ROMPgel Reagents in Parallel Synthesis

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ROMPgel Reagents in Parallel Synthesis

A. G. M. Barrett,* B. T. Hopkins, and J. Köbberling

Department of Chemistry, Imperial College of Science, Technology and Medicine, London SW7 2AY, United Kingdom

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I. Introduction

The increased demands for small but diverse libraries in the drug discovery process within recent years has led to a shift in attention away from classical solid-supported organic chemistry (SPOS) toward liquid phase parallel synthesis. Due to the fact that generating a library by SPOS is associated with lengthy optimization processes, when compared to the actual synthesis of the library, large libraries were favored in order to use the developed synthetic routes efficiently. Unfortunately, these large libraries often lack appropriate diversity and the "design" followed frequently only from pragmatism. Classical liquid phase parallel synthesis starts to deliver compounds far more rapidly and is thus also effective in the production of smaller libraries. The biggest problems associated with liquid phase synthesis are the tedious workup to separate the product from excess reagents, catalysts, and side products. This problem can be very elegantly addressed by the use of immobilized reagents, catalysts, and scavenger reagents. With the aid of these reagents the need for chromatography or other separation techniques in workup can be virtually excluded, because a simple filtration separates the soluble product from all insoluble or immobilized impurities. It is therefore not surprising that the use of supported reagents has become the subject of considerable emphasis within recent years, although it should be stated that the initial pioneering work on this subject by the groups of Frechet,[1,2] Hodges,[3] Hutchins,[4] and Sherrington[5] dates back to the mid-1970s. Recently, several extensive reviews comparing all of the available reagents have been published.[6−8] Most supported reagents are based on either polystyrene beads[9] or inorganic supports.[10] Reagents based on polystyrene beads are mostly macroporous ion exchange type resins[11,12] or low cross-linked gel type polystyrene beads derivatized either directly from polystyrene or from Merrifield's chloromethylated polystyrene. In the latter cases the loading of active functional groups on the resin is limited due to the fact that not all of the styrene units of the polymer backbone actually are functionalized. Reagents based of this type usually have loadings of 1−1.5 mmol/gram, although recently significant efforts have been devoted to increasing these values.[9] A large increase in the loading of resins can be achieved if every monomer unit of the polymer contains the desired active functionality. To allow this, the monomer needs to be functionalized before polymerization, and therefore it is necessary to find polymerization conditions that are compatible with diverse different functional groups. This is ideally fulfilled using

* To whom correspondence should be addressed. E-mail: agmb@ic.ac.uk.

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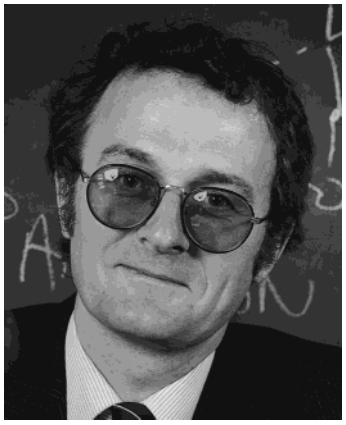


Tony Barrett started his academic career at Imperial College, London (B.Sc. 1973; Ph.D. 1975, with Derek H. R. Barton; Lecturer, 1975; and Senior Lecturer, 1982). He was appointed a full professor of Chemistry at Northwestern University, Evanston, IL (1983), and at Colorado State University (1990). In 1993 he returned to his alma mater, IC, as Glaxo Professor of Chemistry, Sir Derek Barton Professor of Synthesis, Director of the Wolfson Centre for Organic Chemistry in Medical Science and Head of Synthesis. His research interests include the total synthesis of bioactive natural products, porphyrazine chemistry, the design of methods for organic synthesis including novel catalysis, enantioselective transformations, and supported reagents.

Brian Hopkins was born in Dublin, Ireland, in 1973. He received his National Diploma from the Institute of Technology at Waterford in 1993, followed by his B.Sc. (Honors) in chemistry from the University of Glamorgan in 1994. In 2000 he completed his Ph.D. in chemistry from the State University of New York at Buffalo, where he worked with Professor Wayne K. Anderson on the synthesis of bioisosteres of mycophenolic acid. Brian was a postdoctoral fellow at Imperial College London for two years working with A.G.M.B. on the development of ROMPgels. He is currently employed at Infinity Pharmaceutical Inc., Boston, MA.

Johannes Köbberling was born in Göttingen, Germany. He received his chemical education at the Technical University in Aachen (RWTH), where he received his diploma in 1997. He then worked on the development of new linkers for solid phase chemistry under the guidance of D. Enders and received his Ph.D. in Aachen in 2001. During his one-year postdoctoral stay at Imperial College, London, in the group of A.G.M.B., he conducted research on ROMPgels. He is currently working in the pharmaceuticals division of Bayer AG, Wuppertal, Germany.

polymer supports derived from the ring-opening metathesis polymerization (ROM polymerization) of strained cyclic monomers.[13,14] Such polymerization reactions are especially valuable given the functional group tolerance of the Grubbs' catalyst **1** and related ruthenium carbenes.[15,16] Additionally, the less stable but highly active molybdenum carbenes **2** introduced by Schrock[17,18] are also of considerable value in the elaboration of ROM polymers.

This review will summarize how ROM polymerization can be used to produce functionalized polymers for organic synthesis. The use of ROM polymerization in the preparation of surface-functionalized inorganic and organic supports for application in heterogeneous catalysis will also be discussed.[14,19] Functionalized ROM polymers can also be utilized in a number of different applications: polymers functionalized, for example, with penicillin,[20] nucleoside,[21] or peptide,[22,23] are of biological interest. The synthesis of more complex neobiopolymers based on ROM polymerization leads to materials used, for example, in the exploration of the underlying features governing protein−carbohydrate interactions.[24−34] Furthermore, supports generated by ROM polymerization have extensively been used in chromatography,[35−37] for example, with cyclodextrin-derived supports[38−40] and in solid phase extraction (SPE) of, for example, lanthanides.[41−43] Hodges et al. follow an alternative approach to high-loading polymers by immobilizing functionalized monomers onto polystyrene cores utilizing a living free radical polymerization.[44−46] Because the grafted polymer chains grow outward from the beads in a linear fashion reminiscent of dreadlocks, they have been named Rasta resins. Up to now a high-loading isocyanate scavenger resin,[47] a Rasta silane resin,[44] and immobilized carbodiimides[46] have been published.

The core of this review deals with an approach devised by Barrett to synthesize highly functionalized ROM polymers utilizing Grubbs ruthenium catalyst $Cl_2(Cy_3)_2Ru{=}CHPh$ (**1**) to perform ring-opening metathesis, thus generating living polymers. This approach has led to the ROM polymers as templates for the construction of synthetic libraries,[48] as ROMPgel-supported reagents for solution phase combinatorial chemistry, and also as high-loading scavengers for impurity annihilation. The polymerization is facilitated by release of ring strain from the readily available and inexpensive norbornene or 7-oxanorbornene monomer building blocks to afford a polymeric material with a loading identical to the molarity of the monomer. These polymers consist of a repeating functionalized monomer unit having a statistical *E*/*Z* mixture relative to the olefins in the polymer backbone. Such ROM polymers can be

readily prepared as either soluble or insoluble polymers depending on whether a cross-linker is utilized.

A. Catalysts Used in ROM Polymerizations

Generally all transition metal complexes used in metathesis reactions can also be employed for the synthesis of ROM polymers.[13] A current review on the different catalytic systems and their properties has recently been published by Fürstner.[49] In practical applications only the molybdenum and especially the ruthenium-based catalytic systems are employed.[16] The molybdenum catalysts **2**[17,18] have a much higher activity and therefore permit also the polymerization of sterically very hindered monomers. The ruthenium-based catalysts **1**, **3**, and **4** display a greater tolerance to different functional groups and are generally stable toward air and moisture, which makes them much more convenient to use.[15,50] The development of ruthenium catalysts in which one of the phosphine ligands has been replaced by an electron-rich *N*-heterocyclic carbene ligand (**3**, **4**) leads to a highly increased activity and greater thermal stability. The initial catalytic systems first developed by Nolan[51,52] and Grubbs[16] (**3**) contained an unsaturated carbene ligand. The highest catalytic activities, which rival and sometimes even exceed Schrock molybdenum systems **2**, are shown by complexes containing a saturated carbene ligand, particularly catalyst **4** with the SIMES ligand.[16] This catalyst as well as some molybdenum systems **2** and the "classical" Grubbs catalyst **1** are now commercially available. Some ligating functional groups such as thiols, phosphines, and amines are not tolerated by the early Ru-based catalysts, thus inhibiting polymerization. Amines can be polymerized when BOC-protected or as their salts, if these are sufficiently soluble. Phosphines can be polymerized after protection as borane adducts or after protonation as the phosphonium salts using catalyst **1** or directly using carbene **4**. Some other functionalities such as isonitriles and azodicarboxylates also inhibit polymerization but can be introduced postpolymerization (Figure 1).

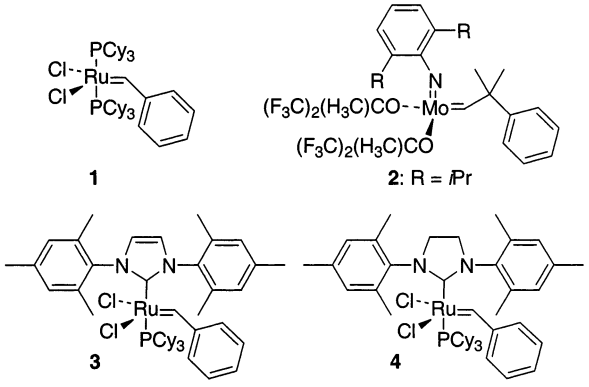


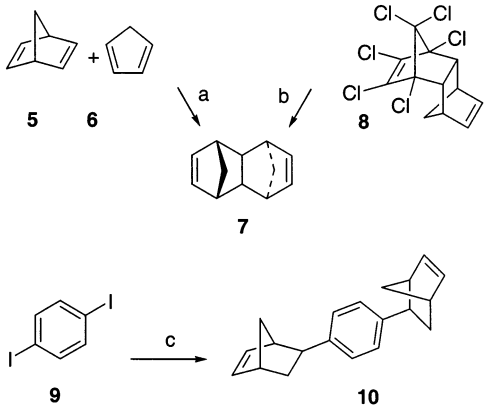
Figure 1. Catalysts for ROM polymerizations.

