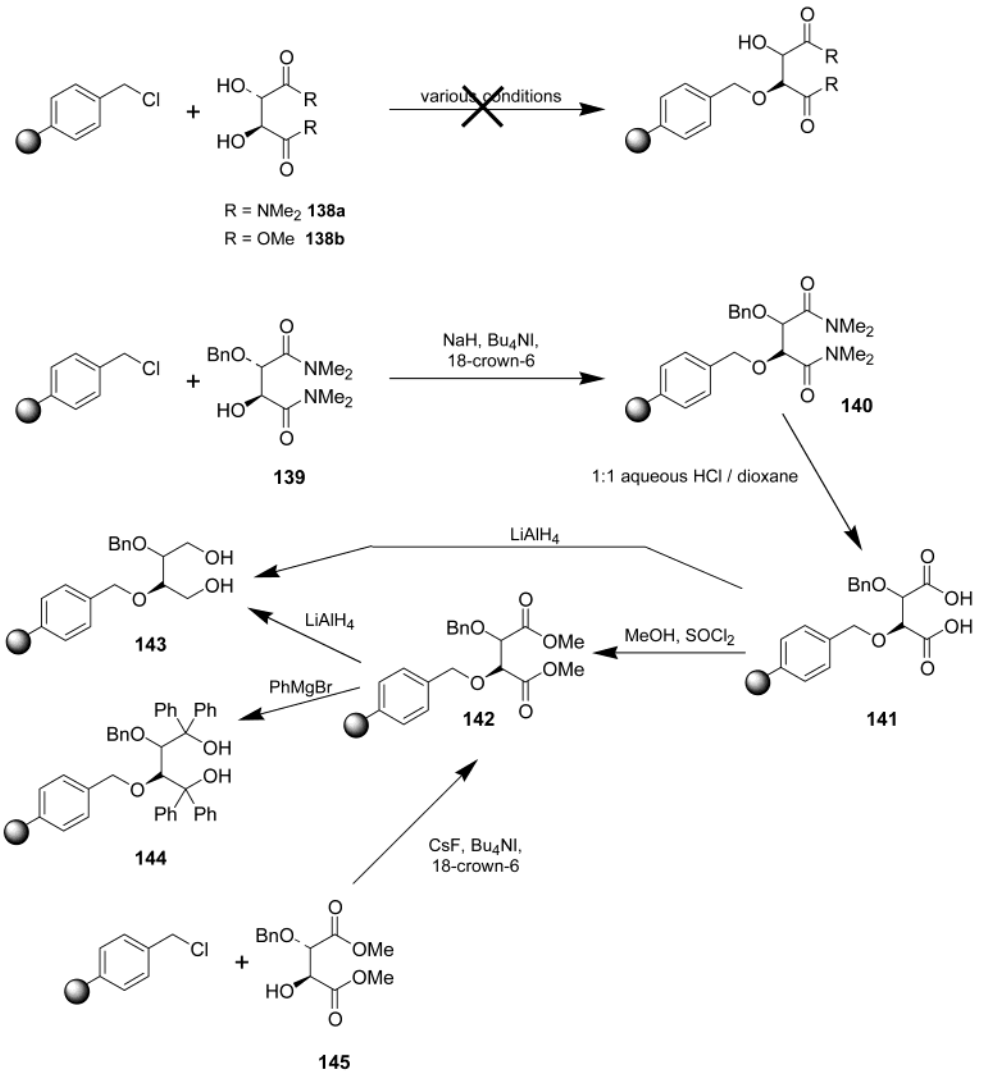


137

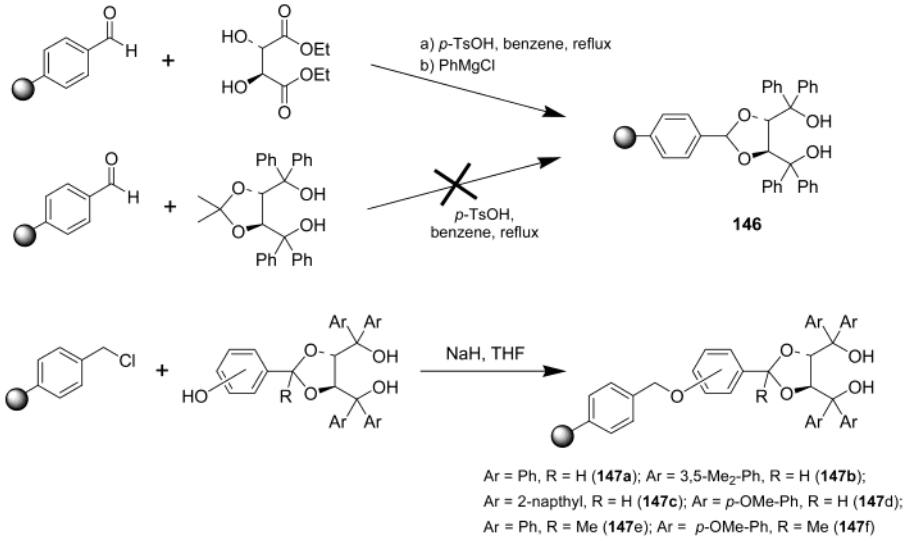
Burguete and co-workers[96] have attempted to prepare supported tartrate derivatives by reaction of Merrifield's resin with the alkoxylate of *N*,*N*,*N*′,*N*′-tetramethyltartramide (**138a**) or dimethyl tartrate (**138b**) followed by on-support elaboration (Scheme 46). The synthesis shows some of the problems of attaching homogeneous ligands to a polymer support. Direct monoalkylation of **138a** and **138b** with Merrifield's resin was found to give only low loadings of the desired supported complex. In an alternate strategy, they attempted to immobilize **139**, the monobenzylated analogue of **138a**, on Merrifield's resin using NaH to deprotonate it (Scheme 46). They established that phase-transfer agents were essential for obtaining even modest levels of attachment, finding that the use of Bu_4NI and 18-crown-6 together gave the best loadings of 0.42 mmol/g based on Merrifield's resin with a loading of 1 mmol of Cl/g. Having attached the tartramide to form **140**, conversion to the supported acid **141** was not easily accomplished either. The highly acidic conditions used for the hydrolysis of homogeneous analogues were not compatible with the hydrophobic nature of the polymer backbone, so they had to be modified, the best results being found when using a 1:1 aqueous HCl/dioxane mixture. The final step of the synthesis, namely, either reaction with $LiAlH_4$ or, after protection of the OH functionalities to give **142**, reaction with excess PhMgBr to give **143** and **144**, respectively, was much easier, going to completion in each case. However, having had problems not only with loading but also with hydrolysis, the authors attempted to prepare **143** and **144** from a different monoprotected tartaric acid derivative, **145**. This was much more successful, giving loadings of 0.75 mmol/g of **142** when treated with Merrifield's resin (1 mmol of Cl/g), CsF, Bu_4NI, and 18-crown-6. **142** was converted to **143** by treatment with $LiAlH_4$ and to **144** again by treatment with PhMgBr.

As a continuation of their work, Burguete and co-workers[97−99] have also prepared supported TADDOLs

Scheme 46

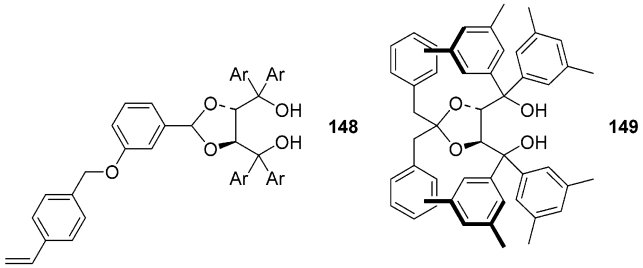


Scheme 47



from polymer-supported benzaldehyde employing a methodology similar to that used in the early stages by Kagan[64] and Stille[65−67] to generate their polymer-supported chiral phosphines from tartaric acid derivatives (Scheme 47). In the presence of a catalytic quantity of *p*-toluenesulfonic acid, reaction of polymer-supported benzaldehyde with (*R*,*R*)-diethyl tartrate gave the corresponding supported acetal in quantitative yield. This was converted to polymer-supported TADDOL **146** in quantitative yield by treatment with excess phenylmagnesium bromide; however, the resulting resin was contaminated by the presence of magnesium salts deposited on the beads. They tried to overcome this problem in two ways. First, they tried preparing **146** directly from commercial TADDOL and polymer-supported benzaldehyde by a transacetylization reaction, but this was unsuccessful (Scheme 47). Second, and with much more success, they prepared a range of supported TADDOLs via initial formation of homogeneous phenol-derivatized TADDOL derivatives, which were then attached to Merrifield's resin using NaH (Scheme 47). They prepared a number of phenol-derivatized TADDOL complexes from *m*- and *p*-hydroxybenzoic acid but found that only the *meta*-substituted compounds were stable to acid hydrolysis and thus only attached these to the polymer support to give analogues **147a**−**f** with ligand loadings of approximately 0.69−1.02 mmol/g depending on the loading of the starting Merrifield's resin. Ti−TADDOLate derivatives were prepared by reaction of the supported ligands with $Ti(OCHMe_2)_2Cl_2$ under reflux for 24 h, with very respectable metal loadings of between 0.42 and 0.72 mmol/g being obtained. These supported TADDOLates proved very efficient as catalysts for the Diels−Alder reaction but, with the exception of those derived from **147b**, with no asymmetric induction.

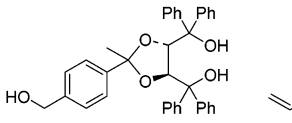
In an interesting extension to the work, Burguete and co-workers[100] have investigated how important the polymer support is in enantiomeric catalysis when using supported Ti−TADDOLates. They compared the activity of Ti−TADDOLates grafted onto Merrifield's resin, prepared using the methods outlined above, with that of monolithic columns of immobilized Ti−TADDOLates prepared by polymerization of styrene-derivatized TADDOLs **148** with divinylbenzene. Monoliths of the desired morphology and properties were obtained by AIBN-initiated polymerization of a mixture containing 40% monomers (ratio of DVB to **148** of 60:40) and 60% porogenic toluene/1-decanol mixture, the corresponding Ti−TADDOLates being formed by reaction with $Ti(O^iPr)_2Cl_2$. The remarkable observation was that, when used as catalysts in the Diels−Alder reaction, the major isomer of the product generated using the monolithic columns was of topicity (handedness) opposite that obtained when using the grafted Ti−TADDOLates or homogeneous Ti−TADDOL complexes. It must however be stressed that this effect is only observed when the immobilized TADDOLates contain 3,5-dimethylphenyl groups at the α positions. This is the first example of an immobilized enantioselective catalyst where the morphology of the support determines the topicity of the products. Similar changes in topicity have been observed in homogeneous catalysts using TADDOLs bearing a phenyl group at the 2 position of the dioxolane ring and one or more 3,5-dimethylphenyl groups at the α positions (**149**).[101] This effect has been attributed to $\pi-\pi$



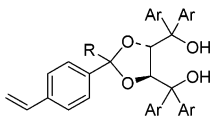
stacking interactions between an aromatic ring at the 2 position of the dioxolane ring and one of the 3,5-dimethylphenyl groups, decreasing the energy of the intermediates formed along the pathway leading to the topicity-inverted enantiomer. The authors argue that the TADDOL functionalities in the supported complex prepared by grafting would be fairly flexible and thus could mimic the solution phenomena. That

prepared by copolymerization methods would be expected to have the active TADDOL moieties in an area of high cross-linking and hence increased steric crowding in close proximity to the acetal, making $\pi-\pi$ stacking interactions less favorable and, as a consequence, leading to formation of the opposite enantiomer. Although this and other postulations have been put forward, it would be fair to say that currently the exact reason for the observations is not fully understood.

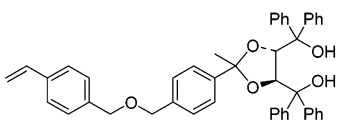
Seebach and co-workers[102,103] have prepared a range of immobilized TADDOLs by immobilization on Merrifield's resin or by copolymerizing styryl-substituted TADDOL molecules with styrene and DVB. They chose to derivatize TADDOL units at the *para* positions of either an aryl ring on the dioxolane ring or an aryl ring of a diarylmethanol moiety. For attachment to Merrifield's resin they prepared TADDOL **150** from methyl 4-formylbenzoate in four steps. For copolymerization they prepared a range of styryl-substituted dimethyl tartrate-derived dioxolanes from *p*-styryl aldehydes, ketones, and acetals by reaction with enantiometically pure dimethyl tartrate. The esters were then allowed to react with a large excess of arylmagnesium bromides to give the class of TADDOLs **151**, the key to the success of this being to perform the reaction at room temperature or below, thus avoiding polymerization of the styryl groups. Analogues bearing a spacer between the TADDOL and the styryl functionality were prepared from **150** and 4-vinylbenzyl chloride or acryloyl chloride, giving **152** and **153**, respectively. TADDOL **154** was prepared from **155** by treatment with excess (4-vinylphenyl)magnesium bromide.



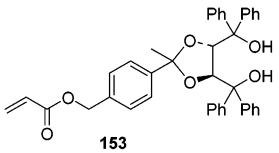
150



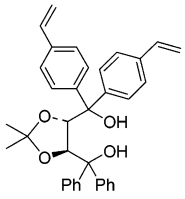
151



152



153



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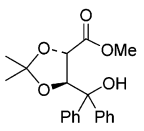
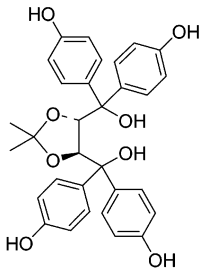


155

The alkoxide of **150**, prepared by reaction of the parent TADDOL with NaH, was immobilized on Merrifield's resin (0.7 mmol of Cl/g) with a TADDOL loading of 0.3 mmol/g. The styryl-functionalized TADDOLs were suspension polymerized with varying amounts of styrene and DVB using AIBN as initiator to give a range of immobilized TADDOLs. Supported Ti−TADDOLate complexes were prepared by treatment of the immobilized TADDOLs with $Ti(O^iPr)_4$ or $Ti(O^iPr)_2Cl_2$ to give TADDOL−$Ti(O^iPr)_2$ and TADDOL−$TiCl_2$, respectively. The supported Ti−TADDOLates were screened for activity in a range of reactions including nucleophilic additions to aldehydes and ketones, cycloadditions, and ring opening reactions. Both chemical yields and enatioselectivities were found to be comparable or identical to those of the homogeneous analogues, repeated recycling of the supported catalysts having only a slightly detrimental effect on activity.

Using methodologies similar to their supported BINOL synthesis,[93] Seebach and co-workers[104] have prepared a range of immobilized dendritic TADDOLs. The requisite styryl precursors were prepared by coupling TADDOL **156** with the styryl-substituted



156

first- and second-generation branches $\mathbf{L}^1$ and $\mathbf{L}^2$ (see Scheme 45 for structures). The styryl-TADDOLs were then copolymerized with styrene using suspension polymerization techniques and the corresponding Ti−TADDOLates formed by reaction with $Ti(O^iPr)_4$. The supported complexes were tested for the catalysis of diethylzinc addition to benzaldehyde and found to have an activity much higher than that of supported TADDOLs prepared by grafting and nearing that of the homogeneous analogues.

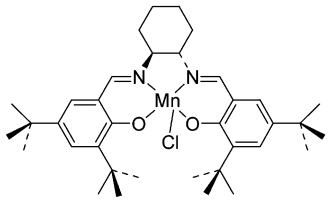
5. Polymer-Supported Salen and Porphyrin Complexes for Use in Oxidation Catalysis

5.1. Introduction

The preparation of polymer-supported catalysts for use in oxidation reactions and assessment of their activity has attracted interest for many years, particular attention being focused on epoxidation. Much of the early work in this area was focused on immobilization of metal complexes on non-polystyrene-based supports, a significant proportion of the pioneering research in the area being undertaken by Sherrington and his group.[105−108] For a discussion of this and other work the reader is directed to two reviews, one from 1988[109] and one from 2000.[110] A further major review this year[111] discusses the general area of immobilization of homogeneous oxidation catalysts. Attention here will be focused on polystyrene-supported salen and porphyrin ligands prepared since 1996 and their corresponding metal complexes. The majority of supported metal salen and porphyrin complexes have been used for oxidation catalysis, but there have been some other uses reported. For completeness these are also discussed in this section.

5.2. Polymer-Supported Metal Salen Complexes

The synthesis of immobilized salen-type ligands by grafting derivatized analogues onto preformed polymer supports has attracted a number of research groups. Complexes such as Jacobsen's catalyst **157**



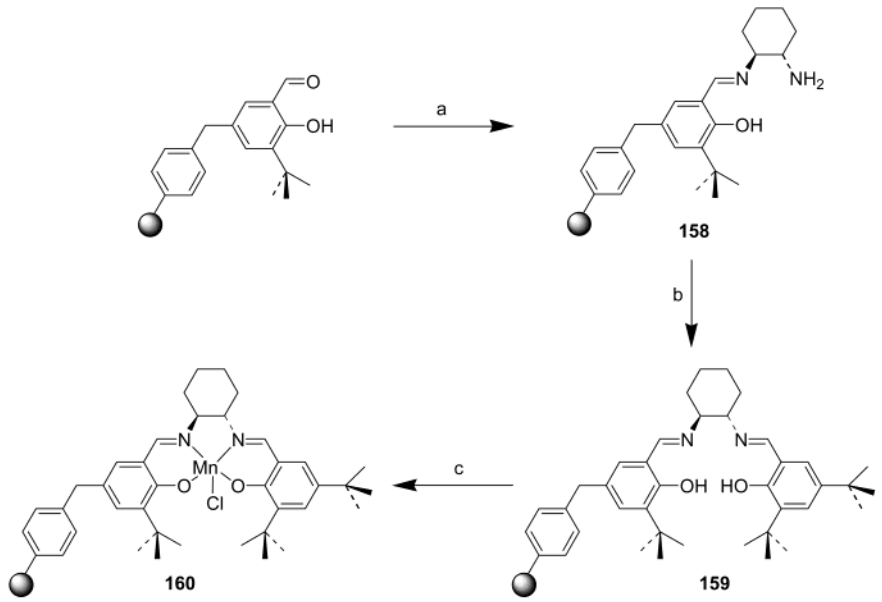
157

are highly active and enantioselective alkene epoxidation catalysts. Sherrington[110] has summarized the key design criteria for immobilizing salen complexes on polymer supports. They are that (a) the local molecular structure of the metal complex should mimic precisely the optimum structure of **157**, (b) the complex should be attached to the support through a single flexible linkage to minimize any local steric restriction, (c) the complex should be attached to the support in a reasonably low loading to ensure site isolation of metal centers, thereby limiting the possibility of oxo-bridged dimer formation, leading to loss of catalytic activity during the course of a reaction, and (d) the morphology of the support should be such that all active sites are available.