B. Aspects of ROM Polymers

ROM polymerizations are commonly referred to as living polymerization reactions owning to the fact that all of the chains generated using an alkylidene transition metal catalyst do not facilitate chain transfer or chain termination. The polymerization results in an equal number of monomers being consumed as the number of active chain ends remains constant. Therefore, the main advantage of a living polymer is the ability to control the synthesis of well-defined polymers with respect to molecular weight and polydispersity, as well as in the synthesis of block and graft copolymers. To achieve this goal a number of factors must be considered.

1. The polydispersity of the ROM polymers can be related to the percentage of catalyst used in the polymerization. Thus, decreasing the amount of catalyst increases the chain lengths and reduces the amount of oligomers due to unexpected chain termination. This results in the formation of polymers that are less soluble than the corresponding polymers prepared using a high percent of catalyst. Within these living polymers there is a linear relationship between the number-average molecular weight (M_n) and the number of equivalents of monomers added to such systems.[53]

Scheme 1. Synthesis of Cross-Linkers[a]

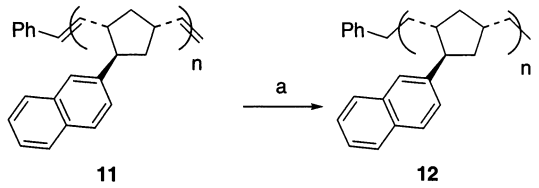


[a] Reagents and conditions: (a) heating; (b) $Na_{(M)}$, NaOEt; (c) $Pd(PPh_3)_2(OAc)_2$, **5**, piperidine, HCO_2H, DMF, 65%.

2. Cross-linkers such as divinylbenzene have been used in the preparation of polystyrene to modify the physical properties and to decrease solubility. A similar strategy has also been adopted for controlling the solubility of the ROM polymers.[54] Buchmeiser[55,56] reported the usage of diene **7** as a suitable cross-linker for decreasing the solubility of ROM polymers. This cross-linker was synthesized either via a Diels−Alder approach or from the dechlorination of Isoaldrin **8**. Alternatively, commercially available norbornadiene **5** has been used as a cross-linker, but it is less effective given that the remaining cyclopentadiene unit, after the initial ROM reaction, is less strained. A possible explanation for this is the slow reactivity of the second cyclopentadiene ring toward ROM polymerization. Recently, Barrett and Hopkins[57] have reported the preparation and usage of diene **10**, which has been found to be widely applicable to reduce the solubility of the ROM polymers with a typical cross-linker loading of 10%. The synthesis of **10** was carried out via the palladium-catalyzed bis-*exo*-hydroarylation[58] of

norbornadiene **5** using 1,4-diiodobenzene **9** (Scheme 1).

Scheme 2. Hydrogenation of the Polymer Backbone[a]



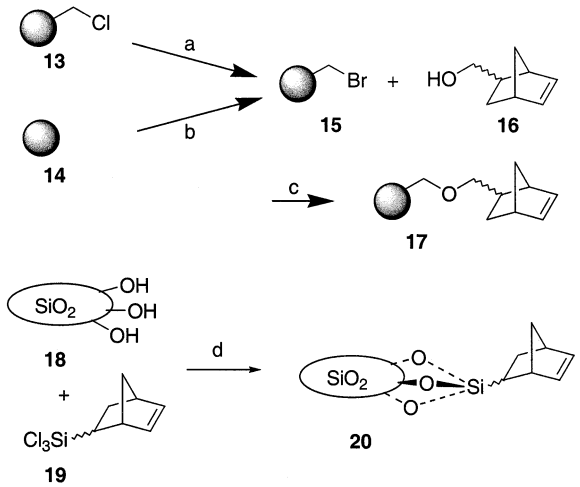
[a] Reagents and conditions: (a) H_2, $Rh(PPh_3)_3Cl$, PhH, 200 psi.

3. The most obvious characteristic feature of ROM polymers is the presence of the olefins within the polymer backbone. This fact has led to much debate with respect to the practicability of attempting certain transformations, which may undergo side reactions with the backbone alkene units. Hydrogenation of the polymer backbone using the homogeneous Wilkinson's catalyst under high-pressure hydrogenation conditions provides the corresponding ROM polymer alkane.[59] This method is superior to the existing diimide reduction using 4-tolenesulfonylhydrazine[60] owing to ease of purification of the produced modified ROM polymer. The ability to saturate the polymer backbone[61,62] through hydrogenation clearly demonstrated a further expansion of the type of transformations that could also be performed using a ROMPgel.

C. Surface-Grafted ROM Polymers

It is possible to polymerize norbornene derivatives onto surfaces that are functionalized with a suitable anchoring monomer due to the living character of the polymerization reaction.[63] Buchmeiser et al. have developed methodology to graft ROM polymers onto polystyrene beads **17** or silica particles **20**. In both cases, a suitably functionalized norbornene monomer was immobilized on the surface of the support onto which polymer chains of different alkene monomers were grown (Scheme 3).[37]

Scheme 3. Grafting of Norbornene onto Supports[a]



[a] Reagents and conditions: (a) NaBr, DMF, CH_2Br_2; (b) $SnBr_4$, Me_3SiBr, trioxane, CH_2Cl_2; (c) NaH, THF; (d) (i) Et_3N, PhMe; (ii) Me_2SiCl_2, Me_3SiCl, Et_3N.

There are generally two feasible approaches for the elaboration of such grafted ROM polymers. It is possible to first grow "living" polymers or oligomers by adding catalyst to the monomer in solution. These are then immobilized onto the support after addition of the latter and cross-metathesis with the immobilized norbornene units. For this approach the polymerization must be at least a class IV living system, therefore having a rate of propagation at least 10000 times higher than the rate of chain termination.[53] Therefore, this was carried out advantageously with Mo-based initiator **2**. Alternatively, the catalyst is first immobilized onto the support and the monomer is added when grafting onto the support occurs. For this approach the Grubbs catalyst **1** is more suitable because it is more stable to decomposition, which could occur, for example, due to residual uncapped hydroxyl functionalities on the silica. In a typical procedure the solid support is reacted with 1% catalyst by weight and 10% monomer by weight. Surface-grafted supports of this type have been utilized in chromatographic applications[35,38,39] or in catalyst immobilization.[19,56,64−66]

II. ROMPgel Reagents

Within the Barrett group the main focus of research on ROM polymers has been their application to immobilize reagents for solution phase parallel synthesis in which the polymer undergoes significant swelling in a range of solvents. These supports have been termed ROMPgels. For a solid-supported reagent to be effective, a number of criteria must be met: (i) ready availability of diverse inexpensive monomer units; (ii) ease of preparation; (iii) simplicity of the experimental procedure; (iv) good yields and purity of products; and (v) sufficiently high loading to be cost-effective. Thus, over two years, an array of ROMPgels have been synthesized and used as solid-supported reagents for parallel synthesis. These supported reagents have been employed in the Horner−Emmons reaction,[67] to immobilize tosmic,[68] for allylboronation reactions,[69] to prepare Mosher amides,[57] in arene lithiation reduction,[59] as an anhydride scavenger,[70] to immobilize triphenylphosphine,[71] and as peptide-coupling reagents.[72] The major advantage of ROMPgel supports is their ease of preparation from cheap and commercially available starting materials as shown in Figure 2. Typically, the key transformations are conducted in solution to afford the monomers, which are easily purified and are fully characterized prior to polymerization. The obvious advantage of this strategy is that the polymerization results in a ROMPgel in which every repeating unit is functionalized with the desired reagent functionality. This also has the advantage of affording polymers that have reasonably high loading and physical properties, which can be easily varied and optimized.