In 1998, both Sherrington[112] and Laibinis[113] independently described methods for the attachment of the salen ligand to a polymer support in a pendent stepwise manner. Sherrington[112,114] and co-workers prepared the supported salen ligand **159** using a range of polymer supports (Scheme 48). Their starting point in each case was an aldehyde- and phenol-derivatized support, these functionalities being positioned *ortho* to each other. The aldehyde moiety of the resin was first condensed with chiral (*R*,*R*)-1,2-diaminocyclohexane to yield the supported monoimine **158**. To ensure that the monoimine was formed rather than a diimine, generated by reaction of the diamine with two neighboring aldehyde functionalities, the synthetic strategy was to use a support with low loading, thereby maximizing site isolation. With the monoimine in hand, a second condensation with a salicylaldehyde was performed, yielding **159**. Reaction with $Mn(OAc)_2$ in ethanol under reflux followed by addition of LiCl yields the corresponding manganese salen complex **160**. Although metal loading onto the ligand is reported as not being complete, it is good enough for catalytic applications but with activities lower than those of the homogeneous analogues. More recently Sherrington and co-workers have prepared a wider range of supported manganese salen complexes and have attempted to recycle the supported catalysts with and without reloading of Mn.[115] They find that although the level of metal leaching is very low, the catalysts show a very rapid fall off in both activity and selectivity after their first use.

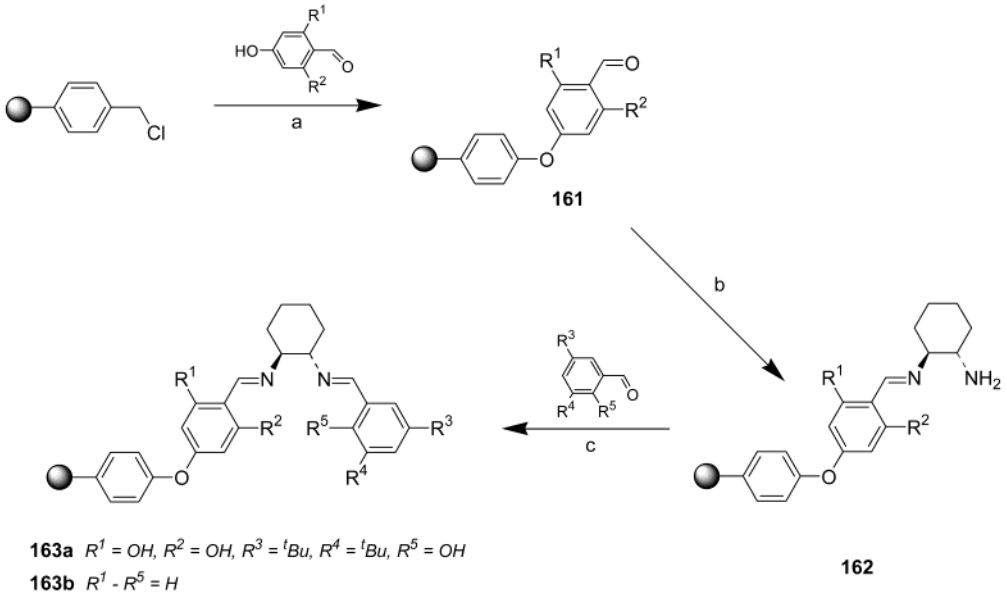
In their approach, Laibinis and Angelino prepared two polymer-supported ligands, **163a** and **163b** (Scheme 49).[113] Like **159**, **163a** bears two phenolic groups, providing the tetradentate chelation required for the incorporation of metals such as Mn for asymmetric epoxidation[116] and Cr and Co for kinetic resolution of terminal epoxides. The other ligand, **163b**, provides a bidentate chelating environment required for metals such as Cu that catalyze aziridination of olefins. Both **163a** and **163b** were prepared using similar methodologies, starting from Merrifield's resin. For **163a**, 2,4,6-trihydroxybenzaldehyde was attached with the resin using K_2CO_3 and 18-crown-6 in either dioxane or DMF to give **161**. The use of 2,4,6-trihydroxybenzaldehyde guarantees that supported **163a** contains a free hydroxyl group adjacent to the aldehyde regardless of which phenol group reacts with the resin. Reaction of the resin-bound aldehyde with resolved *trans*-1,2-diaminocy-

Scheme 48[a]



[a] Reagents and conditions: (a) (*R*,*R*)-1,2-diaminocyclohexane, CH_2Cl_2, rt, 12 h; (b) 2,4-di-*tert*-butylsalicyladehyde, CH_2Cl_2, rt, 12 h; (c) $Mn(OAc)_2 \cdot 4H_2O$, EtOH, air, reflux, 30 h, then LiCl, rt, 4 h.

Scheme 49[a]



[a] Reagents and conditions: (a) aldehyde, K_2CO_3, 18-crown-6, dioxane, 95 °C, 24 h; (b) (*S*,*S*)-1,2-diaminocyclohexane, dioxane, 95 °C, 24 h; (c) aldehyde, dioxane, 95 °C, 24 h.

clohexane, giving **162**, followed by condensation with a second aldehyde yields the desired supported salen ligand **163**. A problem faced by both Sherrington and co-workers and particularly Laibinis and Angelino[113] is that although in the solution-phase synthesis of salen-type ligands ethanol is the solvent of choice, this is not the case when using many polymer supports such as Merrifield's resin which do not swell significantly in alcohols. Instead, 1,4-dioxane is used as the solvent. The drawback with this is that it is necessary to use resolved 1,2-diaminocyclohexane in uncomplexed form rather than, in the homogeneous case, the tartaric acid complex, which is soluble in ethanol but not dioxane.

The extent of reaction in the steps of the synthesis of **163a** was monitored using IR spectroscopy, evidence for the various transformations taking place being clear from the appearance or disappearance of characteristic IR peaks such as for carbonyl and imine functionalities. Starting with Merrifield's resin with a loading of 2 mmol/g of Cl, a final ligand loading of 0.61 mmol/g was obtained. The Mn complex of **163a** was formed by reaction of the supported ligand with $Mn(OAc)_2$ in the presence of Bu_4NCl, Mn analysis suggesting a loading of metal-coordinated salen complex of 0.13 mmol/g.

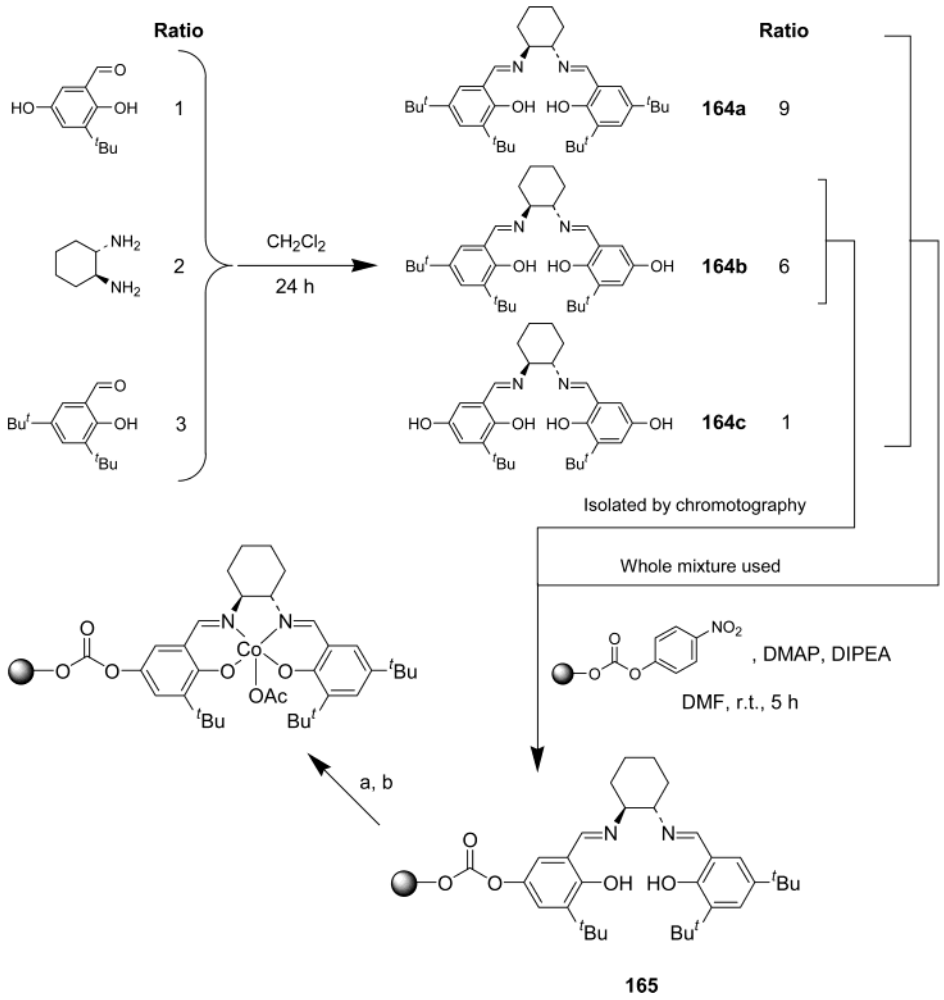
Supported ligand **163b** was prepared using a methodology similar to that for **163a**. The resin-bound aldehyde formed from reaction of Merrifield's resin with 4-hydroxybenzaldehyde was reacted with the diamine and the second imine bond formed by reaction with benzaldehyde.

Jacobsen and Annis[117] have prepared supported ligand **165** directly from a prefabricated salen ligand and a suitably derivatized polymer support, thereby circumventing the need to build the ligand stepwise on the support (Scheme 50). Salen ligand **164b**, which is nonsymmetric with respect to substituents on the benzene rings, is prepared from *trans*-1,2-diaminocyclohexane and the two suitably derivatized aldehydes. As well as forming **164b**, the tetra-*tert*-butyl ligand **164a** and the diphenolic ligand **164c** are also formed. The **164** is then separated and purified using column chromatography. Using commercially available hydroxymethylpolystyrene derivatized as the corresponding 4-nitrophenyl carbonate, **164b** was attached to the support using DMF in the presence of Hünig's base to give **165**. The cobalt complex of **165**, **166**, was formed by treating it with a solution of $Co(OAc)_2$, analysis indicating a metal loading of 0.16 mmol/g.

They found that an alternative and more practical way of preparing **165** is by resin capture of **164b** from the crude ligand mixture (Scheme 50). Use of an excess of di-*tert*-butylsalicylaldehyde relative to 2,5-dihydroxy-3-*tert*-butylbenzaldehyde results in a statistical 9:6:1 ratio of **164a**, **164b**, and **164c**, respectively. Addition of the nitrophenyl carbonate-substituted polymer support allows for the selective capture of **164b** and **164c**, the tetra-*tert*-butyl ligand **164a** being removed by simple washing of the resin. **165** prepared in this way showed activity similar to that of **165** prepared by prepurification of **164b**, the incorporation of small amounts of **164c** into the resin having no apparent effect on selectivity or enantioselectivity of the supported catalyst.

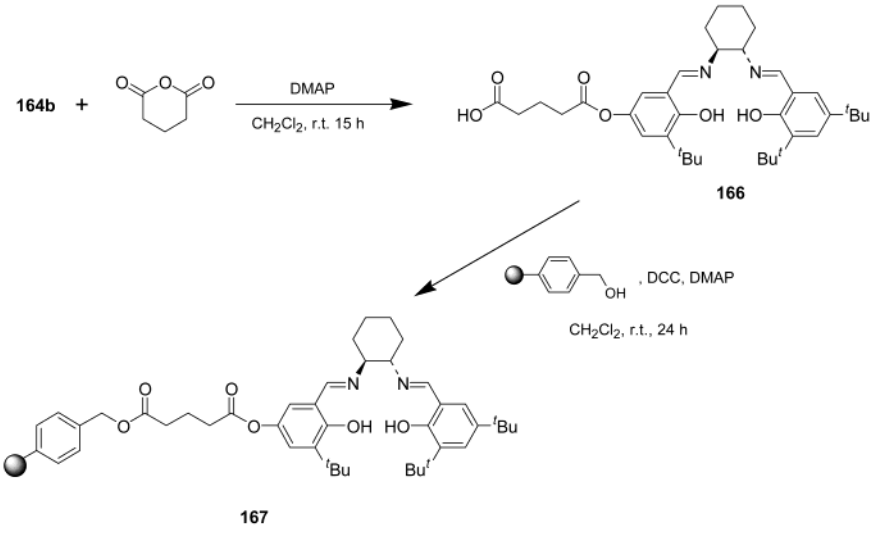
As part of a comparative study of different polymer supports for use in catalysis, Janda and Reger[118] have prepared a polystyrene-supported salen complex starting from **164b** (Scheme 51). Reaction of **164b** with glutaric anhydride and DMAP yielded **166**, which was attached to different resins containing hydroxymethyl functionalities using conventional coupling methods to give **167**. The fact that **166** contains a five-carbon spacer between the salen ligand and acid functionality means that, when attached to the support, the ligand is sufficiently far away from the polymer backbone to allow unimpeded access of reagents both for forming metal complexes of **167** and then for their subsequent use in catalysis.

Scheme 50[a]



[a] Reagents and conditions: (a) $Co(OAc)_2$, methanol/toluene, rt, 1 h; (b) air, toluene/acetic acid.

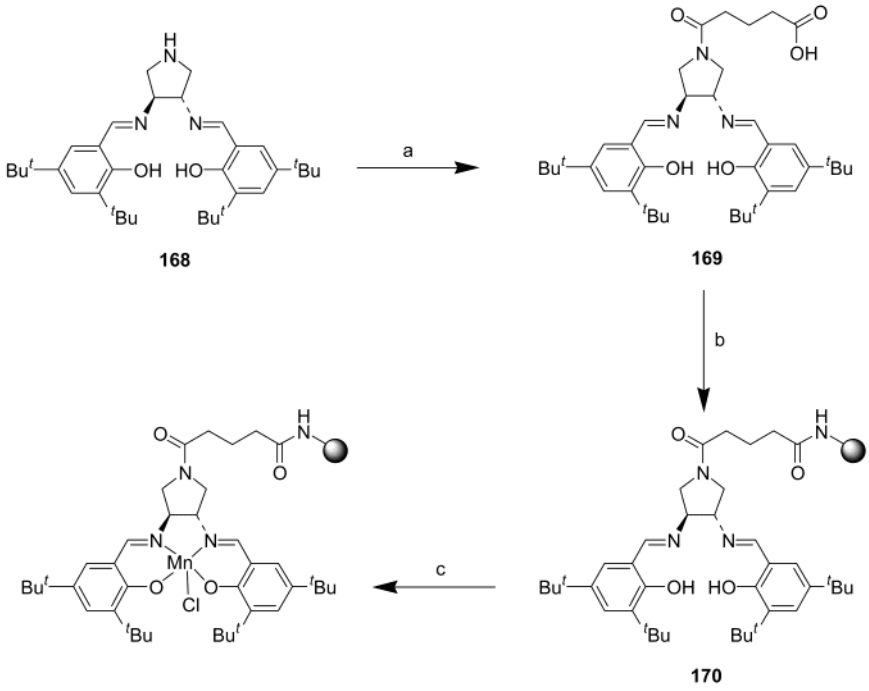
Scheme 51



The Mn complex of **167** was prepared by treatment of the ligand with a DMF/water solution of $Mn(OAc)_2$ in air followed by addition of saturated NaCl, a metal loading of 0.27 mmol/g being obtained.

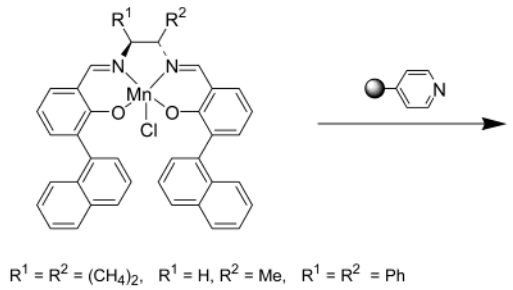
Song and co-workers[119] have reported the preparation and use of a polymer-supported pyrrolidine−salen ligand, **170**, and its corresponding Mn complex (Scheme 52). This is again formed by attachment of a prefabricated salen ligand to a suitably derivatized support using a method similar to that of Janda and Reger.[118] The pyrrolidine−salen ligand **168** is treated with glutaric anhydride to form **169**, which is attached to an amine-derivatized PEG−polystyrene resin, giving **170**. Attachment of the Mn is by the

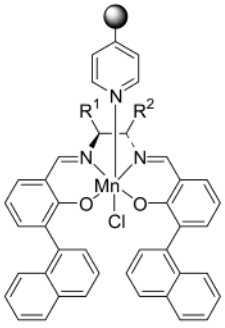
Scheme 52[a]



[a] Reagents and conditions: (a) glutaric anhydride, NEt_3, DMAP, CH_2Cl_2, rt, 12 h; (b) NovaSyn TG amino resin (loading 0.29 mmol of NH_2/g), DIC, HOBt, Net^iPr_2, DMF/CH_2Cl_2, rt, 15 h; (c) $Mn(OAc)_2 \cdot 4H_2O$, EtOH/toluene, air, reflux, 30 h, then NaCl, rt, 4 h.