A. ROMPgel-Supported Horner–Emmons Reagents

The first supported reagents to be published[67] were the phosphite ROMPgels **32** (R = CO_2Et, CN), which

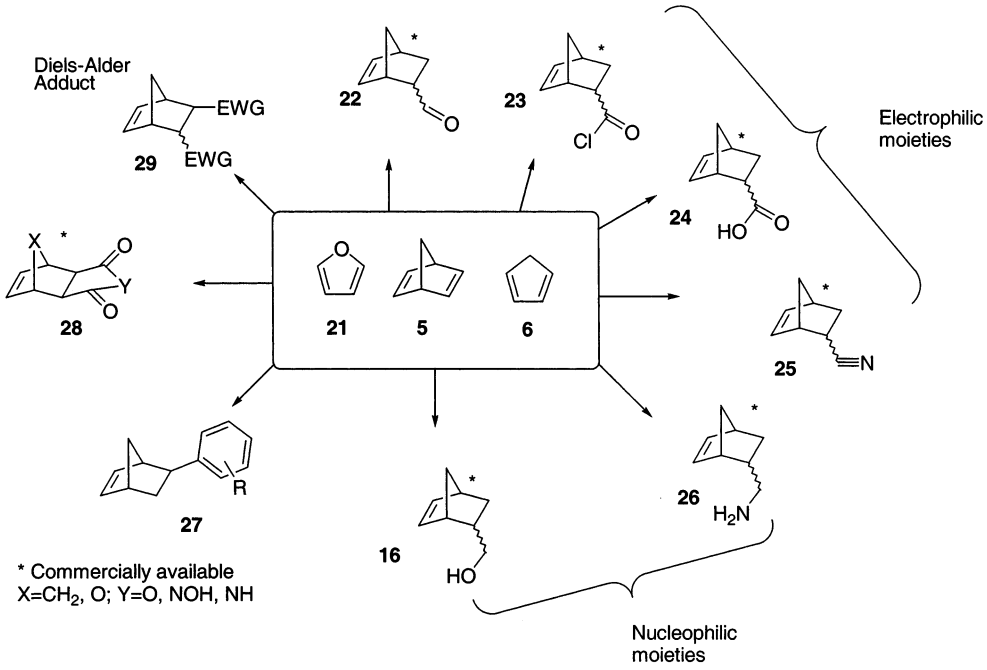
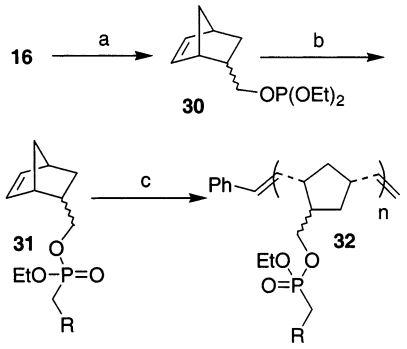


Figure 2. Readily available norbornene derivatives.

facilitated a chromatography-free Horner−Emmons reaction of aldehydes to produce the corresponding α,β-unsaturated ethyl esters and nitriles.[73−75] The Horner−Emmons ROMPgel **32** was synthesized in three steps from commercially available 2-norbornene-5-methanol **16** (a mixture of *endo*- and *exo*-isomers) via initial phosphite formation[76] **30** and an Arbusov reaction[77,78] to give the Horner−Emmons monomer **31**. Subsequent reaction of the monomer **31** with Grubbs catalyst **1** afforded an insoluble ROMPgel **32**, which had loadings of 3.3 mmol/g for the ester and 3.9 mmol/g for the nitrile **38** (Scheme 4).

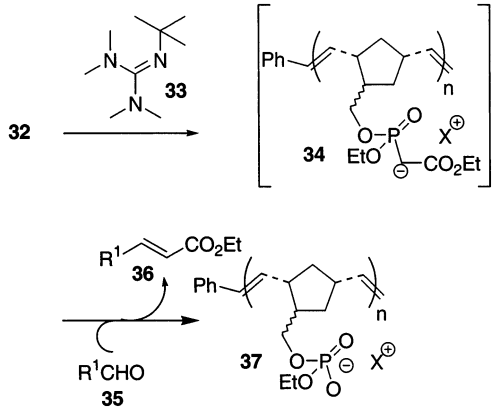
Scheme 4. Synthesis of the ROMPgel Horner−Emmons Reagent[a]



[a] Reagents and conditions: (a) $(EtO)_2PCl$, NEt_3, hexane, 95%; (b) $BrCH_2CO_2Et$, heat, 100%; (c) (i) **1** (1.5 mol %), CH_2Cl_2; (ii) $EtOCH{=}CH_2$, 100%.

Bases such as potassium carbonate (K_2CO_3), sodium hydroxide (NaOH), and sodium methoxide (MeONa) were screened for the carbanion formation from **32** but resulted only in low yields or complex mixtures of products. On the other hand, pretreatment of the polymer **32** with lithium diisopropylamide or potassium hexamethyldisilazide (KHMDS) to generate the carbanion **34** followed by removal of excess base by filtration prior to the addition of the aldehyde **35** afforded the α,β-unsaturated esters in good yields and purities. The most convenient base for this transformation was the Barton base, *N-tert*-butyl-*N′*,*N′*,*N″*,*N″*-tetramethylguanidine **33**, which was found to facilitate the synthesis of α,β-unsaturated esters and nitriles from both aromatic and aliphatic aldehydes in excellent yields and purities while allowing for the removal of excess base via evaporation (Schemes 5 and 6; Tables 1 and 2).

Scheme 5. Application of the ROMPgel Horner−Emmons Reagent



Scheme 6. Synthesis of Nitriles

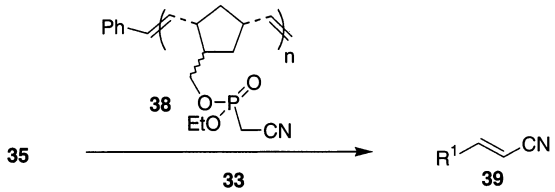


Table 1. ROMPgel 32 Horner−Emmons Reactions[a]

entry	aldehyde **35**	base	*t* (h)	**36** yield (%)	
1	**35a** 4-O_2N−C_6H_4CHO	Barton[b]	4	**36a**	94
2		TMG[c]	4		95
3		LHMDS[d]	4		92
4	**35b** 2-F−C_6H_4CHO	Barton	4	**36b**	84
5		TMG	4		88
6		LHMDS	4		88
7	**35c** 3-Br−C_6H_4CHO	Barton	16	**36c**	88
8		TMG	16		92
9		LHMDS	24		60
10	**35d** 4-pyr-CHO	Barton	4	**36d**	96
11		TMG	4		53
12		LHMDS	4		97
13	**35e** 4-Ph-C_6H_4CHO	Barton	24	**36e**	85
14		LHMDS	24		98
15	**35f** 4-Me-C_6H_4CHO	Barton	48	**36f**	85
16		LHMDS	48		92
17	**35g** $PhCH_2CH_2CHO$	Barton	16	**36g**	88
18		LHMDS	16		
19	**35h** 5-norbornene-2-CHO[e]	Barton	16	**36h**	82
20	**35i** citronellal	Barton	16	**36i**	92

[a] All purities were >95% as measured by GC-MS. All esters were exclusively *trans*. Isolated yields are given. [b] 2.0 equiv. [c] 1.5 equiv. [d] ROMPgel **32** pretreated with 4.0 equiv of base followed by filtration and washing. [e] *exo*:*endo* mixture.

Table 2. ROMPgel 38 Horner−Emmons Reactions[a]

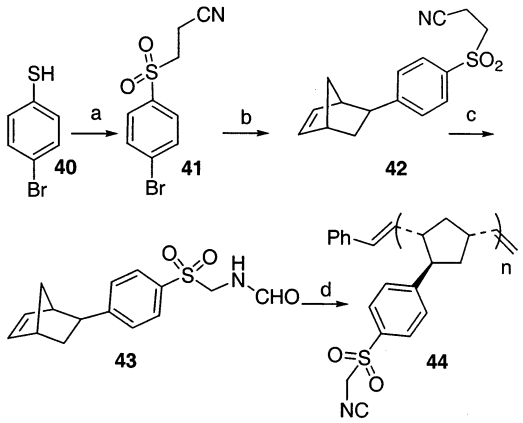
entry	aldehyde **35**	*t* (h)	*E*:*Z* ratio[b]	**39** yield (%)	
1	**35a**	4	80:20	**39a**	95
2	**35b**	4	70:30	**39b**	94
3	**35c**	16	90:10	**39c**	90
4	**35d**	4	100:0	**39d**	86
5	**35e**	16	85:15	**39e**	91
6	**35f**	16	80:20	**39f**	98
7	**35g**	16	70:30	**39g**	93
8	**35h**	16	80:20	**39h**	86
9	**35i**	16	70:30	**39i**	85

[a] All purities were >95% as measured by GC-MS. All yields are isolated yields. [b] Ratio determined by ^1H NMR.

B. ROMPgel-Supported 4-Toluenemethylsulfonyl Isocyanide (Tosmic)

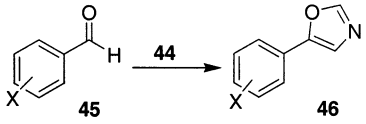
The need for a solid-supported reagent to afford a purification-free synthesis of heterocycles resulted in the development of the tosmic ROMPgel[68] **44**. This reagent was a solid-supported version of the van Leusen tosmic reagent,[79] which has been utilized in the synthesis of oxazoles, pyrroles, imidazole, and thiazoles.[80] The purification of these heterocycles was traditionally achieved using chromatography, although some solid-supported versions of the tosmic reagent have been reported. Ganesan and co-workers had attempted to prepare the tosmic reagent on an Ambersep 900 hydroxyl resin[81] and a Tentagel support,[82] but these supports afforded only oxazoles in moderate crude yields and purities. Thus, due to the versatility of the van Leusen tosmic reagent, it was decided to develop tosmic ROMPgels **44** as an alternative to the pre-existing supports. The initial challenge was to devise an effective synthesis owing to the diverse and sensitive functionalities that were present in the tosmic reagent. As previously dis-

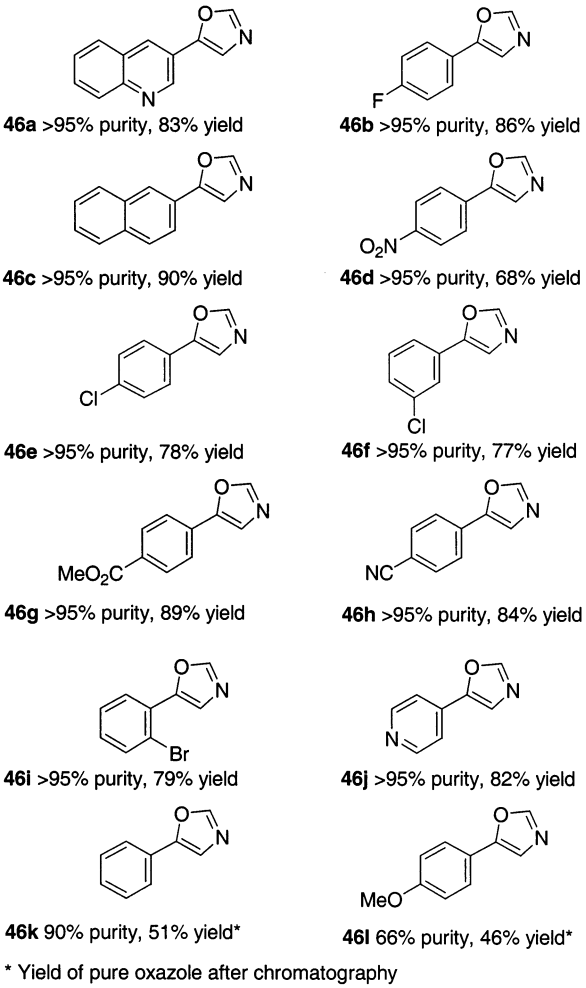
Scheme 7. Synthesis of a ROMPgel Tosmic Reagent[a]



[a] Reagents and conditions: (a) (i) acrylonitrile, Triton B, 92%; (ii) 3-$ClC_6H_4CO_3H$, CH_2Cl_2, 95%; (b) $Pd(PPh_3)_2(OAc)_2$, **5**, piperidine, HCO_2H, DMF, 65%; (ii) NaOEt, EtOH, 100%; (c) paraformaldehyde, formamide, HCOOH, 71%; (d) (i) **1** (0.5%), norbornene (1 equiv), CH_2Cl_2; (ii) $EtOCH{=}CH_2$, 100%; (iii) *i*-Pr_2NH, $POCl_3$, THF, 100%.

Scheme 8. Application of the ROMPgel Tosmic Reagent





* Yield of pure oxazole after chromatography

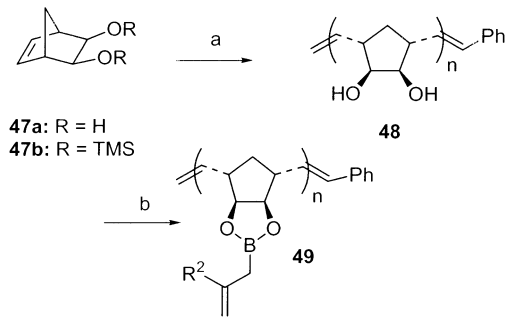
cussed, ROMP reactions using catalyst **1** are suppressed when an isonitrile moiety is present. Therefore, the isonitrile **44** had to be introduced after the polymerization reaction (Scheme 7).

4-Bromothiophenol **40** was chosen as the starting material, which was initially alkylated, subsequently oxidized, and palladium-coupled via an *exo*-hydroarylation[58] reaction to afford the sulfone **42** in good yield. All that remained prior to polymerization was formation of the sulfinate salt[83] and the transformation to the formamide[84] **43**. After the ROM polymerization reaction, the formamide was dehydrated to the active isonitrile using phosphorus oxychloride to afford the polymer **44** having a loading of 2.7 mmol/g. A library of oxazoles was produced in solution when a series of aldehydes **45** were allowed to react with the tosmic ROMPgel **44** in combination with the Barton base **33** to afford the oxazole in good yields and purities. The only aldehydes that afforded compounds of lower purity were electron-rich benzaldehydes **46k**,**l**, which are also known to decrease the rate of reaction even when nonsupported tosmic was used (Scheme 8).[80]

C. ROMPgel-Supported Allylboronates

Solid-supported reagents are generally devised as effective methods for handling problematic substrates or to simplify the purification of final targets. To further extend the scope of the ROMP methodology, an allylboronate ROMPgel[69] **49** was synthesized. This was prepared in three steps from the trimethylsilyl-protected diol **47b**, which was polymerized using Grubbs catalyst **1** and subsequently deprotected using hydrogen fluoride and triethylamine to afford an insoluble ROMPgel **48** containing 15% of cross-linker **7**. Treatment of the ROMPgel **48** with allylboronic acid afforded the ROMPgel boronate **49** having a loading of 5.8 mmol/g (Scheme 9). The

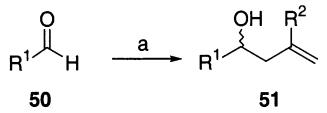
Scheme 9. Synthesis of a ROMPgel Allylboronate Reagent[a]



[a] Reagents and conditions: (a) (i) Me_3SiCl, Et_3N, CH_2Cl_2; (ii) **1** (1.5 Mol %), **7** (15 mol %), CH_2Cl_2; (iii) $EtOCH{=}CH_2$, 100%; (iv) $Et_3N{\cdot}3HF$, CH_2Cl_2; (b) $CH_2{=}CR^2CH_2B(OH)_2$, CH_2Cl_2.

reaction of allylboronates with aldehydes is a well-established protocol for the elaboration of 4-hydroxy-1-alkene derivatives,[85] which can be further transformed into more complex β-hydroxy aldehydes through a simple oxidative cleavage of the alkene. Thus, a library of hydroxy-1-alkenes was synthesized from the treatment of the ROMPgel-supported boronates **49** with both aliphatic and aromatic aldehydes **50** to afford the corresponding homoallylic alcohols **51** in good yields and purities after a simple filtration (Scheme 10; Table 3).

Scheme 10. Application of the ROMPgel Allylboronate Reagent[a]



[a] Reagents and conditions: (a) (i) **49**, CH_2Cl_2, H_2O; (ii) filtration; (iii) evaporation

Table 3. Allylboration of Aldehydes 50 with ROMPgel-Supported Allylboronate To Provide 51

entry	R^1	R^2	*t* (h)	yield (%)
51a	*n*-Bu	H	3	82
51b	*c*-C_6H_{11}	H	3	92
51c	*t*-Bu	H	4	49
51d	$CH_3CH{=}CH$	H	3	70
51e	Ph	H	6	87
51f	4-MeO−C_6H_4	H	7	93
51g	4-Cl−C_6H_4	H	4	85
51h	4-O_2N−C_6H_4	H	3	90
51i	4-MeO_2C−C_6H_4	H	4	95
51j	2-pyridyl	H	3	79
51k	2-furyl	H	6	88
51l	2-thienyl	H	14	95
51m	2,2-dimethyl-1,3-dioxolan-4-yl	H	5	81
51n	*n*-Bu	CH_3	1	68
51o	Ph	CH_3	2	87
51p	4-MeO−C_6H_4	CH_3	5	95
51q	4-O_2N−C_6H_4	CH_3	3	96
51r	2-furyl	CH_3	2	87

D. ROMPgel-Supported Naphthalene and Biphenyl Reagents

The degree of amalgamation of traditional solution phase chemistry with parallel synthesis through automation will be dependent on the diversity of chemistry that can be performed utilizing solid-supported reagents. To further expand the arsenal of transformation that can be achieved utilizing ROMPgel methodology, a ROM polymer-supported naphthalene **12** and biphenyl **54** were synthesized to facilitate arene-catalyzed lithiation reactions.[86] Previously, lower loading polystyrene-supported naphthalene and biphenyl had been reported by Yus and co-workers[87] (Scheme 11).

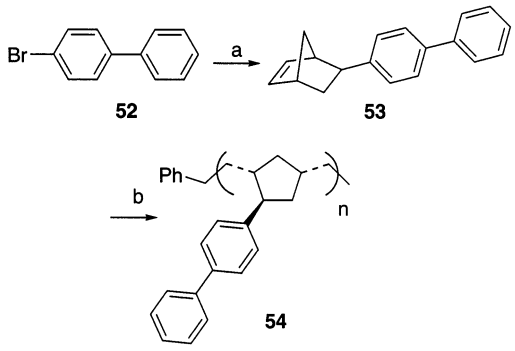
The synthesis of the arene monomers was achieved through a palladium-catalyzed *exo*-hydroarylation reaction. Treatment of the monomer **53** with catalyst **1** (1.5 mol %) afforded an insoluble polymer, which was hydrogenated using Wilkinson's catalyst to afford the reduced polymer **54**. The arene ROMPgels **12** and **54** had excellent swelling properties and were found to be effective at facilitating reductive lithiation reactions using only a catalytic amount of the ROMPgel. Reductive lithiations were performed on a series of chlorinated compounds followed by addition of electrophiles and hydrolysis to afford the expected products in good yields and purities. Both **12** and **54** were also found to be effective for reductive cleavage of benzyl and allyl ether protecting groups, thus emphasizing their practicality as alternatives to the use of naphthalene and biphenyl in solution phase chemistry (Schemes 12 and 13; Tables 4 and 5).

Table 4. Reaction of Aryl and Alkyl Chlorides with Electrophiles

alkyl chloride	polymer	electrophile	*t* (h)	yield[a] (%)	purity[b] (%)
2-(3-chloropropyl)-2-methyl-1,3-dioxolane	**54**	PhAc	20	87	91
2-(3-chloropropyl)-2-methyl-1,3-dioxolane	**54**	PhCHO	20	88	96
2-(3-chloropropyl)-2-methyl-1,3-dioxolane	**12**	*t*-BuPh$_2$SiCl	20	81	92
benzyl chloride	**54**	PhAc	20	85	91
benzyl chloride	**54**	PhCHO	20	78	93
benzyl chloride	**12**	*t*-BuMe$_2$SiCl	20	77	90
1-chloro-4-(1,1-dimethoxypropyl)benzene	**54**	PhAc	30	71	81
1-chloro-4-(1,1-dimethoxypropyl)benzene	**12**	PhCHO	30	65	80

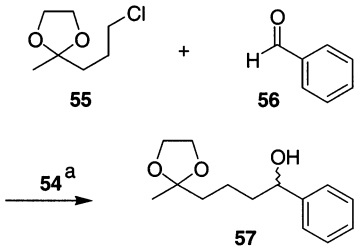
[a] Isolated yields. [b] Purity as determined by GC-MS and ^{1}H NMR.