Scheme 53



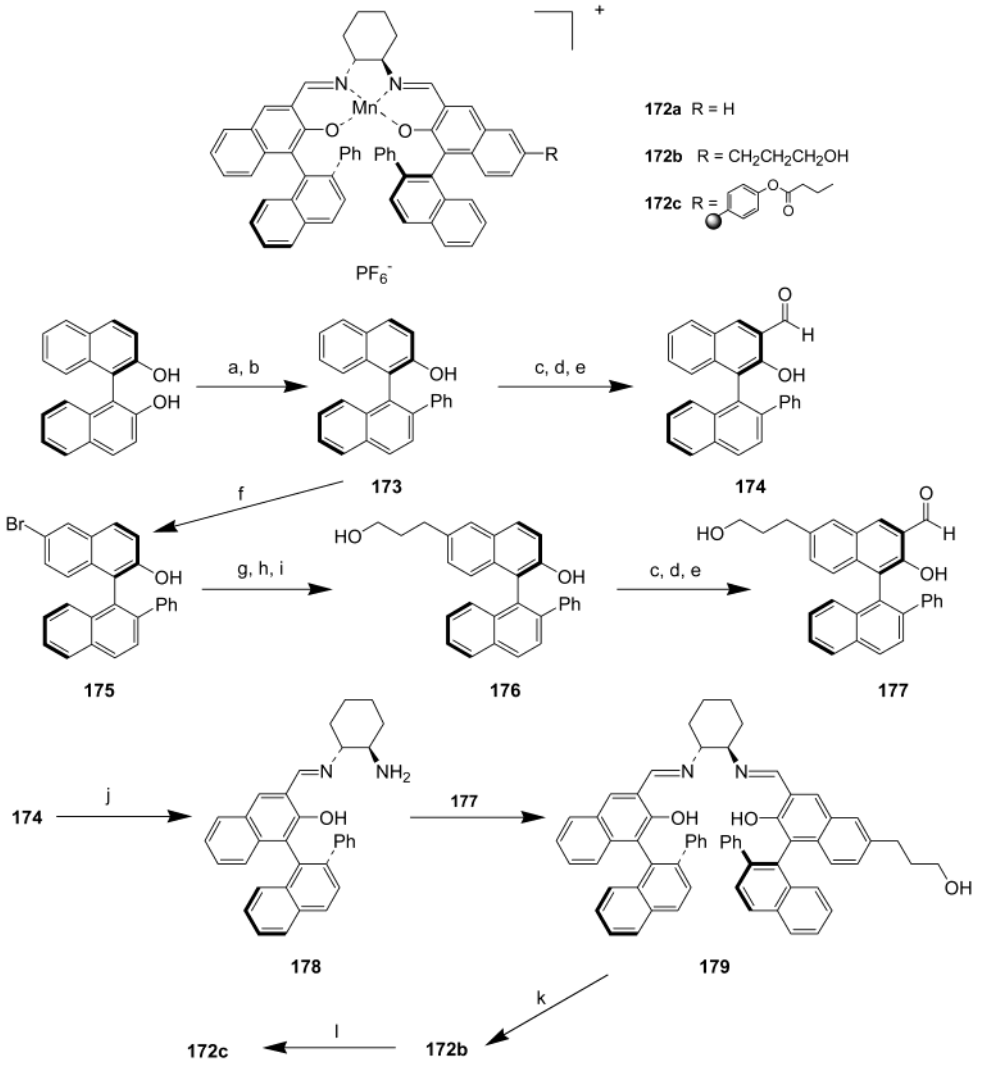


method used by Sherrington and co-workers[112] for **160**, a loading of metal-coordinated salen complex of 0.11 mmol/g being obtained.

Kureshy and co-workers[120] have immobilized manganese salen complexes on a polymeric matrix prepared from suspension polymerization of styrene, 4-vinylpyridine, and DVB (Scheme 53). The salen complex is immobilized not via the salen ligand but through bonding to the supported pyridine functionalities, giving complexes of the form **171**, with a very low metal loading being observed. The logic of immobilization in this way is questionable bearing in mind that the coordination to both axial positions in metal salen compounds is intimately involved in the mechanism of activity of these complexes in epoxidation catalysis. As a result, immobilization at an axial position would be expected either to reduce the catalytic activity of the resultant salen complex or to lead to leaching into solution during the course of a reaction. Having said this, the supported complexes were reportedly used successfully in the enantioselective epoxidation of styrene and recycled 10 times. However, as Sherrington says in his review,[110] this claim does seem rather incredulous.

Smith and Liu have prepared **172c**, a polymer-supported analogue of the Katsuki complex **172a** (Scheme 54).[121] This represents the first example of an immobilized complex of this type. Katsuki-type complexes often give higher enantioselectivities than Jacobsen salen complexes in a range of epoxidation reactions and are less prone to decomposition or oxidative dimerization.[122,123] The approach to the synthesis of **172c** first involved the preparation of aldehydes **174** and **177**. The first steps toward both are identical and involve the preparation of **173** from enantiomerically pure BINOL. From **173**, **174** was formed in three steps. For **177**, **173** was brominated in the 6 position of the naphthol ring, giving **175** followed by Heck coupling with methyl acrylate and reduction to yield **176**. Functionalization of this to the aldehyde **177** was performed using a methodology analogous to that for **174**. Coupling **174** with *trans*-1,2-diaminocyclohexane gave **178**, which in turn was coupled with **177**, yielding **179**. Metalation of **179** by treatment with $Mn(OAc)_2$ in air followed by ion exchange with $NaPF_6$ yields derivatized Katsuki complex **172b**. The complex was attached to the support via an ester linkage by treatment of **172b** with acid chloride-functionalized polystyrene (1.17

Scheme 54[a]



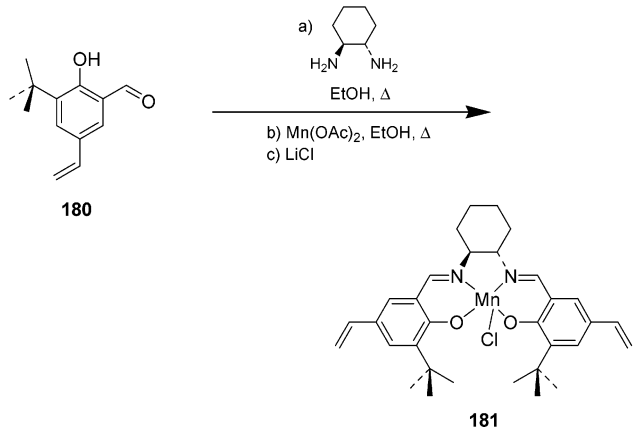
[a] Reagents and conditions: (a) THF_2NPH, 2,4,6-collidine, DMAP, CH_2Cl_2, reflux, 24 h; (b) PhMgBr, $NiCl_2$(dppe), Et_2O, reflux, 2 h; (c) $^iPr_2NEt$, $MeOCH_2Cl$, CH_2Cl_2; (d) BuLi, THF, −78 °C, 3 h, then DMF, 20 °C, 1 h; (e) Me_2SiBr, CH_2Cl_2; (f) Br_2; (g) $CH_2{=}CHCO_2Me$, $Pd(OAc)_2$, P(*o*-tol)$_3$, $MeCO_2Na$, DMF, 180 °C; (h) Mg, MeOH; (i) $LiAlH_4$, Et_2O; (j) 1,2-diaminocyclohexane; (k) $Mn(OAc)_2$, then $NaPF_6$; (l) acid chloride-functionalized polystyrene.

mmol of Cl/g), giving **172c** with a metal loading of approximately 0.24 mmol/g, representing about 45% incorporation of the salen-type complex. The catalytic activity of **172c** in the epoxidation of 1,2-dihydronaphthalene was compared to that of **172a** and **172b**. Although the polymer-supported catalyst exhibited lower rates of reaction, the enantioselectivity was almost identical to that of the homogeneous analogues and remained so in subseqent reuses.

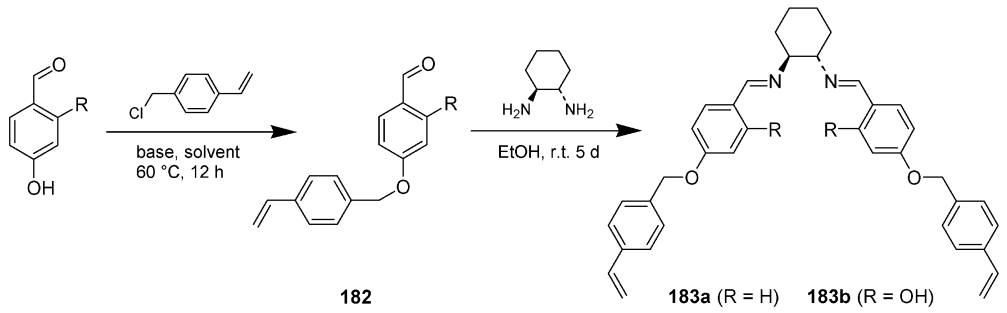
There have been a number of reports of the preparation of supported salen compounds by polymerization of suitably derivatized salen ligands. The first example of this was reported by Sivaram, Dhal, and co-workers, although it is not polystyrene based.[124,125] They copolymerized a styrene-derivatized salen complex with ethylene glycol dimethylacrylate in a ratio of 1:9 and successfully used the resulting polymer in epoxidation reactions although with low enantioselection.

Salvadori and co-workers[126] have prepared immobilized manganese salen complexes using precursor **181** (Scheme 55). The starting aldehyde for the synthesis of **181** is 3-*tert*-butyl-5-vinylsalicylaldehyde, **180**, prepared in three steps from 3-*tert*-butylsalicylaldehyde by chloromethylation at the 5-position, formation of a phosphonium salt, and subsequent Wittig reaction with formaldehyde. The styrene-derivatized salen complex was then prepared from

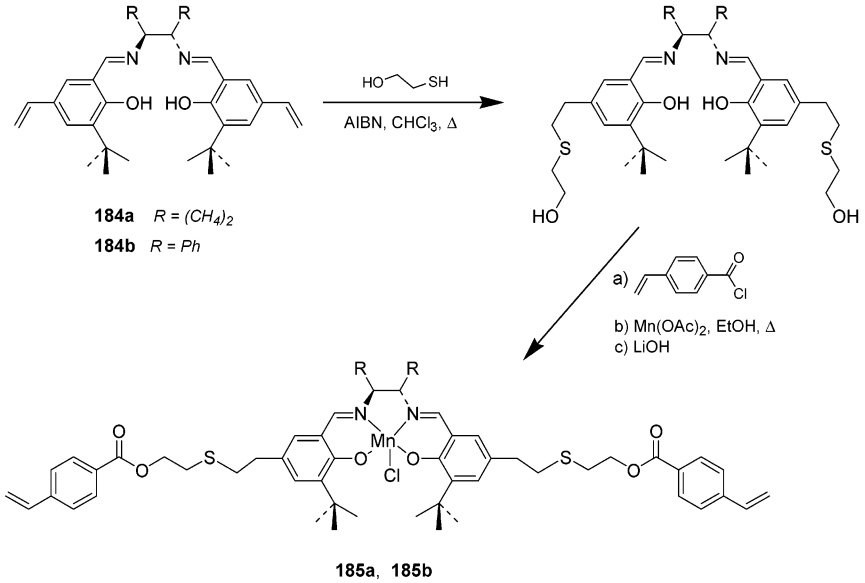
Scheme 55



Scheme 56



Scheme 57



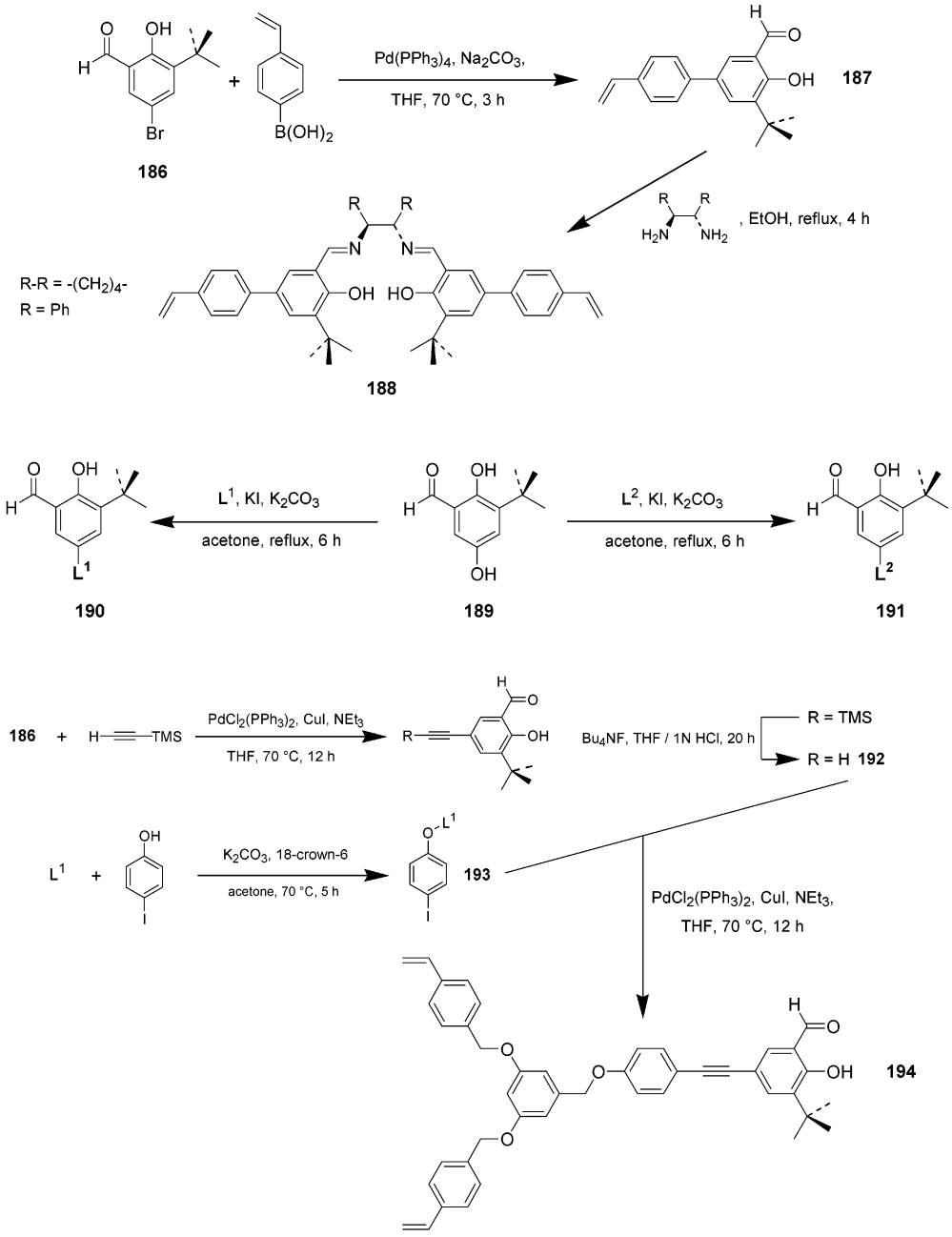
the condensation of **180** and (*R*,*R*)-*trans*-1,2-diaminocyclohexane and the Mn inserted in the usual way. **181** was copolymerized with styrene and DVB (ratio 10:75:15, respectively) using AIBN as initiator. The polymers so formed were used as asymmetric epoxidation catalysts, with good conversion and ee's of up to 41% being observed in the case of *cis*-*β*-methylstyrene.

Using a similar methodology and starting from 4-hydroxybenzaldehyde or 2,4-dihydroxybenzaldehyde, Lemaire and co-workers[127] have prepared two styrene-derivatized salen ligands, **183a** and **183b**, in modest yields (30−40%) by reaction of the aldehyde with 4-chloromethylstyrene to give **182** followed by condensation with (*R*,*R*)-*trans*-1,2-diaminocyclohexane (Scheme 56). These ligands have been copolymerized with various quantities of styrene and/or divinylbenzene to give polymers with different degrees of cross-linking. The Mn complexes of the polymeric salen ligands were formed and the resulting polymers used in asymmetric epoxidation reactions, with low yields and ee's being reported. Also, although not isolated, iridium complexes of the supported salen ligands have also been prepared using $[Ir(COD)Cl]_2$ and used in situ for asymmetric catalytic transfer hydrogenation reactions, mostly with good conversion and moderate ee's (ranging from 21% to 70%).

The problem with immobilization of the salen complexes by polymerization is that the active metal sites end up on cross-links, therefore having limited mobility and accessibility. The effects of this are clearly seen when comparing both the chemical yields and ee's reported in catalysis using the copolymerized complexes as compared to the polymer-grafted analogues. Salvadori and co-workers[128] have prepared a range of second-generation immobilized manganese salen complexes using precursors **186a** and **186b**, which bear a spacer group between the syrene functionality and the salen ligand, thereby increasing the mobility of the active center (Scheme 57). The styrene derivatized precursors are prepared, in the first few steps, in an analogous way to **181**, **180** being condensed with (*R*,*R*)-*trans*-1,2-diaminocyclohexane or (*R*,*R*)-1,2-diphenylethylenediamine to give **184a** and **184b**, respectively. The introduction of the spacer unit was achieved by radical anti-Markovnikov addition of 2-mercaptoethanol to the styrene double bonds of **184** followed by acylation of the free hydroxy groups with 4-vinylbenzoyl chloride. The Mn was then introduced using $Mn(OAc)_2$, giving **185a** and **185b**. Copolymerization of these monomers with styrene and DVB gave macroreticular polymers which were screened for activity in asymmetric epoxidation reactions. Conversions were good, but ee's were still not remarkable, the best being 62%, observed in the case of *cis*-*β*-methylstyrene.