Scheme 11. Synthesis of a ROMPgel Biphenyl Reagent[a]



[a] Reagents and conditions: (a) Pd(PPh$_3$)$_2$(OAc)$_2$, norbornadiene **5**, piperidine, HCO$_2$H, DMF, 75%; (b) (i) **1** (1.5 mol %), CH$_2$Cl$_2$; (ii) EtOCH=CH$_2$, 100%; (iii) H$_2$, Rh(PPh$_3$)$_3$Cl, PhH, 150 psi.

Scheme 12. Application of the ROMPgel Biphenyl Reagent[a]



[a] Reagents and conditions: (a) Li, THF, −78 °C.

Scheme 13. Ether Cleavage with the ROMPgel Biphenyl Reagent

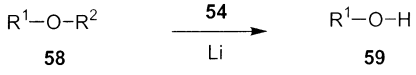


Table 5. Deprotection of Aryl and Alkyl Ethers

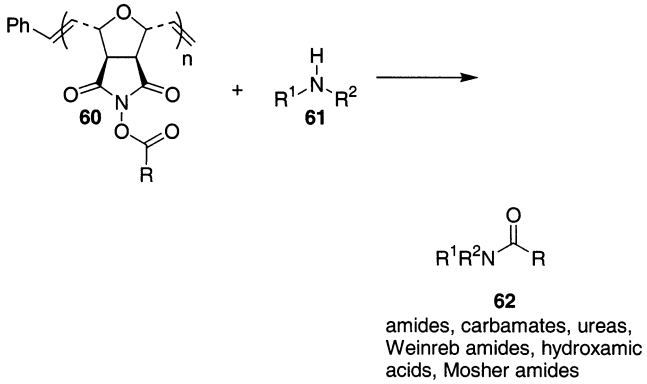
R^1	R^2	polymer	*t* (h)	yield (%)	purity (%)
naphthyl	PhCH$_2$	**54**	40	71	80
naphthyl	allyl	**54**	40	73	83
naphthyl	*t*-BuMe$_2$SiCl	**12**	40	*a*	
citronellyl	PhCH$_2$	**12**	40	89	96
citronellyl	allyl	**12**	40	86	92
citronellyl	*t*-BuMe$_2$SiCl	**54**	40	*a*	

[a] No reaction observed.

E. ROMPgel-Supported *N*-Hydroxysuccinimide Reagents for Acylation Reactions

N-Hydroxysuccinimide esters have previously been reported as acylating agents for the formation of carbamates with activated amino acids and amines,[88] with the subsequent removal of the *N*-hydroxysuccinimide moiety through precipitation and/or chromatography. Utilizing the ROMP methodology, it was possible to synthesize an *N*-hydroxysuccinimide ROMPgel[89] **60** for acylations whereby the discarded *N*-hydroxysuccinimide could be removed from the reaction mixture through simple filtration of the polymer (Scheme 14).

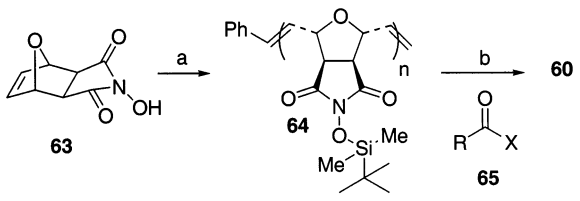
Scheme 14. Application of the ROMPgel *N*-Hydroxysuccinimide Reagents[a]



[a] Reagents and conditions: (a) R^{1}R^{2}NH, EtOH; (b) Et$_3$N.

Two alternative protocols for the synthesis of the ROMPgel acylation reagents were devised. The first strategy was to effect the acylation of commercially available *N*-hydroxysuccinimide **63** prior to polymerization. This afforded a series of insoluble ROMPgels **60** having loadings ranging between 2.1 and 3.8 mmol/g. The second approach was to protect the *N*-hydroxysuccinimide **63** first as a silyl ether prior to polymerization. Subsequent desilylation afforded an insoluble ROMPgel *N*-hydroxyimide having a loading of 5.5 mmol/g, which could be acylated or converted to the carbamate (Scheme 15; Figure 3; Table 6).

Scheme 15. Synthesis of a ROMPgel *N*-Hydroxysuccinimide Reagent[a]



[a] Reagents and conditions: (a) (i) TBDMSCl, imidazole, 99%; (ii) **1** (1.5 mol %), CH$_2$Cl$_2$; (iii) EtOCH=CH$_2$, 100%; (b) (i) Et$_3$N·3HF, THF; (ii) MeOSiMe$_3$; (iii) RCOCl, NEt$_3$, CH$_2$Cl$_2$.

The effectiveness of supported *N*-hydroxysuccinimide **60** as an acylating reagent was clearly dem-

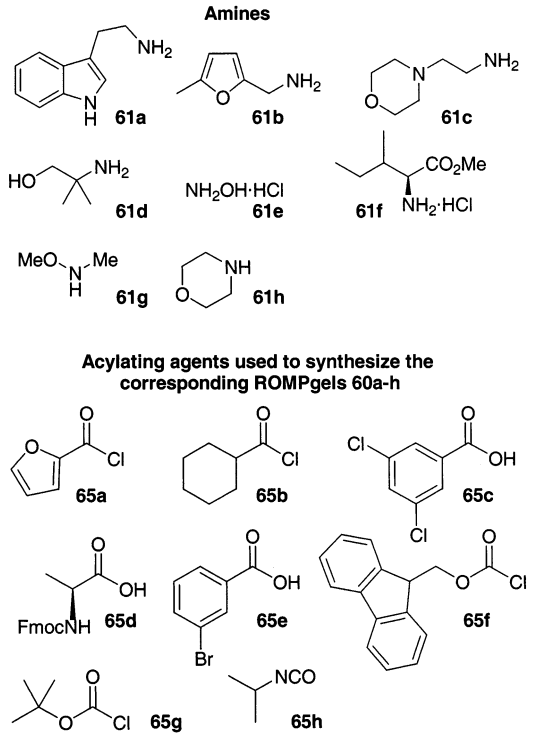


Figure 3. Reagents used in acylations using ROMPgels.

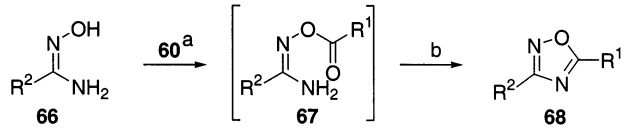
Table 6. Acylation of a Range of Amines Using ROMPgels 60a−h[a]

	60a	60b	60c	60d	60e	60f	60g	60h
61a	95	90	97	95	−[b]	−	−	91
61b	97	93	97	95	95	97	95	98
61c	97	97	98	93	96	93	89	92
61d	89	90	80[c]	−	−	−	−	−
61e	91	90	96	−	−	−	−	−
61f	96	−	98	−	−	−	−	−
61g	95	93	98	−	−	−	−	−
61h	95	98	96	−	−	−	−	−

[a] Isolated yields of products **62** are quoted. All compounds were >95% pure by GC-MS. [b] −, indicates that the reaction was not run. [c] Product contaminated with 20% of the *N*,*O*-bisacylated compound.

onstrated and as such utilized further for the synthesis of heterocycles.[90] 1,2,4-Oxadiazoles **68** are typically synthesized through the *O*-acylation of an amidoxime with an activated carboxylic acid equivalent followed by dehydrative cyclization.[91−99] Thus, treatment of the acyl-supported *N*-hydroxysuccinimide **60** with a series of amidoximes **66** and in-situ treatment with polymer-supported Barton base afforded the substituted 1,2,4-oxadiazoles **68** in good yields and purities (Scheme 16; Figure 4; Table 7).

Scheme 16. Synthesis of 1,2,4-Oxadiazoles[a]



[a] Reagents and conditions: (a) polystyrene-TBD, EtOH; (b) Et_3N.

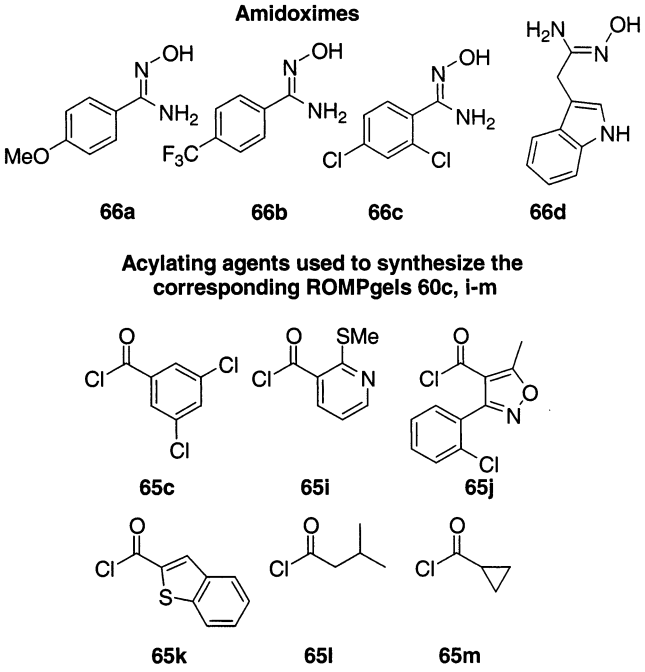


Figure 4. Reagents used in the synthesis of 1,2,4-oxadiazoles.

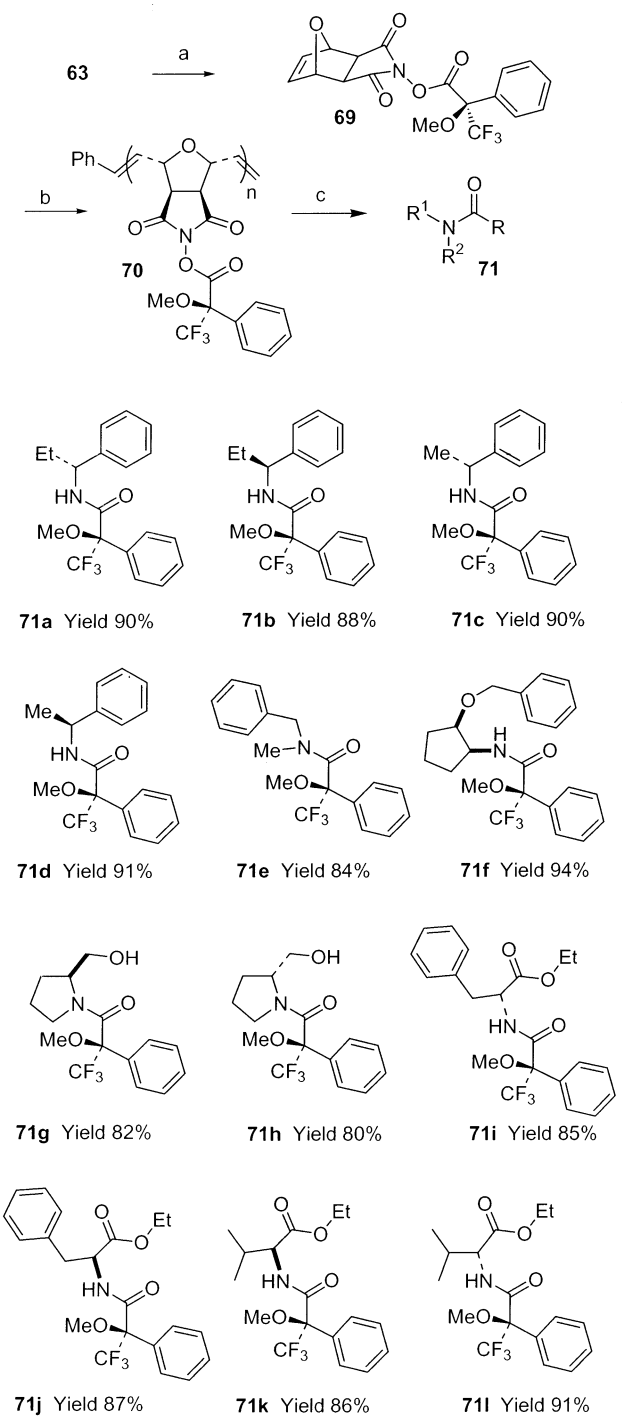
Table 7. Synthesis of a Range of 1,2,4-Oxadiazoles Using ROMPgels 60c,i−m

		isolated yields (%) of oxadiazoles **68** from amidoximes **66**[a]			
ROMPgel	loading[b]	**66a**	**66b**	**66c**	**66d**
60c	2.68	92	94	−[c]	83
60i	3.01	−	80	−	−
60j	2.39	92	89	81	77
60k	3.23	−	82	80	−
60l	3.52	−	80	−	78
60m	3.74	88	81	92	−

[a] All compounds were characterized by ^1H and ^{13}C NMR. Method A: copolymerization of monomer with norbornadiene (20 mol %). Method B: acylation of ROMPgel **64**. [b] Acyl group loading in mmol/g^{-1}. [c] −, indicates that the reaction was not run.

A further extension of this methodology was to attempt directly the acylation of an amine in an NMR tube with an active Mosher acid derivative, which would be a convenient method for the determination of the enantiomeric excess of chiral amines. This would also ensure that there would be no change in diastereoisomeric ratio on handling. Thus, a ROMPgel Mosher ester[57] **70** was synthesized by first coupling the commercially available Mosher ester with the *N*-hydroxysuccinimide **63** to afford the ester **69**, which was treated with Grubbs catalyst **1** in the presence of a cross-linker **10** to afford an insoluble polymer **70**. Treatment of this polymer **70** with a series of primary and secondary amines and amino esters afforded the corresponding Mosher amides in excellent yields and purities, thus eliminating the need for purification. This protocol clearly highlighted the considerable practical advantage of the solid-supported reagents over more conventional solution phase methods for the determination of optical purity in parallel arrays (Scheme 17).

Scheme 17. Synthesis and Application of a ROMPgel Mosher Ester[a]

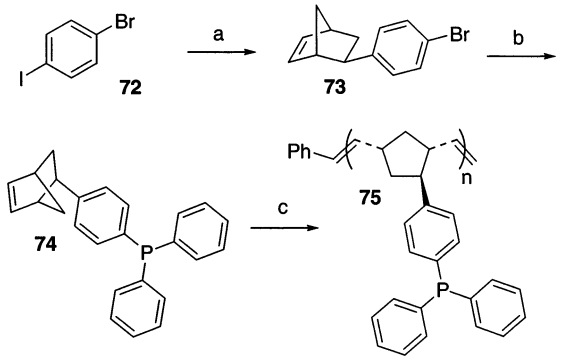


[a] Reagents and conditions: (a) (*R*)-PhC(CF_3)(OMe)CO_2H, DICI, CH_2Cl_2, 95%; (b) (i) **10** (20 mol %), **1** (1.5 mol %), CH_2Cl_2; (ii) EtOCH=CH_2, 75%; (c) R^1R^2NH, CH_2Cl_2, reflux. Isolated yields, >90% purity as determined by GC-MS and ^{1}H NMR, de >95% as only one diastereoisomer was detected by ^{1}H NMR.

F. ROMPgel-Supported Triphenylphosphine Reagents

Immobilized triphenylphosphine was first reported by McKinley et al. using a polystyrene matrix.[100] Subsequently, a variety of different types of triphenylphosphine-supported reagents have been reported and studied for the facilitation of such transformations as the Mitsunobu reaction,[101] halogenation of alcohols,[3,102,103] Staudinger/Aza-Wittig reactions,[103] and Wittig[104,105] olefinations. As a convenient alternative a triphenylphosphine reagent should be available using the ROM polymerization.[71] Two criteria would have to be achieved: syntheses that would easily permit the preparation of mole quantities, as well as being compatible with the ROM polymerization methodology. Thus, iodide **72** was chosen as starting material, which was coupled to norbornadiene **5** via a palladium-catalyzed *exo*-hydroarylation reaction to afford the aryl bromide moiety **73**. This was converted into phosphine **74** via the aryllithium derivative. Initially it was envisioned that it would be necessary to convert the phosphine to the borane adduct to permit ROM polymerization. The protected monomer was polymerized using Grubbs catalyst **1**, and subsequent washing of the ROMPgel with DABCO afforded the phosphine ROMPgel **75** in good yield. Alternatively, the phosphine **74** could also be protonated with an excess of TFA, which also enables polymerization. The use of the more active catalyst **4** allowed the direct polymerization of the unprotected phosphine monomer. This result can be attributed to the lower affinity of the active form of **4** toward phosphine ligands due to the electron-rich heterocyclic carbene ligand (Schemes 18). The supported phosphine **75** was useful in the conversion of alcohols **76** into halides **77** (Scheme 19 and Table 8).

Scheme 18. Synthesis of a ROMPgel Triphenylphosphine[a]



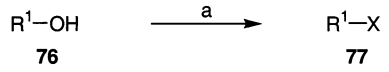
[a] Reagents and conditions: (a) $Pd(PPh_3)_2(OAc)_2$, norbornadiene **5**, piperidine, HCO_2H, DMF, 80%; (b) *n*-BuLi, THF, −78 °C, Ph_2PCl, 92%; (c) **4** (1.5 mol %), **10** (15 mol %), CH_2Cl_2, 40 °C, 91%.

Table 8. Conversion of Alcohols into Halides

entry	R^1−OH	X	*t* (h)	*T* (°C)	yield[a] (%)
1	1-adamantol	Cl	18	45	91
		Cl	0.25	120[b]	89
2	citronellol	Cl	3	45	>95
3	ethyl 6-hydroxyhexanoate	Cl	3	45	>95
4	*N*-Boc-L-*trans*-4-hydroxyproline methyl ester	Cl	1.5	45	>95
5	2[3-(6-methyl-2-pyridyl)-propoxy]ethanol	Cl	3	45	>95
6	2,4,6-trimethylbenzyl alcohol	Cl	6	45	89
7		Br	7	rt	71
8		I	2	rt	74

[a] Yields refer to the isolated products. Purities as judged by ^{1}H and ^{13}C NMR spectra; GC-MS were >95% in every case. [b] With microwave heating in CH_2Cl_2.

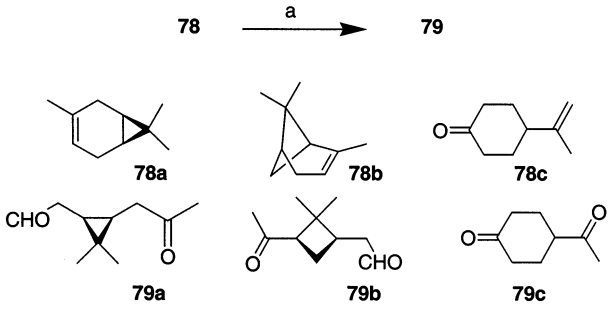
Scheme 19. Application of the ROMPgel Triphenylphosphine in the Halogenation of Alcohols[a]



[a] Reagents and conditions: (a) CCl_4, CBr_4, or I_2, 1.8 equiv, **75** 2 equiv, CH_2Cl_2, reflux for X = Cl, 25 °C for X = Br, I. All purities >95% as detected by GC-MS.