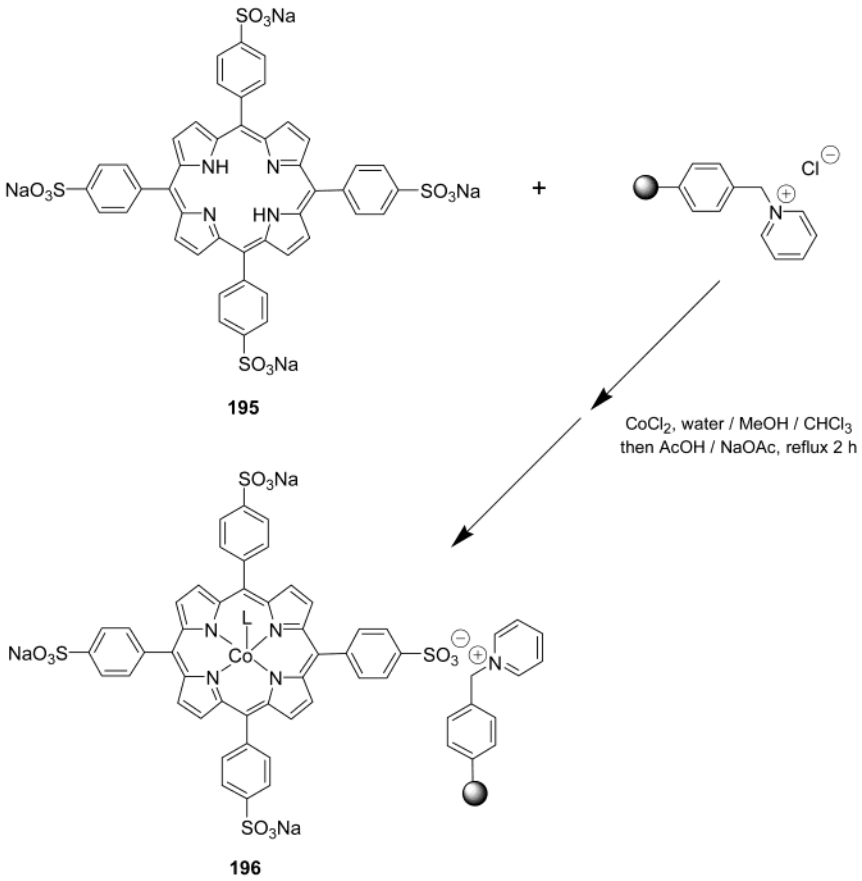
Following their success with the synthesis of supported BINOL[93] and TADDOL[104] complexes, Seebach and co-workers[129] have recently turned their atten-

Scheme 58



tion to preparing a range of styryl-substituted salens for polymerization with styrene (Scheme 58). They first prepared **188**, the analogue of metal-free **181** bearing a phenyl spacer unit. Like **181**, **188** is prepared by reaction of a diamine with a derivatized salicylaldehyde, in this case **187**, which is derived from **186** and styreneboronic acid. They then prepared a range of dendritic styryl-substituted salens. The requisite styryl precursors were prepared by coupling 3-*tert*-butyl-5-hydroxysalicylaldehyde (**189**) with the styryl-substituted first- and second-generation branches $\mathbf{L}^1$ and $\mathbf{L}^2$ (see Scheme 45 for structures), giving **190** and **191**, respectively. These were then coupled with diamines to give the dendritic salen ligands. Anticipating that the dendrimeric salen systems prepared from salicyladehyde branches may be susceptible to oxidation when used as ligands for metal-catalyzed epoxidation reactions, an additional dendritic salen ligand was also prepared using **194** as the branch. As this contains an acetylide linkage between the dendritic subunit and the salicylaldehyde, part it was expected to be more stable toward oxidation. **194** was prepared by $PdCl_2(PPh_3)_2$/CuI-catalyzed Sonogashira coupling of **192** with **193**. The acetylide fragment **192** was prepared from **186** by Sonogashira coupling with trimethylsilylacetylene and the vinyl-substituted branch **193** prepared from $\mathbf{L}^1$ by reaction with 4-iodophenol. All the styryl-substituted salens were then individually copolymerized with styrene using AIBN as initiator to give the immobilized analogues. Supported manganese salen complexes were prepared from $Mn(OAc)_2$ and used successfully in the epoxidation of a range of olefins. Interestingly the activity and enantioselectivity of the immobilized dendritic salen complexes were almost identical to those of the homogeneous analogues,

Scheme 59



particularly with styrene and 3-methylstyrene, demonstrating that placing the catalytic moiety at the cross-link of the polymer within a dendritic environment generates polymers that are catalytically highly active. The supported salen complexes derived from **194** were recyclable at least 10 times, those originating from the other two dendritic salens showing a pronounced drop in activity and selectivity on recycling. This indicates that indeed, without the acetylide spacer, oxidation of the dendritic salen complexes occurs. Chromium complexes of the supported salens were also prepared, this being achieved by agitating the ligand with a THF solution of $CrCl_2$ for 12 h. The complexes formed were screened for activity in the hetero-Diels−Alder reaction of Danishefsky's diene with a range of aldehydes and again showed excellent catalytic activity and enantioselectivity, some of them getting better with reuse.

5.3. Polymer-Supported Metal Porphyrin Complexes

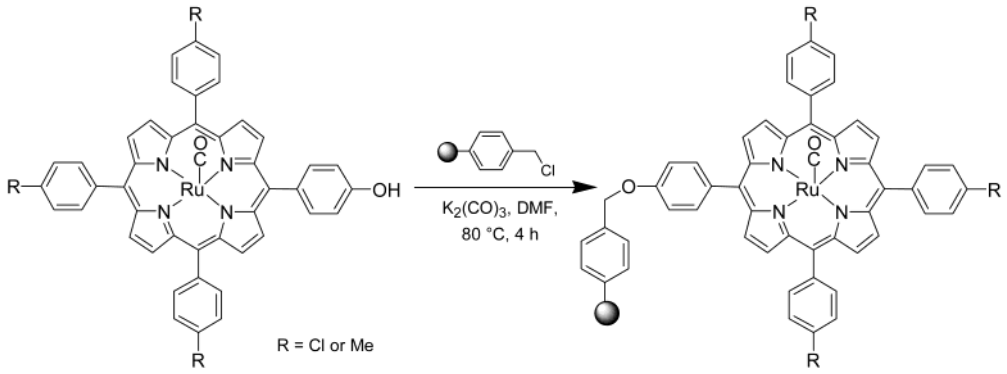
Metalloporphyrins have interesting physical properties and have found uses as catalysts in a range of reactions, often showing high regio- and enantioselectivity, but they are expensive and time-consuming to prepare.[130,131] As such they are clear candidates for immobilization on solid supports since if they were recoverable and recyclable, they would be more cost-effective.

Since 1996 there have been a number of reports of immobilized metalloporphyrins. Using a pyridinium chloride support prepared from Merrifield's resin and pyridine, Kuriakose and co-workers[132] have immobilized a cobalt porphyrin complex, **196**, through an ionic linkage by stirring tetrakissulfonylporphyrin complex **195** with the support for 4 h in water and reacting the supported porphyrin with $CoCl_2$, acetic acid, and sodium acetate (Scheme 59). The supported complex was used as a catalyst for the oxidation of dithiocarbamates to their corresponding disulfides. Using an identical methodology, Tangestaninejad and co-workers[133] have prepared a manganese analogue of **196** and used it as an alkene epoxidation and alkane hydroxylation catalyst.

Che and co-workers[134] have immobilized ruthenium porphyrins bearing a peripheral hydroxyl group to Merrifield's resin using K_2CO_3 as coupling agent (Scheme 60). Two different loadings (8.6 and 0.17 wt %) of ruthenium porphyrin **197** were immobilized on the support by varying the amount of **197** used in the coupling reaction. The immobilized porphyrins were characterized by IR and Raman spectroscopy, the ν_{CO} stretch observed being characteristic of the presence of a metal carbonyl functionality. The supported metalloporphyrins were used in epoxidation reactions with success and could be recycled a number of times.

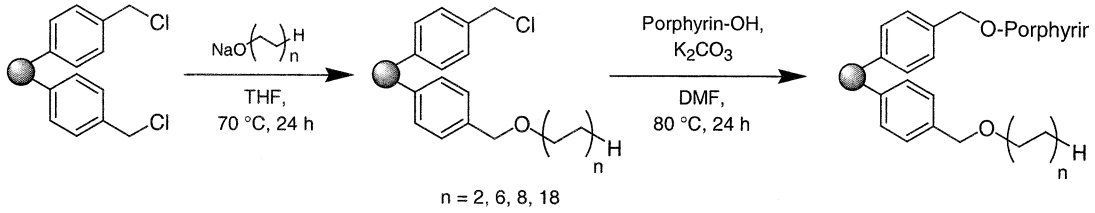
Wang and co-workers[135] have used the same methodology to prepare a number of immobilized transition-metal porphyrin complexes starting from 4-hydroxyphenylporphyrin and Merrifield's resin. They then used the complexes in the hydrogenation of cyclohexene. Likewise, Huang and co-workers have

Scheme 60



197

Scheme 61



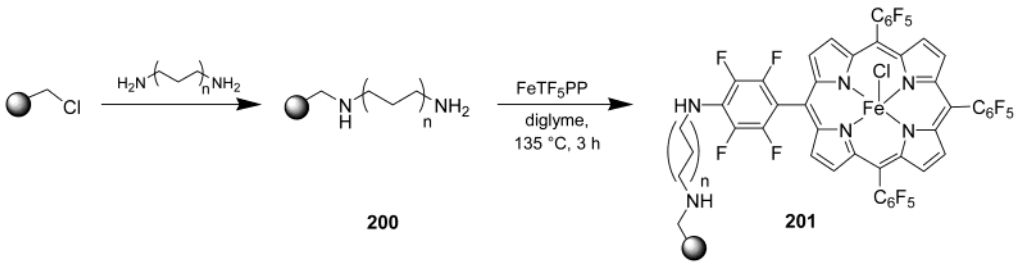
198 **199**

prepared a range of iron[136] and manganese[137] porphyrins using a metalloporphyrin bearing peripheral hydroxyl groups, Merrifield's resin as the support, and K_2CO_3 as coupling agent (Scheme 61). They have immobilized a mono- and tetrahydroxy-functionalized iron porphyrin in this way.[136] They have used the two supported iron porphyrins as catalysts for the hydroxylation of cyclohexene with dioxygen and found that the one derived from the monohydroxy-functionalized iron porphyrin is more active than that prepared from the tetrahydroxy-functionalized analogue. They propose that the former is bound to the support through one bond but the latter is bound through four, thereby increasing the steric crowding around the active metal site and reducing catalytic activity. However, while bonding through more than one hydroxy functionality may certainly be an option, it would however be unlikely that the metalloporphyrin would be bound to the support through all four hydroxy functions even though they use highly loaded Merrifield's resin (4.8 mmol of Cl/g) for the immobilization. In their immobilization of manganese porphyrins,[137] the workers first react the starting Merrifield's resin (4.8 mmol of Cl/g) with a sodium salt of a primary aliphatic alcohol (ranging from C_2H_5OH to $C_{18}H_{37}OH$) to form a mixed chloromethyl/alkyl-substituted support (**198**). They find that the alkyl loading decreases with increasing chain length, that with ethyl functionalities being 1.76 mmol/g and that with octadecyl functionalities being 0.33 mmol/g. They then couple the porphyrin to the support to give **199**. The first step of the synthesis in effect removes a significant number of otherwise active Cl sites to which the metalloporphyrin can bond and thus lowers the metal loading on the support significantly (0.01−0.05 mmol/g). Not unexpectedly the metal loading is greatest when the alkyl loading is lowest (alkyl chain longest). As with the iron complexes, they use the supported manganese porphyrin complexes for the hydroxylation of cyclohexene with dioxygen. They report that the catalytic activity increases with increasing length of the alkyl chains attached to the support in the first step. They attribute this to the formation of hydrophobic environments around the active metal centers as a result of intertwining of hydrocarbon functionalities. What would appear more likely is the fact that there are more metal sites when the alkyl chains are long and thus more catalytic activity.

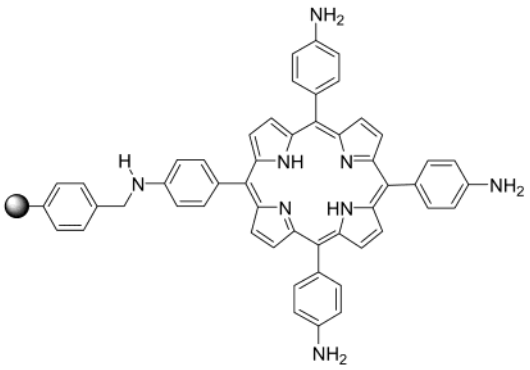
You and co-workers[138,139] prepared some supported complexes bearing both metalloporphyrin and crown ether functionalities, again starting from Merrifield's resin. They first attach the crown ether functions and then the hydroxy-functionalized manganese porphyrin. They have used these complexes as catalysts for the epoxidation of olefins.

Evans and Lindsay-Smith[140] have immobilized iron tetrakis(pentafluorophenyl)porphyrin ($FeTF_5PP$) on a range of supports including polystyrene to give **201** (Scheme 62). They use differing length α,ω-diamines, $H_2N(CH_2)_nNH_2$ (n = 3, 6, 9, 12), as spacer units. Starting from Merrifield's resin, they prepared the corresponding amine-functionalized supports **200** by reaction with the diamine, the loading of primary amine sites decreasing with increasing alkyl chain length, this being attributed to increased tendency for cross-linking of the diamine to the support with the long-chain linkers. The metal complex is then attached by nucleophilic substitution of the *p*-fluorines on the porphyrin by heating a suspension of the support in a solution of $FeTF_5PP$. Not surprisingly, metal loadings increase with decreasing spacer length, more primary amine sites being available. The sup-

Scheme 62



ported complexes were used as catalysts for the oxidation of ethylbenzene with dioxygen.

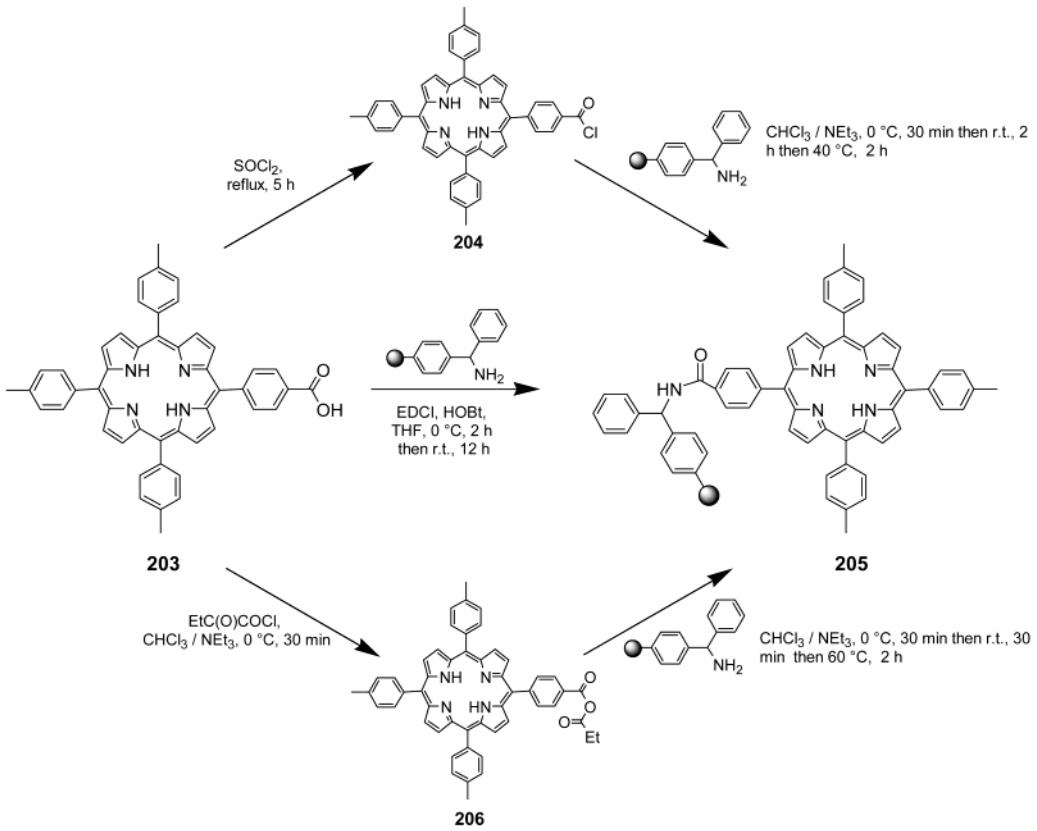


202

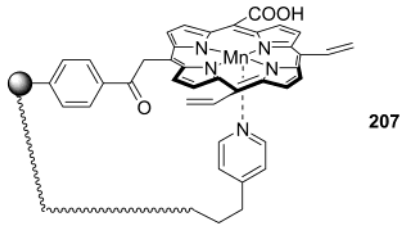
Mathew and Kuriakose[141] have used a similar methodology to immobilize tetraamino-substituted porphyrins on Merrifield's resin, giving **202**. *o*-, *m*-, and *p*-amino-substituted porphyrins were used and, once attached to the support, cobalt complexes formed and their dioxygen binding affinity studied using ESR spectroscopy. They have also prepared the imine analogue of **202** by treatment of aldehyde-derivatized polystyrene with the tetraamino-substituted porphyrins.[142] Silver and copper complexes have been prepared by treatment of the imine-bound porphyrins with $Cu(OAc)_2$ and $Ag(OAc)_2$, respectively.

Azenbacher and co-workers[143] have immobilized iron and manganese complexes of porphyrin **205** on amine-derivatized polystyrene using three different methods (Scheme 63). Starting from **203**, they have prepared the acid chloride and acid anhydride derivatives **204** and **206**, respectively, and coupled each of these to the support. They have also used standard peptide coupling conditions to prepare **205**. They find that each method gives essentially the same loading of porphyrin. The metalated complexes were formed by reaction of the supported ligand with the appropriate $M(acac)_n$ complex (acac = 2,4-pentanedione), with metal loadings of around 0.1 mmol/g being obtained. The supported metalloporphyrins were used in epoxidation reactions.