Supported triphenylphosphine is also a very valuable reagent to facilitate the workup of ozonolysis reactions. The ozonides derived from several olefins **78a**−**c** were cleanly converted to the corresponding aldehydes and ketones **79a**−**c** by allowing them to react with 1.5 equiv **75** at ambient temperature for 2 h. The isolated yields were >96%, and the purities, as judged by ^1H and ^{13}C NMR spectra and GC-MS, were >95% in every case (Scheme 20).

Scheme 20. Immobilized Triphenylphosphine in the Workup of Ozonides[a]



[a] Reagents and conditions: (a) (i) O_3, CH_2Cl_2, −78 °C; (ii) argon, CH_2Cl_2, −78 °C; (iii) **75** 1.5 equiv, CH_2Cl_2, 25 °C.

Triphenylphosphine can also be utilized in the Staudinger reaction.[103] Thus, **75** was examined in the reduction of azides to the corresponding amines. In a representative procedure the azide was heated to reflux in THF with 2 equiv of **75** until all starting material was consumed. After the mixture had cooled to room temperature, aqueous ammonia (35%) was added. The mixture was heated to reflux for an additional 1−3 h. This afforded the amino derivatives **80a**−**d** in high yield (87−100%) and purity (90−98%) after filtration and evaporation (Figure 5).

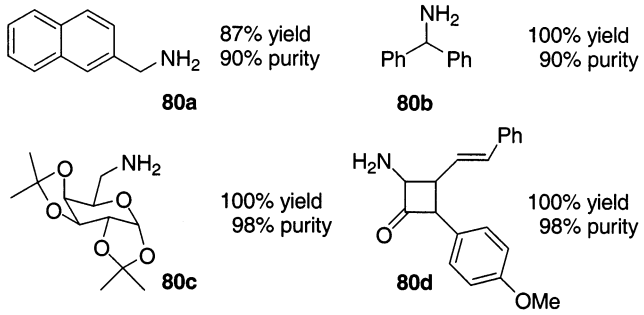


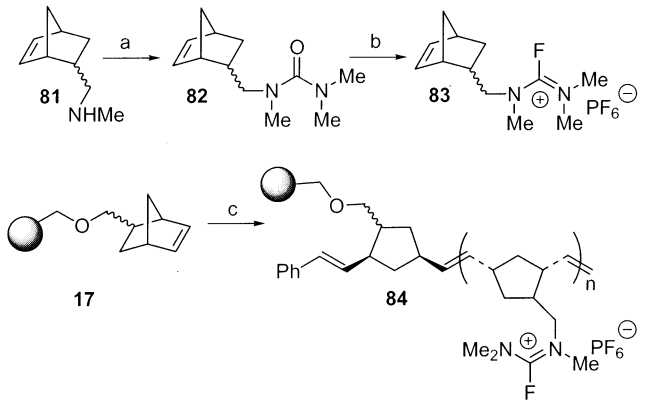
Figure 5. Conversion of azides to amines.

G. ROMPgel- and ROMPsphere-Supported Peptide-Coupling Reagents

One of the most important reactions in organic synthesis is the formation of amides or peptide bonds. The most commonly used peptide-coupling reagents are 1,3-dicyclohexylcarbodiimide (DCC) and derivatives thereof in the presence of additives such as 1-hydroxybenzotriazole (HOBt).[106] A big advance in coupling efficiency was achieved by the introduction of phosphonium salts such as (1-benzotriazolyoxy)-tris(dimethylamino)phosphonium hexafluorophosphate (BOP)[107] and (1-benzotriazolyoxy)tris(pyrrolidino)phosphonium hexafluorophosphate (PyBOP).[108] Due to their toxicity they were soon replaced by uronium reagents such as *O*-(benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU)[109] and *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU).[110] The newest and most effective classes of peptide-coupling reagents are based on fluoroformamidinium salts[111] and 2-halopyridinium salts.[112] All of these reagents work very well in solid phase peptide synthesis (SPPS) because the side products can easily be removed. In liquid phase synthesis, however, they produce side products such as ureas that are cumbersome to extract. The Barrett group recently reported the first synthesis of two onium-type coupling reagents **84** and **87** that are immobilized on ROM polymer supports.[72] These reagents have the advantage that after completion of the coupling reaction, the only side products in solution are salts of the trialkylamine base added in the coupling step. These can very easily be removed either by extraction or by workup utilizing a mixed-bed ion-exchange resin.

The fluoroformamidinium-based coupling reagent is derived from tetramethylfluoroformamidinium hexafluorophosphate (TFFH).[111] It can easily be synthesized from **81** by reaction with dimethylcarbamoyl chloride, followed by conversion to the chloroformamidinium chloride by reaction with phosgene. Subsequent ion exchange and halogen substitution with potassium hexafluorophosphate and potassium fluoride in acetonitrile yield **83** as a crystalline solid. This was converted into a ROMPgel **84** by polymerization in the presence of a cross-linker **10 (**15 mol %). The produced gel underwent slight swelling in dichloromethane. An alternative approach is the graft polymerization of norbornene **83** onto polystyrene-supported norbornene **17**, yielding spherical beads with 20% polystyrene content by weight (vide infra, section III.C) (Scheme 21). These beads show a remarkable rate increase in the efficiency of the coupling procedure.

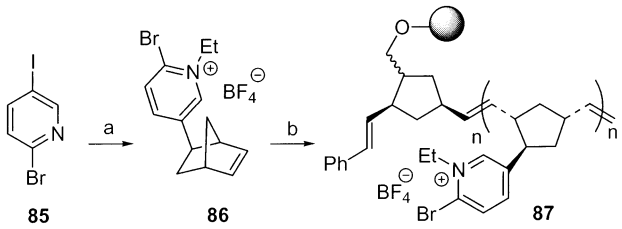
Scheme 21. Synthesis of ROMPsphere-Supported Formamidinium Peptide Coupling Reagent[a]



[a] Reagents and conditions: (a) $(CH_3)_2NCOCl$, Et_3N, 89%; (b) (i) $(COCl)_2$, PhMe; (ii) KF, KPF_6, CH_3CN, 64%; (c) **4**, CH_2Cl_2, 75%.

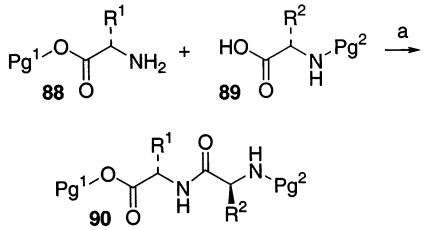
An alternative coupling reagent was developed as an immobilized variant of the 2-bromo-1-ethylpyridinium tertrafluoroborate (BEP) coupling reagent.[112] In this case 2-bromo-5-iodopyridine **85** was linked to a norbornene moiety through a reductive Heck coupling. The pyridine was subsequently quaternized with triethyloxonium tetrafluoroborate to yield salt **86**, which was polymerized to provide the ROMPgel **87** (Schemes 22). Both ROMPspheres **84** and **87** were

Scheme 22. Synthesis of a ROMPgel-Supported Pyridinium Peptide Coupling Reagent[a]



[a] Reagents and conditions: (a) (i) $Pd(PPh_3)_2(OAc)_2$, norbornadiene **5**, piperidine, HCO_2H, DMF, 66%; (ii) $Et_3O^+BF_4^-$, CH_2Cl_2, 81%; (b) (i) **4** (1.5 mol %), **17**, CH_2Cl_2.

Scheme 23. Peptide Couplings Carried out with the Rompsphere Reagents[a]



[a] Reagents and conditions: (a) (i) 1.3 equiv of **84** or **87**, 3 equiv of *i*-Pr_2NEt, CH_2Cl_2; (ii) addition of mixed bed ion-exchange resin, extraction with CH_2Cl_2.

Table 9. Yields and Purities of the Synthesized Dipeptides[a]

AA1	AA2	coupling reagent, equiv	equiv of DIEA	*t* (h)	yield[a] (%)	purity[b] (%)
Z-Gly	Phe-OEt·HCl	**84**, 2.2	3	12	95	95
Boc-Aib	Gly-OEt·HCl	**84**, 2.2	3	12	97	98
Z-Gly	Aib-OMe·HCl	**84**, 2.2	3	12	97	98
Z-Gly	Aib-OMe·HCl	**87**, 2.2	3	12	84	96
Boc-Aib	Aib-OMe·HCl	**84**, 2.2	3	12	90	98
Z-Leu	Gly-OEt·HCl	**84**, 2.2	3	12	96	92
Z-Leu	Gly-OEt·HCl	**87**, 2.2	3	12	92	94
Z-Gly-Phe	Val-OMe·HCl	**84**, 2.2	3	12	95	90
Z-Gly-Phe	Val-OMe·HCl	**87**, 2.2	3	12	87	87
Z-Gly	Phe-OEt·HCl	**87**, 2.2	3	12	86	87
N-Fmoc-Aib	Gly-OEt·HCl	**87**, 2.2	3	12	85	88
N-Fmoc-Aib	Ala-OEt·HCl	**87**, 2.2	3	12	80	89

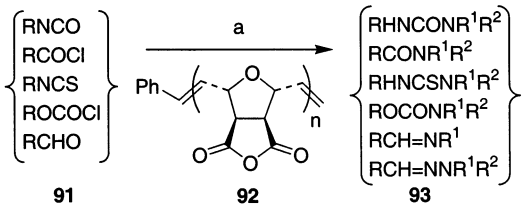
[a] All compounds were characterized by ^1H NMR, ^{13}C NMR, and LCMS; purities were determined by NMR with 2,5-dimethylfuran as an internal standard.[113]

effective in peptide coupling reactions (Scheme 23, Table 9).