Scheme 63



Oh and co-workers[144,145] have prepared a polymer-supported analogue (**207**) of manganese protoporphyrin IX, Mn−ppIX, by coupling the porphyrin to a pyridine-derivatized polystyrene support made by copolymerization of styrene and 4-vinylpyridine. Following one of the methods for immobilization of **207**,[143] the first step of the preparation was conversion of the Mn−ppIX to its acid chloride analogue using $SOCl_2$. This was then attached to aryl moieties of the support via a Friedel−Crafts acylation reaction. In addition to this point of immobilization, the authors also propose an interaction between pyridine groups on the support and the metal of the porphyrin. The potentiometric behavior of **207** has been studied[144] and the supported complex used as an ionophore for ion-selective electrodes.[145]

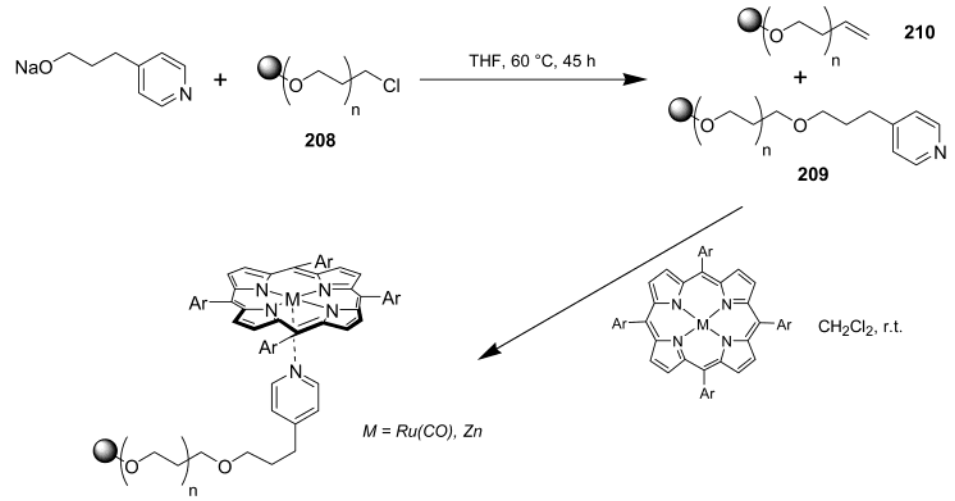


207

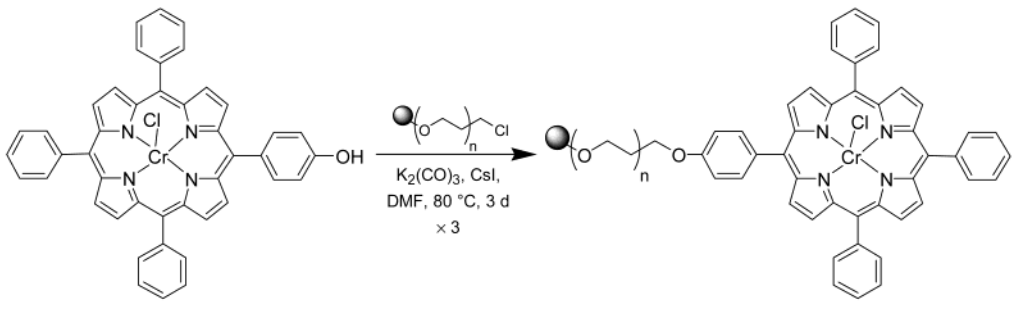
Sanders and co-workers[146] have attached ruthenium and zinc porphyrin complexes to pyridine-derivatized PEG-grafted polystyrene (ArgoGel) support **209** through noncovalent interactions and studied the bonding by gel-phase ^1H NMR spectroscopy (Scheme 64). The support was prepared by treating the sodium salt of 3-pyridylpropan-1-ol with ArgoGel−Cl (**208**). Of interest is that microanalysis data on **209** suggested complete chloride replacement, but the nitrogen content was significantly lower than that expected for total pyridine substitution. Gel-phase NMR spectroscopy showed that, as well as forming **209**, the enol ether byproduct **210** was also formed in the reaction, explaining the anomaly in the microanalysis data and highlighting the danger of relying only on microanalysis as an analytical tool when determining yields of solid-phase reactions. The metalloporphyrins were attached to **209** by treatment with a solution of excess metalloporphyrin. The supported ruthenium complex was resistant to leaching in noncoordinating solvents such as dichloromethane, but the zinc complex was not. This is attributed to the difference in binding coefficients of the two metalloporphyins, that of the ruthenium complex being 2 orders of magnitude greater than that of the zinc complex. A bipyridine-derivatized support has also been prepared using the same method as that for **209** and a Zn_3–butadiyne-linked cyclic porphyrin trimer attached.

Holmes, de Miguel, and co-workers[147] have prepared an ArgoGel-immobilized chromium porphyrin (**212**) by treatment of **208** with phenol-functionalized porphyrin **211** three times, each for 3 days, using K_2CO_3 and KI as coupling agents (Scheme 65). The supported porphyrin was used as a catalyst for polycarbonate formation in supercritical carbon dioxide.

Scheme 64

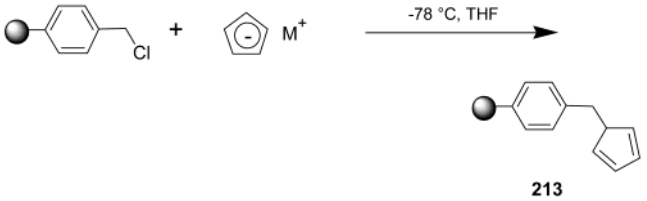


Scheme 65

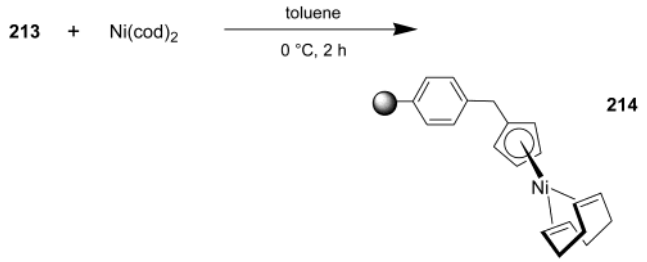


211 **212**

Scheme 66



Scheme 67



6. Polymer-Supported Metallocenes

The synthesis and reactivity of transition-metal metallocene complexes has attracted much research interest, particularly with their wide catalytic applications in processes such as hydrogenation, hydroformylation, and olefin polymerization.[17,148] Like their homogeneous analogues, polymer-bound metallocenes have found many applications in catalysis, much of the initial work being carried out in the 1970s.[17]

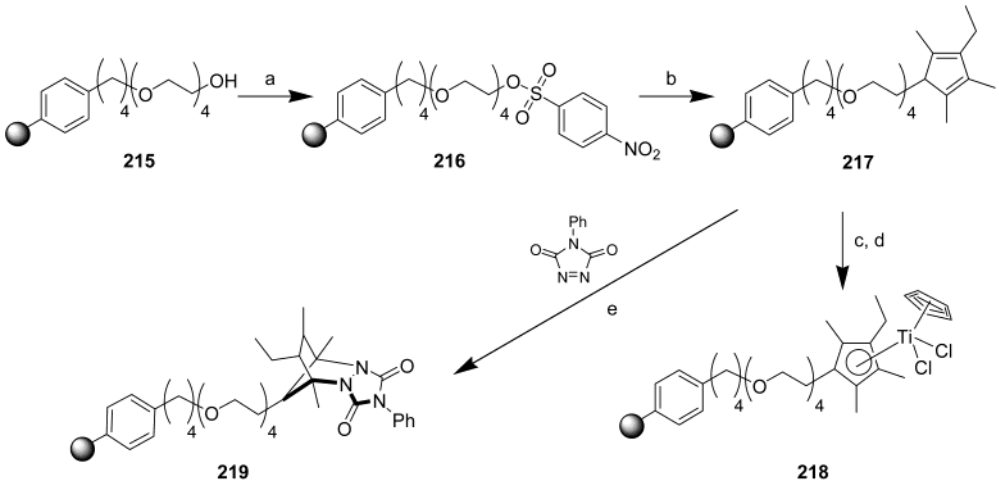
Simple supported cyclopentadiene (Cp) ligands have traditionally been prepared in only one way, namely, by treating a suitably functionalized polymer support with an alkali-metal cyclopentadienide (Scheme 66). Merrifield's resin proved to be the support of choice for a number of the early experiments, giving the simple supported complex **213**. A range of metals have been attached to **213**.[17]

Since 1996, there have been a number of reports of polystyrene-supported cyclopentadiene metal complexes, the majority being used as heterogeneous single-site catalysts for olefin polymerization.[149] A polymer-supported cyclooctadiene nickel complex, CpNi(cod) **214**, has been prepared by Sbrana and co-workers[150] by treating **213** with $Ni(cod)_2$ at 0 °C in toluene (Scheme 67). Care was taken in the preparation of **213** for use in the immobilization of the $Ni(cod)_2$, any remaining chloro functionalities left after treatment of Merrifield's resin with NaCp being removed by reaction of the support with excess methyllithium followed by reprotonation with ethanol. This was necessary because of the propensity of $Ni(cod)_2$ toward oxidative addition to alkyl and aryl halides. **214** was found to be an active catalyst for olefin polymerization, the selectivity of the process being dramatically different from that of the homogeneous analogue, the former giving high-density polyethylene, the latter giving lower oligomers (the majority being C_4–C_6).

Barrett and de Miguel[151,152] have prepared an immobilized $CpTiCpCl_2$ complex (**218**) and used it for ethylene polymerization (Scheme 68). The ligand bearing a spacer group between the polymer matrix and the Ti complex has the objective of optimizing the accessibility of the metal centers. The polymer-supported Cp ligand was prepared by initial attachment of a glycol spacer unit to poly(styryllithium). After elaboration, the corresponding supported nosyl complex **216** was treated with $NaCpMe_3Et$ to form the supported Cp ligand **217**. The metal complex **218** was then prepared by lithiation of the supported Cp ligand followed by addition of $CpTiCl_3$. The loading of the Cp on the support was estimated to be 0.28 mmol/g by derivitization with 4-phenyl-1,2,4-triazoline-3,5-dione (Cookson's reagent) and subsequent analysis of the Diels−Alder product **219**. The metal loading of **218** was estimated at 0.07 mmol/g. **218** was used as a catalyst for ethane polymerization, but activity was not as high as expected. This may be due to poor swelling of the supported catalyst and therefore limited accessibility of the metal centers.

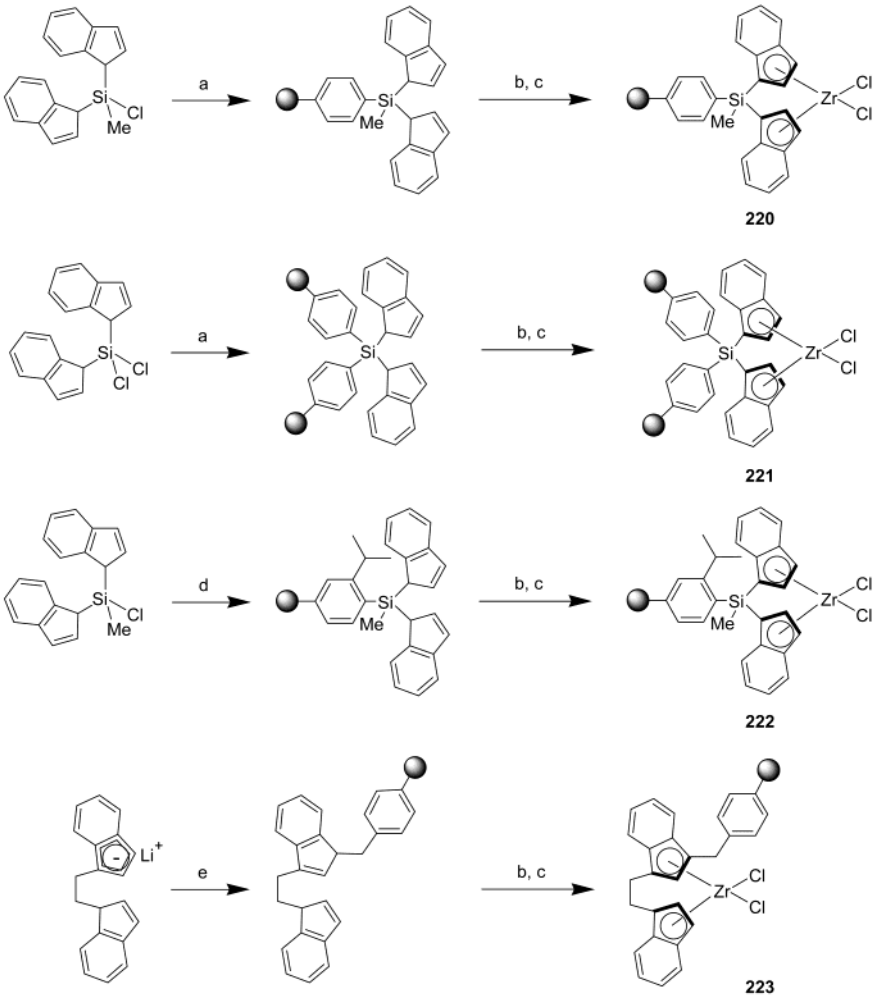
Soga and co-workers[153] have prepared four supported zirconocenes bearing indenyl (C_9H_7, Ind) groups (**220**−**223**) either by treating lithiated polystyrene with Ind-derivatized chlorosilanes or by treating Merrifield's resin with Li−Ind and then treating the lithiated supported ligand with $ZrCl_4$

Scheme 68[a]



[a] Reagents and conditions: (a) 2 × *p*-O_2NPhSO_2Cl, pyridine, CH_2Cl_2; (b) $NaCpMe_3Et$, THF; (c) MeLi, THF; (d) $CPTiCl_3$, toluene; (e) −78 °C, CH_2Cl_2.

Scheme 69[a]



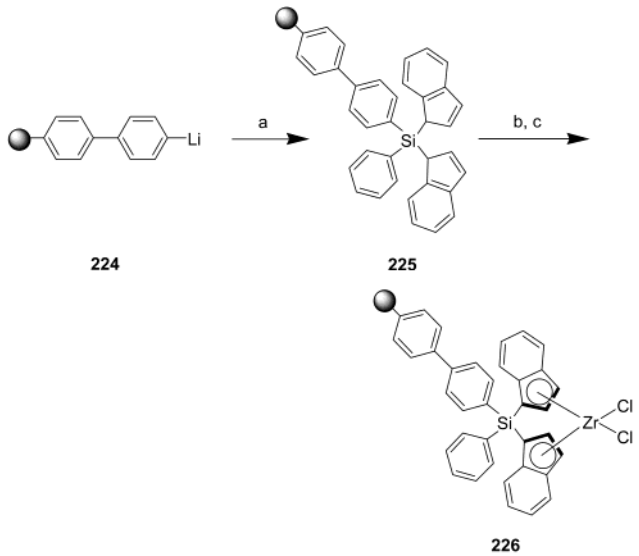
[a] Reagents and conditions: (a) lithiated polystyrene, toluene, 40 °C, 8 h; (b) BuLi, THF, 0 °C → rt, 6 h; (c) $ZrCl_4$, THF, 0 °C → rt, 12 h; (d) lithiated polymer-supported cumene, toluene, 40 °C, 8 h; (e) Merrifield's resin, toluene, 40 °C, 8 h.

(Scheme 69). Metal loadings ranging from 0.017 to 0.0017 mmol/g were obtained. The supported complexes have been used in polymerization of ethene and propene.

As an extension to their work, Soga and co-workers[154] have prepared polymer-supported Zr−di-Ind complex **226** from polystyrene (Scheme 70). Lithiation of the polystyrene, treatment with 1,4-dibromobenzene, and further lithiation gave **224**, which was treated with $PhSi(Ind)_2Cl$ to give the supported ligand **225**. The metal complex **226** was formed by treatment of this with $ZrCl_4$. The use of **226** for ethane polymerization was assessed, and subsequently[155] the mechanism of polyethylene growth on the surface of the supported catalyst beads was studied.

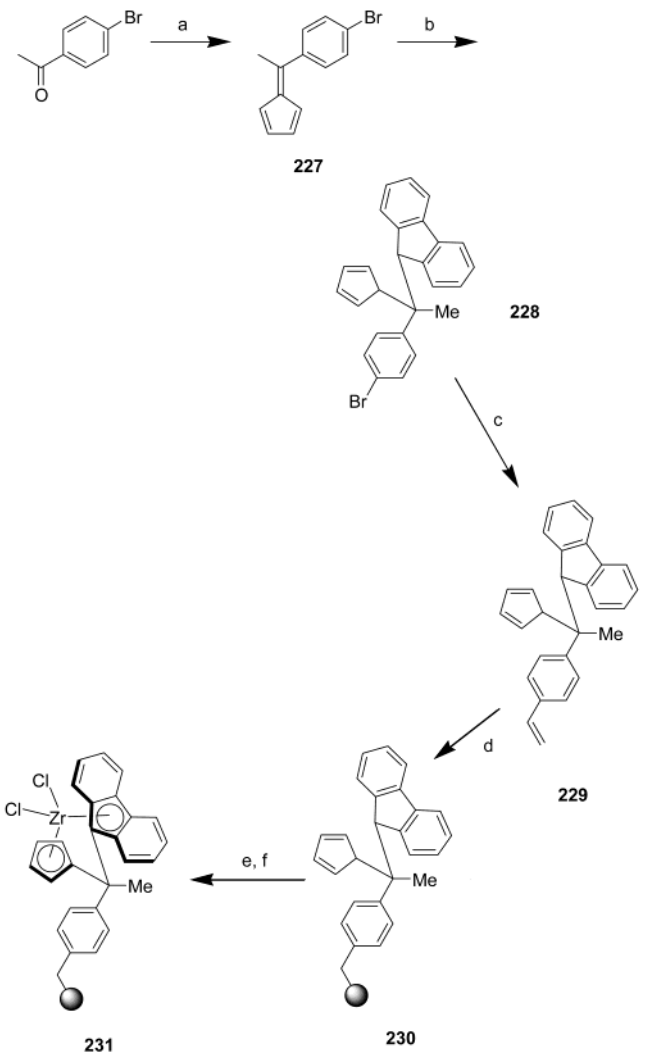
Soga and co-workers[156] have prepared a supported Cp/fluorene ligand by AIBN-initiated polymerization of a styrene-derivatized monomer, **229**, with styrene (Scheme 71). The monomer was prepared in three steps from bromoacetophenone. First the ketone was treated with CpLi to generate methylfulvene **227**. Lithiated fluorene (FluLi) was then added to form a Cp/Flu-functionalized compound, **228**, which was converted to **229** by a $Pd(PPh_3)_4$-mediated Stille coupling with vinyltributyltin. Once **229** was polymerized with styrene to form **230**, a Zr complex (**231**) was generated by treatment of the supported ligand with $ZrCl_4$. Analysis of **231** showed that less than 25% of the ligand sites were metalated. As well as

Scheme 70[a]



[a] Reagents and conditions: (a) $PhSi(Ind)_2Cl$, toluene, 40 °C, 8 h; (b) BuLi, THF, 0 °C → rt, 6 h; (c) $ZrCl_4$, THF, 0 °C → rt, 12 h.

Scheme 71[a]



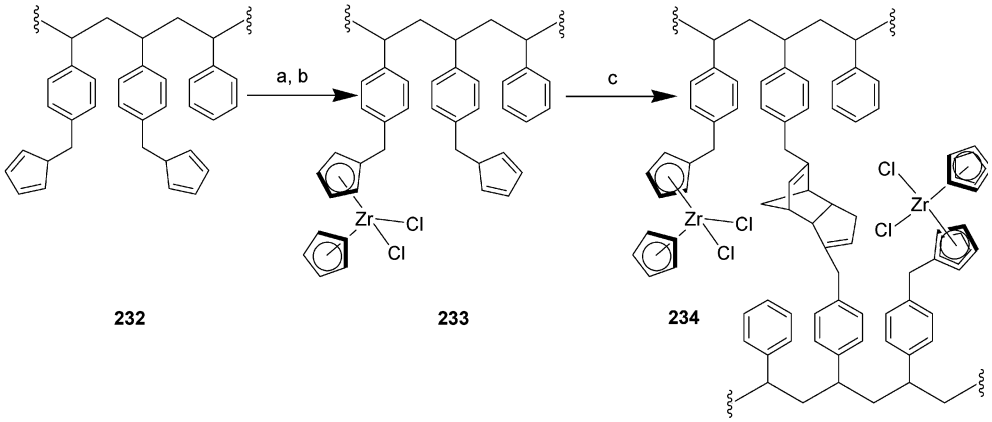
[a] Reagents and conditions: (a) CpLi, THF, 0 °C → reflux, 3 h; (b) FluLi, Et_2O, 0 °C → rt, 8 h; (c) vinyltributyltin, $Pd(PPh_3)_4$, toluene, reflux, 8 h; (d) styrene, AIBN, toluene, 60 °C, 12 h; (e) BuLi, THF, 0 °C → rt, 6 h; (f) $ZrCl_4$, THF, 0 °C → rt, 12 h.

the problems of the accessibility of ligand sites, a competing side reaction was found to be occurring, forming a supported cyclobutane, rendering a significant proportion of the ligand sites of no use. Three supported complexes were prepared with Zr loadings ranging from 0.04 to 0.31 mmol/g, and although all were found to be active for the polymerization of propene, the activity is very low compared to that of the homogeneous analogue.

Mullen and co-workers[157] have prepared a supported Zr complex (**234**) starting from **232**, a soluble polystyrene support bearing Cp functionalities, and found it to be very active in ethene polymerization (Scheme 72). $CpZrCl_3$ was added to lithiated **232**, leading to the supported zirconocene **233**. This was then dried and heated at 50 °C for 24 h, during which time Diels−Alder reactions occurred between unmetalated cyclopentadiene functionalities, thereby forming reversibly cross-linked polymer-supported metallocene **234**. This method of preparation has the advantage that the metal sites can be more uniformly distributed across the particles as there are no steric constraints in the metal loading step since at that stage the polymer is soluble. In addition, as the Diels−Alder reaction forming the cross-linking is reversible, this allows for fragmentation of the catalyst support during polyethylene processing.

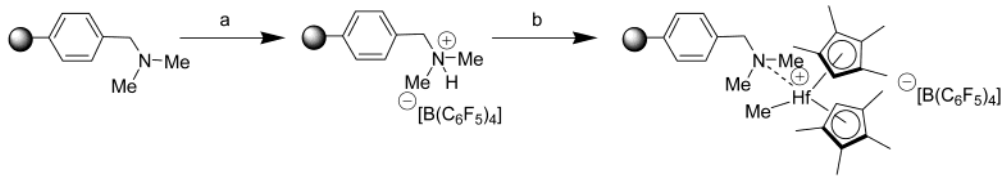
As well as immobilizing metallocenes via supported Cp or Ind functionalities, there have been reports of other methods of attachment (Scheme 73). Frechet and co-workers[158] have immobilized metal cyclopentadienyl complexes on a noninteracting polystyrene support. The aim of the work was to prepare a supported catalyst that allowed a nominally heterogeneous polymerization to proceed in a microscopically homogeneous solution-like environment. The supported catalysts were prepared by first treating lightly cross-linked Merrifield's resin with dimethylamine to form the corresponding supported amine **235**. This was then treated with $[PhNMe_2H]^+$-$[B(C_6F_5)_4]^-$, which protonates the basic support and binds the perfluorinated borate anion to the support by ion pairing, giving **236**. The active catalyst **237** is formed by reacting the borated support with the neutral dialkylmetallocene $(C_5HMe_4)_2HfMe_2$, generating the free supported amine, the metallocenium cation $[(C_5HMe_4)_2HfMe]^+$, and methane. Metal loadings of 0.14−0.77 mmol/g are reported depending on the initial loading of Merrifield's resin. The metal complex is bound to the support through a weakly coordinating interaction between the Hf and the N of the supported amine. The catalyst proves very active in ethene/1-hexene copolymerization, the weak

Scheme 72[a]



[a] Reagents and conditions: (a) MeLi, toluene, −10 °C, 1 h; (b) $CpZrCl_3$, 0 °C, 12 h, then 20 °C, 12 h; (c) dry in vacuuo, 50 °C, 24 h.

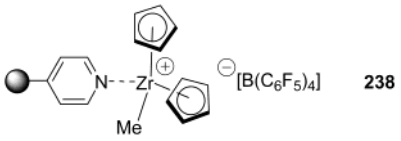
Scheme 73[a]



[a] Reagents and conditions: (a) $[PhNMe_2H]^+[B(C_6F_5)_4)^-$, CH_2Cl_2, rt, 1.5 h; (b) $(Me_4C_5H)_2HfMe_2$, toluene, rt, 1 h.

coordination between metallocene and this support being strong enough to retain the metal complex on the support during the course of the reaction. The appealing feature of this polymer-supported catalyst is that the modular synthesis allows for simple variation of each of the components (amine, ammonium salt, and metallocene), thereby opening avenues to parallel and combinatorial catalyst preparation and screening. The only requirements are that the amine component must be nucleophilic enough to displace a benzylic halide, the ammonium salt must be more acidic than the supported amine, and the metallocene must be capable of reacting with a tertiary ammonium cation to generate a free amine, methane, and a metallocenium cation. Indeed the authors have since prepared a range of other supported metallocenes using this methodology[159] and have screened them for activity in olefin polymerization, looking at both the polymer composition and morphology. They have investigated the effects of varying the amine, metallocene, and also the degree of cross-linking (and hence swelling ability) of the polymer support.

Uozumi and co-workers[160] have used a similar methodology to prepare supported Zr metallocene catalyst **238**. Using a pyridine-derivatized support, they have attached the cationic Zr complex $[Cp_2ZrMe]^+[B(C_6F_5)_4]^-$ by treating the support with a mixture of Cp_2ZrMe and $[PhNMe_2H]^+[B(C_6F_5)_4]^-$, with B and Zr loadings of 0.083 and 0.069 mmol/g, respectively, being obtained. The supported catalyst shows high activity in ethene polymerization.

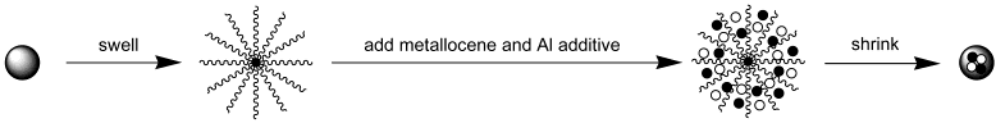


Hong, Kristen, and Reif[161] have immobilized metallocenes in polystyrene, taking advantage of the swelling−shrinking characteristics of poly(styrene-*co*-divinylbenzene) beads (Scheme 74). They prepare the immobilized metallocenes by swelling the polystyrene in toluene and then adding a slurry of the beads to a solution of metallocene. They add triisobutylaluminum or methylaluminoxane (MAO) and then remove the solvent from the mixture to leave dry beads with the metal encapsulated within them. These are then washed with heptane, a nonswelling solvent, to remove traces of metal from the surface of the beads and obtain a free-flowing consistency. Among other techniques, electron probe microanalysis was used to study the composition of the beads. This technique essentially allows for the spacial distribution of various components across the beads to be established. In this case the distribution of Zr, Al, and F was determined and found to be homogeneous over the polystyrene bead particles. The beads were then used for ethene copolymerization. They show a slow initiation toward polymerization, but then activity increases with time. Clearly with this method of immobilization the main concern is leaching of the metal out of the support during the course of the reaction, but the authors report that they have investigated this and found no evidence for metal leaching. As well as being simple to prepare, this method of immobilization has the advantage that because the metal is encapsulated within the support and not on the surface, the metallocenes are more air and moisture stable, exposure to air for a few seconds or prolonged storage under nitrogen for months not affecting the catalytic activity. It should be noted at this stage that usually these catalysts have to be used in thoroughly dried and argon-degassed solvents.

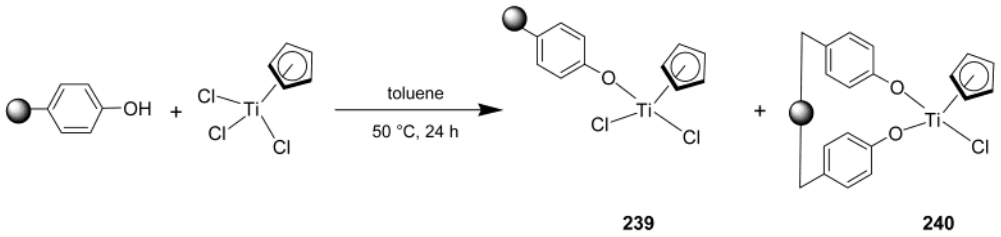
Zu and co-workers[162] have immobilized $TiCpCl_3$ on hydroxy-functionalized polystyrene supports by simply heating the two together (Scheme 75). They propose that the two supported complexes **239** and **240** are formed, the ratio of one to the other presumably depending on the metal loading. They have used the supported complexes in styrene polymerization, but not unsuprisingly there is significant leaching of the metal complex off the support when MAO is added to the reaction mixture at the start of the polymerization reaction.

Mullen and co-workers[163] have extended their work using reversibly cross-linked polystyrene supports to immobilize metallocenes through noncovalent bonding (Scheme 76). This is achieved by functionalizing the support with nucleophilic groups which, like the amine examples discussed previously, can then bind to the metallocene complex in a noncovalent manner. Heterogeneous support **241** was prepared from the

Scheme 74

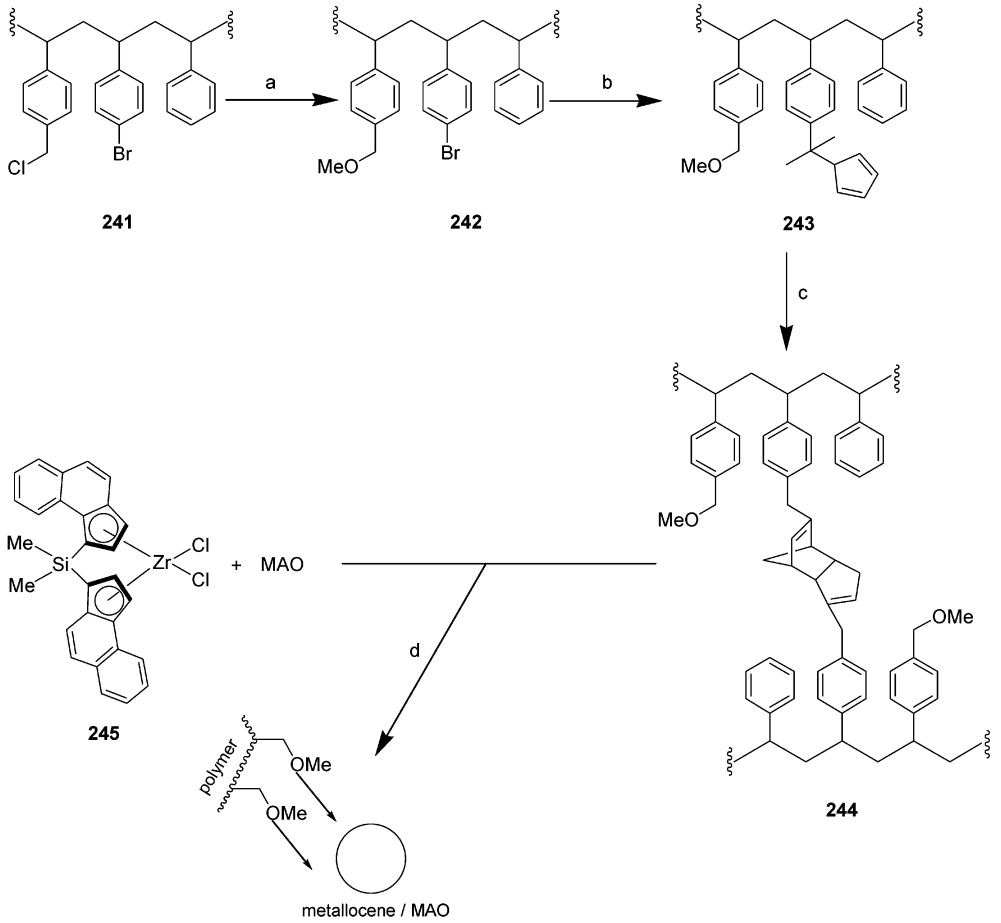


Scheme 75



239 240

Scheme 76[a]

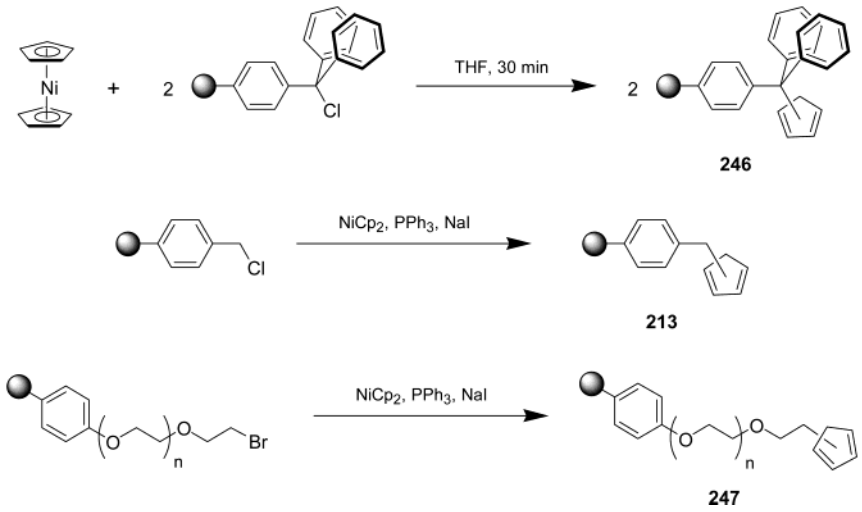


[a] Reagents and conditions: (a) NaOMe, THF/MeOH (2:1), 60 °C, 18 h; (b) BuLi, dimethylfulvene, THF, $CpZrCl_3$, −78 °C → rt, 1 h; (c) toluene, 85 °C, 18 h; (d) metallocene and MAO in toluene, rt, 10 min, then polymer added, rt, 30 min.

soluble terpolymer of 4-bromostyrene, 4-chloromethylstyrene, and styrene. After complete etherification of the chloromethyl groups using NaOMe to form **242**, the Cp functionalities are introduced via the 4-bromophenyl substituents by reaction of the polymer with dimethylfulvene, yielding **243**. The cross-linking to give **244** is then achieved by heating **243** to 85 °C overnight. The metal complex is supported by treating **244** with a solution of metallocene **245** and MAO. The MAO plays a key role in the immobilization process, and it is not possible in its absence. This is believed to be due to the fact that the methoxy groups on the support coordinate to the MAO to form a cagelike structure around the metallocene complex. An optimum MAO:Zr ratio of 730:1 was found at which catalytic activity was greatest and no leaching was observed. At lower MAO:Zr ratios, i.e., with more metallocene, activity decreases and leaching is observed.

There are a number of problems involved when using the alkali-metal cyclopentadienide route to prepare polymer-supported Cp ligands. In particular, purification of the resin at the end of the reaction can be difficult and time-consuming, the alkali-metal cyclopentadienide partaking in undesired side reactions, leading to degradation of the polymer support or formation of intractable byproducts coating the surface of the polymer spheres. This is especially the case when the polymer backbone contains polyglycol functionalities. Leadbeater has recently reported a new route to polymer-supported cyclopentadienes that circumvents the use of alkali-metal cyclopentadienides (Scheme 77).[164] Using nickelocene ($NiCp_2$), it is possible to transfer the Cp rings from the metallocene to polymer-supported trityl chloride to give **246**, both cyclopentadiene moieties on the nickelocene being transferred to the polymer support. A ratio of $NiCp_2$ to supported trityl chloride of 0.55:1

Scheme 77



is used with a total reaction time of 30 min. Using polymer-supported trityl chloride with a loading of 1.25 mmol of Cl/g resin, a Cp loading of 1.15 mmol/g is obtained. Merrifield's resin does not react directly with $NiCp_2$, but in the presence of 1 equiv of NaI and 1 equiv of PPh_3, Cp transfer occurs, forming **213**. The NaI is used for an in situ Finkelstein reaction, turning Merrifield's resin to the corresponding iodo derivative. The PPh_3 promotes the reaction between the supported iodide and nickelocene. Using Merrifield's resin with a loading of 1.8 mmol of Cl/g of resin, a loading of cyclopentadiene of 1.1 mmol/g is obtained. Using a similar methodology, a cyclopentadiene-derivatized PEG-based resin, **247**, was also prepared. A point of interest is that, in addition to elemental analysis, Cookson's reagent was used as a method for determining the Cp loading on the resins. The author reports however that the values obtained from this method were significantly higher than those obtained independently from microanalysis on the resins. It is proposed that the anomalously high values obtained are a result of Cookson's reagent undergoing not only a Diels−Alder reaction with the supported Cp but also a competitive ene reaction with the cross-links of the support.

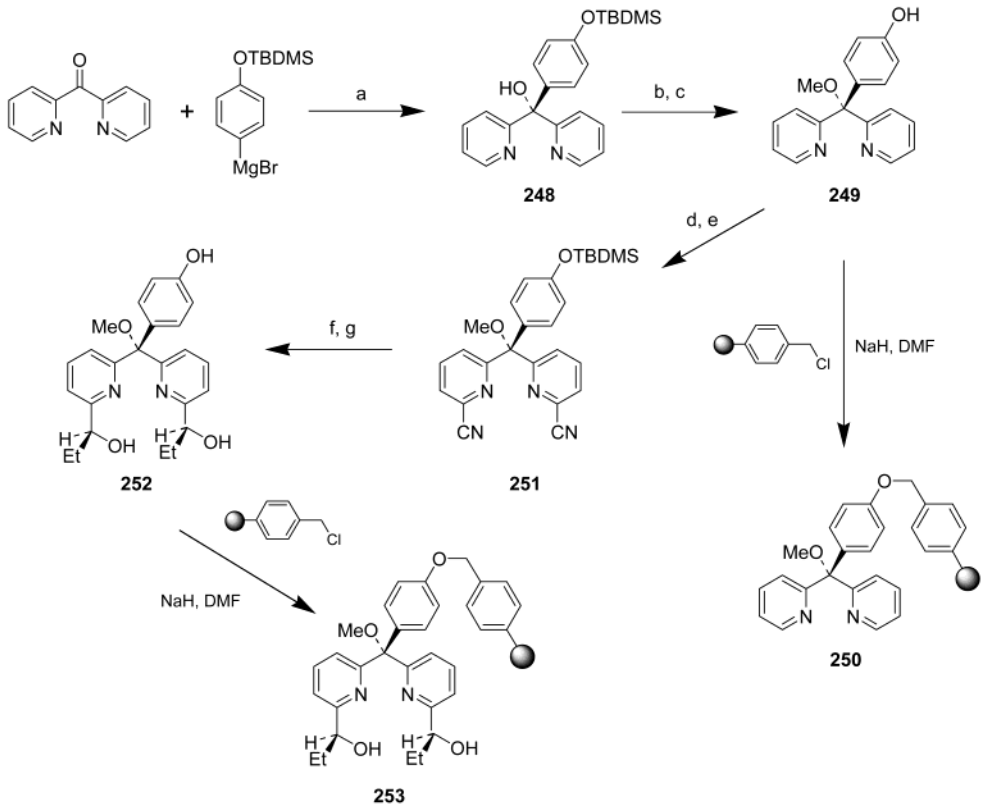
7. Preparation of Other Selected Supported Ligands and Metal Complexes

7.1. Polymer-Supported Dipyridylmethane, Pyridinooxazolines, and Bisoxazoline Ligands and Their Metal Complexes

Metal complexes of asymmetric dipyridylmethane ligands have been used as enantioselective catalysts for a range of reactions.[165] Polymer-supported pseudo-C_2-symmetric dipyridylmethane ligands have been prepared by Moberg and Levacher[166] starting from phenolic analogues of homogeneous ligands (Scheme 78). These phenolic analogues prove a synthetic challenge in themselves even before attachment to the support. Ligand **249** was prepared in two methods, the higher yielding of which was by reaction of di(2-pyridyl) ketone with TBDMS-protected *p*-hydroxyphenylmagnesium bromide followed by methylation of the methylene hydroxy function and then deprotection of the phenolic group, giving **249** in 63% overall yield. Ligand **252** was prepared from TBDMS-protected **249** by first forming the bis-*N*-oxide using *m*-chloroperbenzoic acid and then treatment with *N*,*N*-dimethylcarbamoyl chloride and trimethylsilyl cyanide to form dinitrile **251**, which was subsequently treated with ethylmagnesium bromide to give a diketone. Reduction of the ketone functionalities with (−)-(*S*)-chlorodiisopinocamphenylborane [(−)-(*S*)-Ipc_2BCl] gave **252** after acidic workup. Ligands **249** and **252** were attached to a range of chloromethylated polymers including simple Merrifield's resin to give polymer-supported dipyridylmethanes **250** and **253**, respectively. The *tert*-butyl-substituted analogue of **253** was also prepared but via a supported ketone followed by on-support asymmetric reduction of the carbonyl by treatment with (−)-(*S*)-Ipc_2BCl in THF for 3 days. This offers a better route than via the corresponding *tert*-butyl analogue of **249**, which is not only arduous to prepare but also difficult to isolate in high yield.

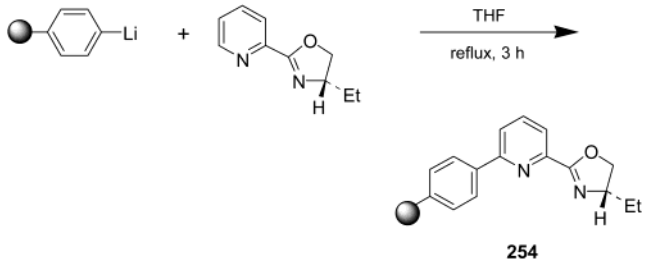
Metal complexes of pyridinooxazolines have found uses in a range of metal-mediated transformations including palladium-catalyzed allylic alkylations.[167] There have been two reports of the preparation of supported pyridinooxazolines. Brunner and Brandl[168] chose as their point of immobilization the 6 position of the pyridine ring (Scheme 79). They attached the ligand to the support by direct reaction of lithiated polystyrene with an unfunctionalized pyridineoxazoline to give **254**. A rhodium complex of **254** was prepared by reaction of the supported ligand with $[Rh(cod)Cl]_2$ but not characterized. It was used as a catalyst for the enatioselective hydrosilylation of acetophenone. The authors report that the supported metal complex is recyclable, but after 8−10 times of use, the chemical yield drops substantially, but what is noteworthy is that together with this there is an inversion in the stereochemistry of the product. This indicates that there may well be a number of different metal complexes formed when the supported ligand is treated with $[Rh(cod)Cl]_2$, each with differing stabilities and enatioselectivities, the ratio of these changing with use of the supported catalyst. This is a clear example of where characterization of

Scheme 78[a]



[a] Reagents and conditions: (a) THF, rt, 12 h; (b) NaH, MeI, THF, rt, 12 h; (c) 1 M H_2SO_4, rt, 12 h; (d) (starting from TBDMS-protected **252**) *m*CPBA, CH_2Cl_2, rt, 12 h; (e) 3 × dimethylcarbamoyl chloride, TMS−CN, CH_2Cl_2 rt, 12 h; (f) EtMgBr, benzene/Et_2O (1:1), rt, 2 h, (g) (−)-(*S*)-Ipc_2BCl, THF, rt, 2 d, then propionaldehyde, 0 °C → rt, 24 h.

Scheme 79

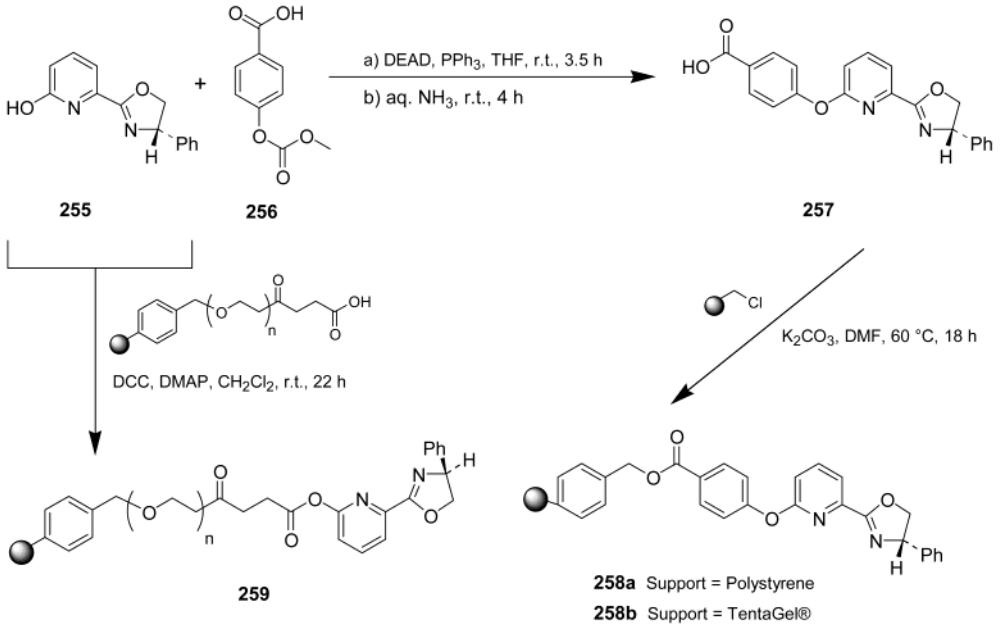


the supported metal complexes would be hugely beneficial to understanding their reactivity and exploiting their use in synthesis.

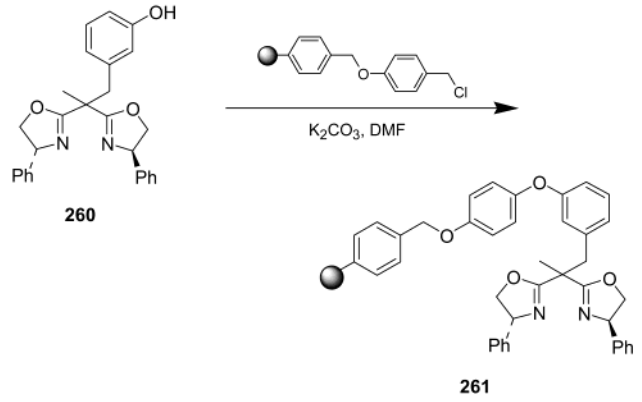
Moberg and co-workers[169] have immobilized a range of pyridinooxazolines bearing an ether linkage on the 6 position of the pyridine ring on three different supports (Scheme 80). Ligand **257**, prepared from pyridinooxazoline **255** and carbonate **256** by Mitsunobu coupling followed by deprotection with aqueous ammonia, was attached to Merrifield's resin using K_2CO_3 in DMF, giving **258a**, the coupling occurring in 51% conversion. Using the same methodology, **257** was attached to PS−PEG-based resin Argogel−Wang−Cl to give **258b**. A further PS−PEG-based resin, TentaGel−COOH, was used as a support, **255** being attached directly to this to give **259**. A range of substituted pyridinooxazolines were also attached to the three supports using identical methods. Palladium complexes of all the supported pyridinooxazolines were prepared by reaction with $[PdCl(\mu^3\text{-}C_3H_5)]_2$ and used in situ in allylic substitution reactions, results comparable to a homogeneous model being obtained with all the supported complexes except those on TentaGel. This is probably due to the increased proximity of the ligand to the support and hence increased steric crowding around the pyridinooxazoline, limiting both metal loading and also approach by reaction substrates.

Chiral C_2-symmetric bisoxazolines are well-known chiral ligands, forming complexes with a variety of metals. They have been used successfully as enatioselective catalysts in a range of reactions.[170] There have been three reports of the preparation and use of polymer-supported bisoxazoline ligands and metal complexes. Moberg and Hallman[171] prepared **261** from hydroxy-functionalized bisoxazoline **260** and a chloromethyl-derivatized PS−PEG−Wang−Cl resin by reaction in DMF in the presence of potassium carbonate, a ligand loading of 0.071 mmol/g being achieved (Scheme 81). Although not characterized, a palladium complex of **261** was prepared by treatment of the supported bisoxazoline with $[(\eta^3\text{-}C_3H_5)PdCl]_2$ in a 3:1 molar ratio and was used in palladium-catalyzed allylic substitution reactions with enantioselectivity similar to that of the homogeneous analogue being observed. Metallic palladium precipitates during the course of the reaction, thereby precluding recycling of the supported complex unless removal of the palladium using saturated KCN in DMSO is undertaken. The supported ligand was also used in a zinc-catalyzed Diels−Alder reaction but with lower reactivity and selectivity compared to those of the homogeneous analogue.

Scheme 80



Scheme 81



Luis, Mayoral, and co-workers[172] prepared **263** by AIBN-initiated suspension polymerization of styrene derivative **262**, prepared by double alkylation of the methylene bridge of simple bisoxazolines with *p*-vinylbenzyl chloride and with styrene using toluene and dodecanol as porogens (Scheme 82). Dialkylation of the methylene bridge was considered more advantageous than monoalkylation as the former maintains the C_2 symmetry of the ligand. As well as polymerization of **262** with styrene, three classes of homopolymerized solid were also prepared (Scheme 82). In the first, **262** was left to polymerize thermally, and in the second and third, AIBN was used to initiate the reaction and toluene or a mixture of 1-dodecanol and toluene was used as a porogenic agent. Copper complexes of all the polymers were formed by reaction of the immobilized bisoxazolines with $Cu(OTf)_2$. The metal loadings obtained with **263** were substantially higher than those using the self-polymerized solids. All the immobilized complexes were screened for their catalytic activity in asymmetric styrene cyclopropanation reactions. The yields and enatioselectivities reported are similar to or, in some cases, better than those obtained with homogeneous analogues, the best results being obtained with the homopolymers.

As an extension to this work, the same group[173] have copolymerized **262** with styrene and different cross-linking agents to prepare a range of bisoxazoline-functionalized monolithic resins. They have grafted a bisoxazoline onto a polystyrene support, forming **264**. This was achieved by double alkylation of the bisoxazoline ligand with Merrifield's resin using methyllithium as a base. Also a range of silica-immobilized bisoxazolines have been prepared using **262** as a precursor. Having prepared the range of immobilized bisoxazolines, the copper complexes of each were formed using $Cu(OTf)_2$ and screened using the metal complexes as cyclopropanation catalysts. The activities of all of these complexes were inferior to those obtained when using the homopolymers.

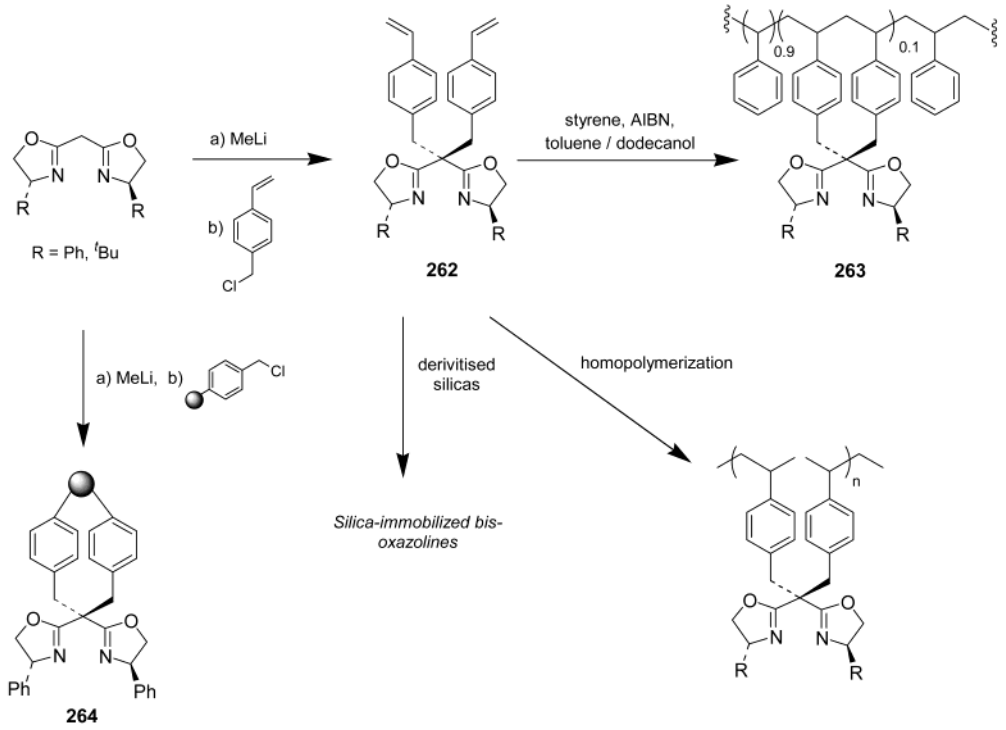
Salvadori and co-workers[174] have also prepared an immobilized bisoxazoline, **266**, by AIBN-initiated copolymerization of styrene-derivatized precursors, this time with styrene and divinylbenzene (Scheme 83). However, the styrene-derivatized bisoxazoline precursor **265** has a C_4 ether linkage between the ligand and the vinyl functionality, thereby increasing the flexibility of the active sites in the resultant polymer. The copper complex of **266** was formed by reaction with $Cu(OTf)_2$, maximum metal loadings 0.18 mmol/g being obtained, and used successfully in the enantioselective Mukaiyama aldol reaction, similar reactivity and activity being found with the supported and homogeneous analogues.

Although not within the limit of this review, it is worth noting that azabisoxazolines have been successfully immobilized on soluble supports and their copper complexes used in asymmetric cyclopropanation reactions.[175]

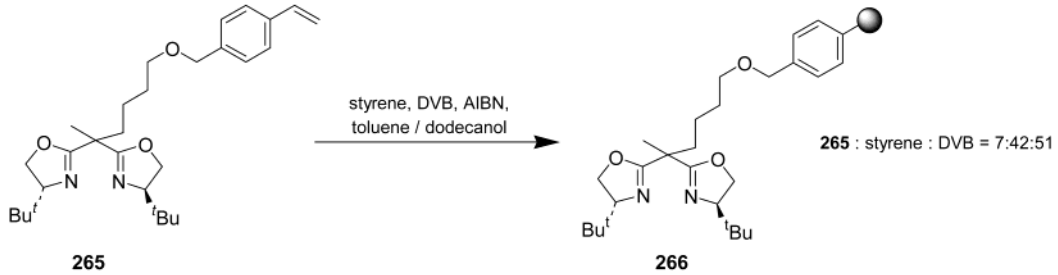
7.2. Polymer-Supported *N*-Heterocyclic Carbene Ligands and Immobilized Metal Complexes

A polymer-supported *N*-heterocyclic carbene (NHC) palladium complex (**269**) has been prepared by Herrmann and co-workers.[176] This has been achieved by

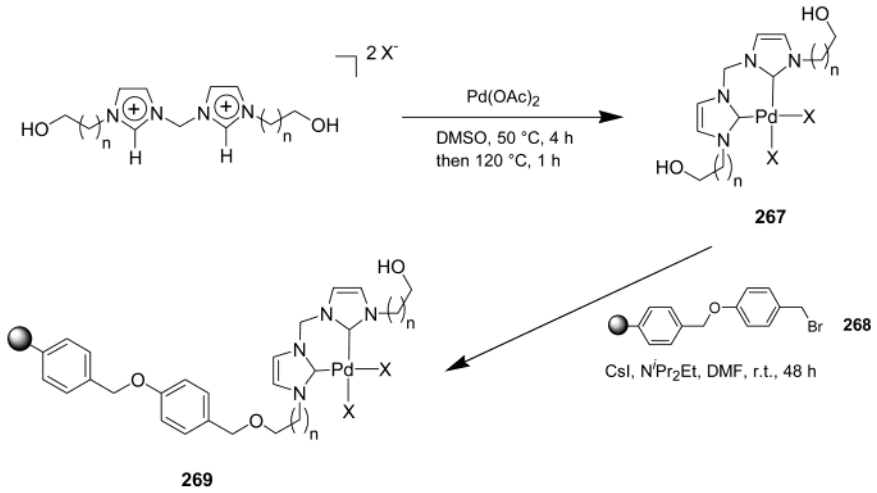
Scheme 82



Scheme 83

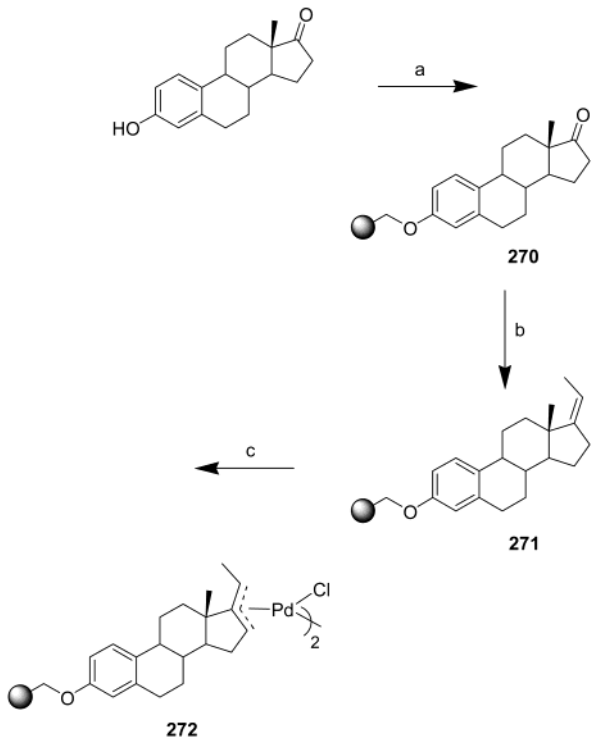


Scheme 84



the direct reaction of readily prepared alcohol-functionalized palladium carbene complexes **267** with *p*-(bromomethyl)phenoxymethyl-functionalized polystyrene (Wang bromopolystyrene, **268**) using N^iPr_2Et and CsI as coupling agents (Scheme 84). The loading of the metal complex on the support was found to be substantially lower than estimated for one molecule of carbene complex being bound to each bromomethylphenyl functional group of the support, indicating that only a small proportion of the functionalized sites on the support are accessible for attaching the complex.

Scheme 85[a]



[a] Reagents and conditions: (a) $^{n}Bu_4NOH$, KOH in H_2O, *o*-dichlorobenzene, 80 °C, 3 d; (b) 10 equiv of $^{+}PPh_3CH_2CH_3Br^{-}$, 9.5 equiv of $^{t}BuOK$, THF, 41 h; (c) $Pd(O_2CCF_3)_2$, THF, rt, 6 h, then $^{n}Bu_4NCl$, THF, rt, 1 h.

7.3. A Polymer-Supported π-Allylpalladium Complex

A polymer-supported π-allylpalladium complex, **272**, has been prepared by Yamamoto and co-workers[177] and used as a catalyst for the asymmetric allylation of imines, yields being good but enantioselectivity quite low. The immobilized ligand **271** is formed by coupling of Merrifield's resin with estrone using a mixture of Bu_4NOH and aqueous KOH to give **270** followed by a Wittig reaction with triphenylphosphonium ethyl bromide. Reaction of **271** with palladium trifluoroacetate followed by addition of $^{t}Bu_4NCl$ gives **272** with a Pd content of 4.6 wt % (Scheme 85). Notably, the enantioselectivity of these complexes is significantly less than that reported by Chan and co-workers[77] when using supported chiral ferrocenylphosphinimines.

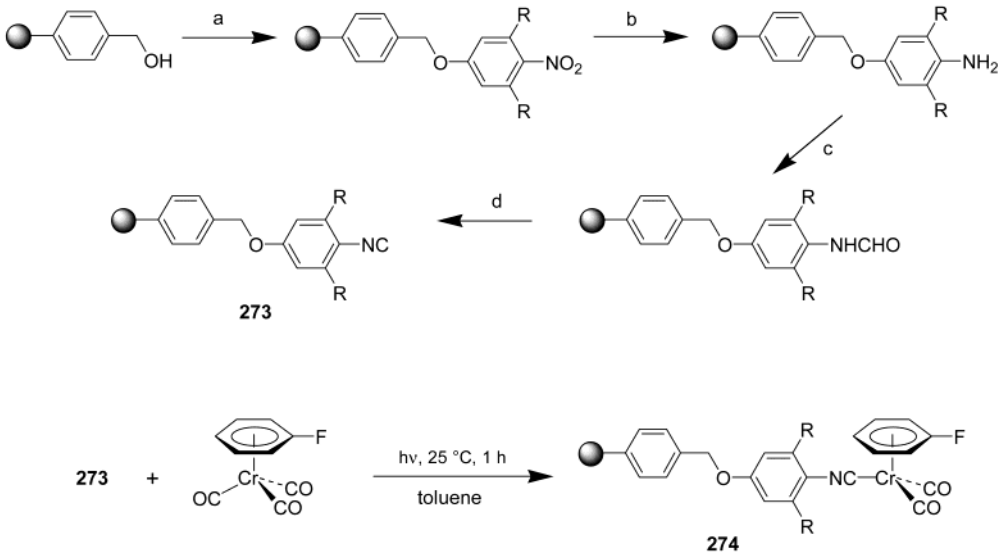
7.4. Polymer-Supported Chromium Isocyanides

Building on the results of Semmelhack and co-workers[42] studying the effects on the rate of nucleophilic substitution in fluoroarene−$Cr(CO)_2L$ complexes of changing the ligand L, Maiorana and co-workers[178] have prepared polymer-supported fluorobenzene−chromium complex **274** using an isocyanide moiety as linker. The isocyanide-derivatized polymer support **273** was prepared from hydroxymethylpolystyrene in four steps, giving ligand loadings of approximately 0.85−0.9 mmol/g (Scheme 86). After the synthesis and reactivity of homogeneous analogues were studied, $Cr(CO)_3(C_6H_5F)$ was attached to the support by direct photolysis with **273**, giving **274** with a metal loading of 0.3 mmol/g. The supported complex was subsequently used successfully in S_NAr reactions.

7.5. Polymer-Supported Scandium Triflate

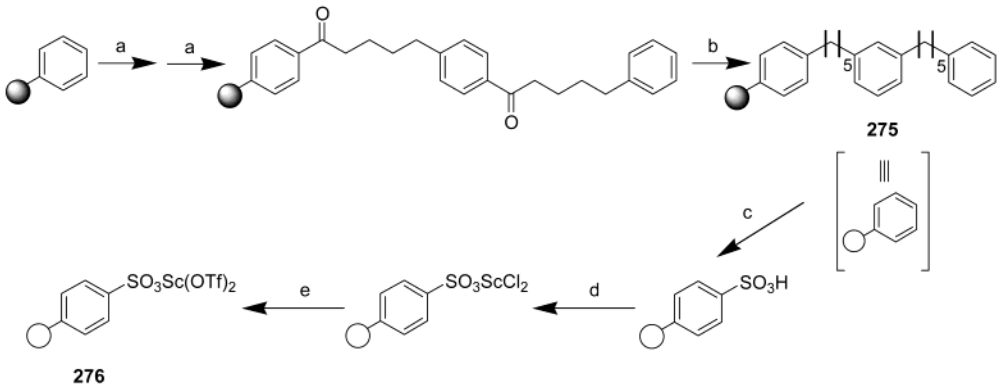
Kobayashi and co-workers have developed a range of Lewis acid surfactant combined complexes such as scandium tris(dodecyl sulfate) and scandium tris(dodecanesulfonate) which can be used in water as catalysts for Aldol reactions of silyl enol ethers with aldehydes.[179] As an extension to this, Kobayashi and Nagayama[180] have developed a polystyrene-supported scandium catalyst, **276**, which shows high activity in water (Scheme 87). Starting from polystyrene cross-linked with 1% divinylbenzene, alkylaromatic spacer groups were attached by reaction twice in succession with 5-phenylvaleryl chloride and $AlCl_3$ in carbon disulfide followed by reduction of the

Scheme 86[a]



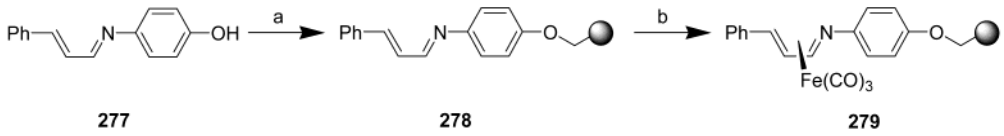
[a] Reagents and conditions: (a) 3 equiv of PPh_3, 3 equiv of DEAD, 3 equiv of *p*-NO_2ArOH, THF, rt, 24 h; (b) 9 equiv of $SnCl_2$, DMF, rt, 24 h; (c) 30 equiv of Ac_2O/HCOOH, THF, 60 °C, 2 h; (d) 5.5 equiv of PPh_3, 11 equiv of NEt_3, 5.5 equiv of CCl_4, CH_2Cl_2, rt, 36 h.

Scheme 87[a]



[a] Reagents and conditions: (a) $Ph(CH_2)_4COCl$, $AlCl_3$, CS_2, rt, 24 h; (b) $AlCl_3$, $LiAlH_4$, Et_2O, reflux, 12 h; (c) $ClSO_3H$, CH_2Cl_2, 0 °C, 12 h; (d) $ScCl_3$, MeCN, reflux, 24 h; (e) TfOH, CH_2Cl_2, CH_2Cl_2, rt, 12 h.

Scheme 88[a]



[a] Reagents and conditions: (a) Merrifield's resin, NaH, DMF; (b) $Fe_2(CO)_9$, THF, rt.

carbonyl groups using $AlCl_3$–$LiAlH_4$ in diethyl ether to form **275**. The terminal aryl groups were then sulfonated using a chlorosulfonic acid/acetic acid mixture, and the supported sulfonyl complex was treated with $ScCl_3$ and then trifluoromethanesulfonic acid (TfOH) to give **276**.

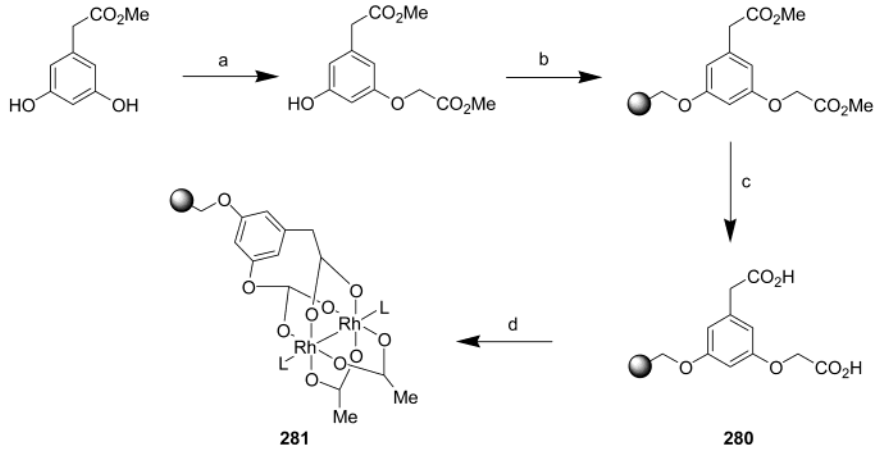
7.6. A Polymer-Supported $Fe(CO)_3$ Transfer Agent

Tricarbonyliron diene complexes have found many uses in synthetic chemistry, but their synthesis is often not easy. Knölker has developed a range of tricarbonyl(η^4-1-aza-1,3-butadiene)iron complexes that are excellent transfer agents for the $Fe(CO)_3$ complexation of 1,3-dienes and shown their versatility.[181,182] As an extension to this work, Knölker and Gonser[183] have prepared a polymer-supported 1-aza-1,3-butadiene, **278**, by reaction of Merrifield's resin with phenolic 1-aza-1,3-butadiene **277**, formed from cinnamaldehyde and *p*-hydroxyaniline (Scheme 88). The corresponding tricarbonyliron complex **279** was formed by treatment of **278** with an excess of $Fe_2(CO)_9$ in THF using ultrasound. The iron complex was subsequently used efficiently as a transfer agent for the tricarbonyliron complexation of 1,3-dienes.

7.7. Polymer-Supported $Rh_2(OAc)_4$

Gani, Andersen, and co-workers[184] have developed a polymer-supported analogue (**281**) of dirhodium tetraacetate for use as an alkene hydrogenation and hydroformylation catalyst (Scheme 89). Their methodology involves the replacement of two of the carboxylate groups in $Rh_2(OAc)_4$ by a templated dicarboxylate ligand that positions each carboxyl group in a position to adjacent groups similar to that in the parent complex, this being attached to the polymer support via a linker. Using molecular modeling, they found that *meta*-substituted arenes capable of forming two μ-coordinated 11- or 12-membered rings

Scheme 89[a]



[a] Reagents and conditions: (a) NaH, $BrCH_2CO_2Me$, THF, rt,16 h; (b) Merrifield's resin (1.1. mmol of Cl/g), NaH, DMF, 60 °C, 3 h; (c) (i) 0.1 M NaOH in THF/H_2O (9:1), rt, 72 h, or (ii) then 10% TFA in CH_2Cl_2, rt, 2 h; (d) $Rh_2(OAc)_4(MeOH)_2$, THF, reflux, 48 h.

caused minimum perturbation of the carboxylate groups in $Rh_2(OAc)_4$ and so built ligand **280** on the basis of this. Starting from 3,5-dihydroxyphenylacetic acid, **280** was prepared in four steps. The methyl ester of the acid was formed followed by *O*-alkylation with either methyl- or butylbromoacetic acid and the phenolic diester reacted with Merrifield's resin (Cl loading 1.1 mmol/g) using NaH to form the corresponding immobilized bis(carboxylic ester) in quantitative yield. Hydrolysis of the ester functionalities gave **280**, and refluxing a THF solution of $Rh_2(OAc)_4$ with this for 2 days gave **281** containing approximately 10% Rh by mass. The corresponding supported ligand and metal complex starting from 3,4-dihydroxyphenylacetic acid were also prepared, but the metal loading was approximately half that of **281**, this being due to the formation of a 1:1 mixture of the *meta*- and *para*-substituted isomers of the diacid ligand, only the *meta* isomer going on to react with $Rh_2(OAc)_4$.

8. Concluding Remarks

As this review has shown, a large number of supported ligands and corresponding metal complexes have been prepared and used as catalysts for synthetic organic chemistry, this growing at a very fast rate. A wide and diverse range of ligands have been attached to polystyrene by reaction of simple derivatized polystyrenes with suitable derivatives of the ligands. In addition a number of supported ligands have been prepared by copolymerization of styryl derivatives with styrene and divinylbenzene.

There are several key areas that need to be developed to be able to prepare supported metal complexes more reliably and better understand their activity. As this review has shown there are a wide range of supports available onto which ligands and metal complexes can be grafted. New methods of support preparation and functionalization are important, and with this comes the idea of developing designer supports for particular catalytic applications. Polymer supports are still expensive to purchase, and for them to have more widespread use it will be necessary to develop more cost-effective routes for their preparation.[185] It is important to understand the role of the polymeric backbone in the catalytic activity of immobilized metal complexes and to realize that very different reactivities and selectivities can be found if, for example, the linker or the degree of cross-linking is altered. This is clearly shown by Burguete and co-workers in their studies on immobilized TADDOL complexes discussed here[100] and also in related work on supported amino alcohols.[186,187] Other reports of studies on microenvironmental effects are also appearing in the literature.[188,189] In addition, the polymeric backbone is important in the recycling of supported catalysts. If the support is brittle or too rigid, it can break down after a few uses. Also, polystyrene supports are susceptible to osmotic shock, this breaking down the support as it is washed between uses. Both these factors make recycling difficult. Ways around this include the development of new more robust supports and also of flow reactors[16] where the substrate is passed through a bed of the immobilized catalyst, without significant perturbation of the support.

The development of new analytical tools that can be applied to the characterization of polymer-supported metal complexes is proving ever more important. There are already a wide range of techniques that have been used. These include gel-phase and solid-state NMR,[190] Mössbauer,[191] IR, and FT-Raman[192] spectrocopies, together with elemental analysis, chemical titration, cyclic and rotating-disk voltammetry,[193] and a range of X-ray techniques. It is however fair to say that there are still gaps that need to be filled together with addressing matters such as quality of data and ease of use. Also it is important that more than one technique is used to characterize supported catalysts since, as seen a number of times in this review, one technique in isolation may give erroneous results so confirmation from another method is invaluable. A number of the supported complexes discussed in this review have not been fully characterized. This is of particular concern if the metal complexes are going to be used in catalysis and especially if comparisons are going to be made with "homogeneous analogues". Also if a supported metal complex is recycled numerous times in catalysis, it is important to know whether the metal complex used in subsequent runs is the same as that prepared and used initially. A clear example of where this is not the case is the supported rhodium pyridinooxazoline complex **254**, which shows changing activity and enantioselectivity when it is recycled more than six times.[168]

As shown elegantly by Semmelhack and co-workers[42] and by Gani, Andersen, and co-workers[184] in their preparation of chromium phosphine complexes and supported rhodium acetate, respectively, it is important to think about how best to immobilize a metal complex on a polymer support before embarking on the project. By preparing homogeneous analogues, Semmelhack showed that certain phosphine ligands were unsuitable for use as linkers for chromium arene complexes if they were to be used in S_NAr reactions. Gani and Andersen showed how molecular modeling can be used to find the optimum supported ligand for immobilization of $Rh_2(OAc)_4$.

Another point for attention is eradication or at least minimization of leaching of the metal complex off the support during the course of a reaction. This is a particular problem when they are being used in applications such as synthesis of fine chemicals where contamination of the product with heavy metals is highly undesirable. Leaching still proves to be a weakness of supported metal catalysis, and the development of new ligands that hold the metal complex firmly during the course of a reaction proves an exciting avenue for future research. If only a small amount of leaching is observed, then one option would be to use polymer-supported scavengers to remove the small quantities of metal from the product solution. Within the organic chemistry community a range of polymer-supported scavengers have been developed recently for use in purification of reaction mixtures, but attention has been focused primarily on removal of organic substrates.[16,194,195]

This being said, there have been a number of reports dating from the 1970s forward on preparing and screening scavengers that will sequester metal complexes from solution.[196] Most of these have been related to polymer-supported crown ether or calixerene complexes, a recent example being from Alexandratos and Natesan,[197] who have prepared a range of polymer-supported calix[4]arenes that show quantitative complexation of Fe(II) and Pb(II) from 0.01 M nitric acid. However, it will not always be possible to remove metal complexes from solution using crown ethers or other cryptands, so this area still needs considerable development if they are to be used in purification steps in conjunction with polymer-supported catalysts for the preparation of fine chemicals.

In conclusion, with the ever-increasing drive to develop more environmentally benign synthetic routes to target compounds, supported metal catalysts will become increasingly important. The development of the field will involve organic, inorganic, and physical chemists as well as chemical engineers. It is proving to be an inspiring and fast growing area, and the future is very exciting.

9. Acknowledgment

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