H. ROMPgel-Supported Scavengers

An additional application for polymer-supported reagents was initially devised by Kaldor and coworkers, whereby polystyrene isocyanate resins were used as scavengers for the removal of excess amine reactants to facilitate the purification and isolation of target compounds. Since their conception, an arsenal of scavengers have been published utilizing Merrifield resin[114] as the support, and as such the issues of cost, resin loading, swelling, and site accessibility come into play. As previously discussed, ROMPgels have been devised as alternative supports to address these problems. An important issue regarding scavengers is their cost. Thus, it is desirable to have a cheap and easily prepared reagent, which will be effective with a broad range of nucleophiles, particularly as scavengers are used in excess (Scheme 24).

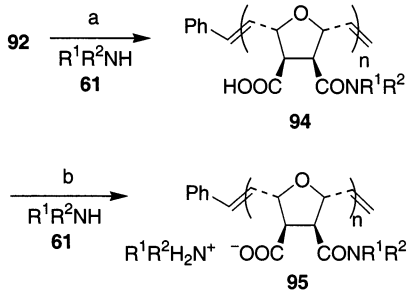
Scheme 24. Synthesis of Ureas, Thioureas, Amides, Sulfonamides, Carbamates, Imines, and Hydrazones Utilizing an Amine Scavenger[a]



[a] Reagents and conditions: (a) R^1R^2NH or $R^1R^2NNH_2$, CH_2Cl_2.

The ROMPgel anhydride[70] **92** was prepared through a simple ROM polymerization of the commercially available monomer, the furan maleic anhydride Diels–Alder adduct, to afford an insoluble polymer having a scavenging capability of 10.8 mmol/g. A library of ureas, thioureas, amides, sulfonamides, carbamates, imines, and hydrazones was synthesized by the removal of the excess amines and hydrazines from solution using anhydride **92** to afford the library in good yield and purity (Scheme 25).

Scheme 25. Application of the ROMPgel Anhydride as an Amine Scavenger[a]



[a] Reagents and conditions: (a) R^1R^2NH; (b) R^1R^2NH.

In the case of formation of urea, thiourea, imine, and hydrazone, where no hydrogen chloride was produced during the reaction, 1.5 equiv of ROMPgel **92** (based on the loading of 10.8 mmol/g) per equivalent of excess amine was needed to cleanly afford the desired product (compounds **93a**–**c**,**f**–**h**,**t**–**w**,**y**). Surprisingly, even when the nucleophile possessed a second tertiary amine (compounds **93d** and **93e**) or a basic moiety (**93x**), the corresponding amino ureas or hydrazones, which could in theory also be scavenged as an ammonium salt, were isolated in excellent yields and purities using 3 equiv of ROMPgel **92**. Presumably, the excess diamine is scavenged as its amine salt, thereby tying up the carboxylic acid functionality. Amides, sulfonamides, and carbamates (compounds **93i**–**s**) were prepared in excellent yields

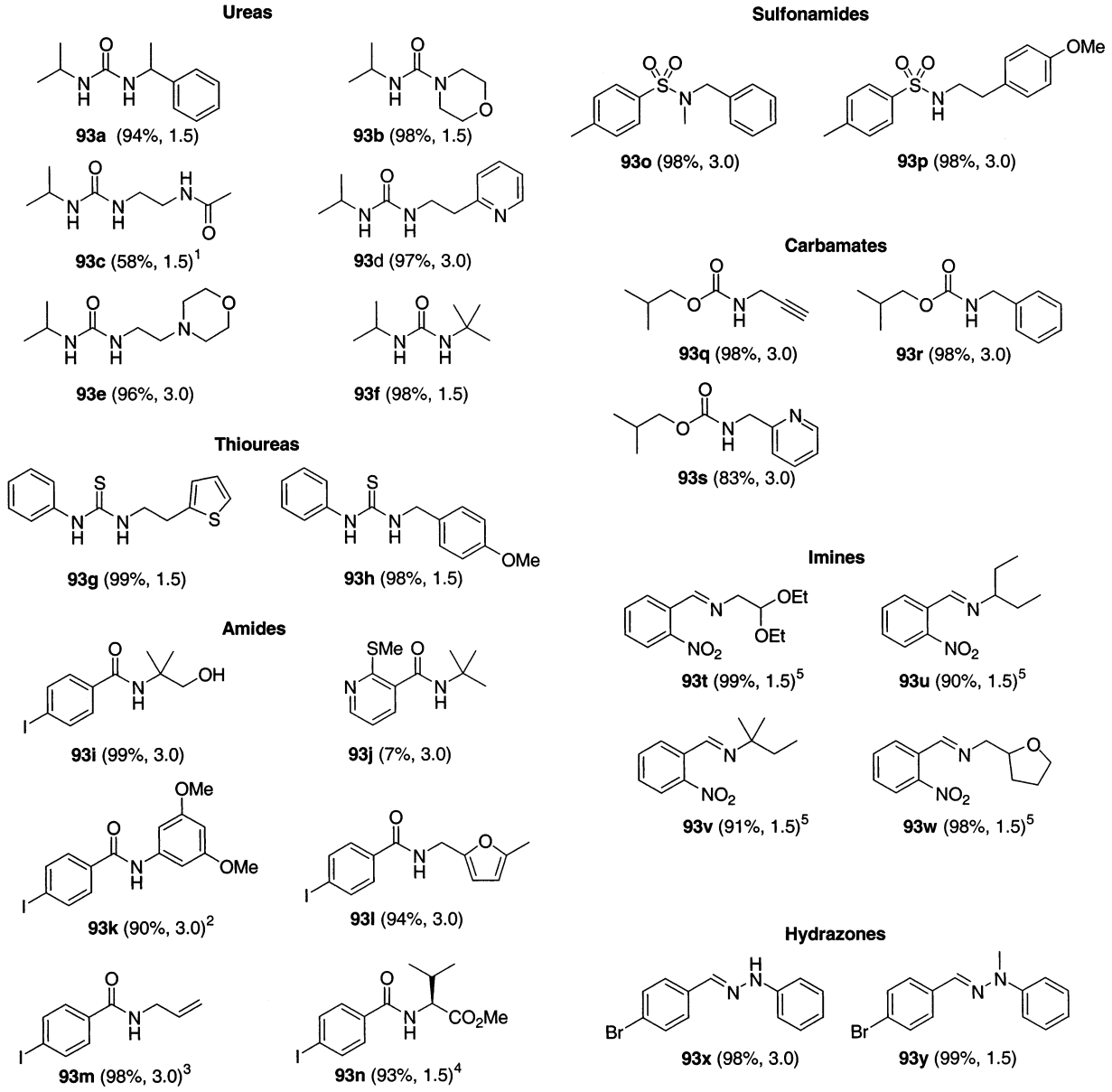


Figure 6. Coupling products gained after scavenging excess amine. All of the reactions were carried out with 3 equiv of the nucleophile relative to the electrophile. Parentheses refer to the isolated yield and the number of equivalents of anhydride scavenger **92** used (10.8 mmol/g loading) relative to the excess amine. All of the products have been characterized by ^{1}H NMR, ^{13}C NMR, GC-MS (one peak), IR, and HRMS. [1]Product was mostly insoluble in CH_2Cl_2; [2]overnight, room temperature for the scavenging step; [3]ROMPgel-supported morpholine **96** was used instead of polyvinylpyridine; [4]the hydrochloride salt of the amino ester was used; [5]ether was used instead of CH_2Cl_2 and 4 Å molecular sieves were added to the mixture.

and purities by reaction of excess amines with acyl or arenesulfonyl chlorides or chloroformates. In these cases, polyvinylpyridine was added to the reaction mixture to scavenge hydrogen chloride. Three equivalents of scavenger **92** per equivalent of excess amine was used to trap the unreacted amine. The larger amount was required due to the formation of hydrogen chloride and the necessity to avoid formation of the ammonium salt in the solution phase. Presumably the yield of amide **93j** was low under the standard reaction conditions due to poor conversion as a result of steric congestion. As an alternative to polyvinylpyridine, ROMPgel-supported morpholine reagent **96** could be used instead. Compound **93m** was isolated in 98% yield and excellent purity (>95% by ^{1}H NMR) using 1.5 equiv of ROMPgel morpholine **96** instead of polyvinylpyridine (Figures 6 and 7).

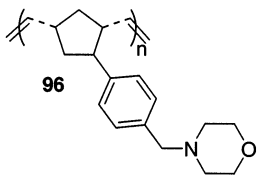


Figure 7. ROMPgel-based morpholine derivative.

III. Other Applications of ROM Polymers in Parallel Synthesis

A. Polymerizable Templates and Vanishing Supports

The initial ROM polymers prepared in the Barrett group were devised as an alternative approach to

address the problem of low loading of substrates on a polymer support in the preparation of a synthetic library. The use of polyethylene glycol (PEG) supports clearly demonstrates the advantages of easy solution-based analysis.[115] They can be used in a variety of solvents such as dichloromethane while being separated from the reaction mixture utilizing their differential solubility by precipitation with MeOH, ether, or *tert*-butyl methyl ether. Unfortunately, these supports are not ideal in terms of loading. On the other hand, the preparation of polymer-supported dendritic materials led to improved loading yet did not greatly facilitate analytical tracking during reaction.[116]

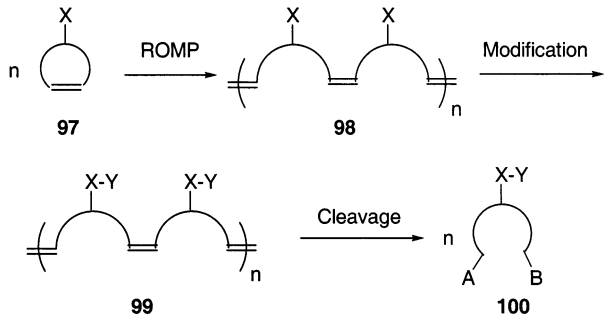


Figure 8. Schematic illustration of the synthetic concept.

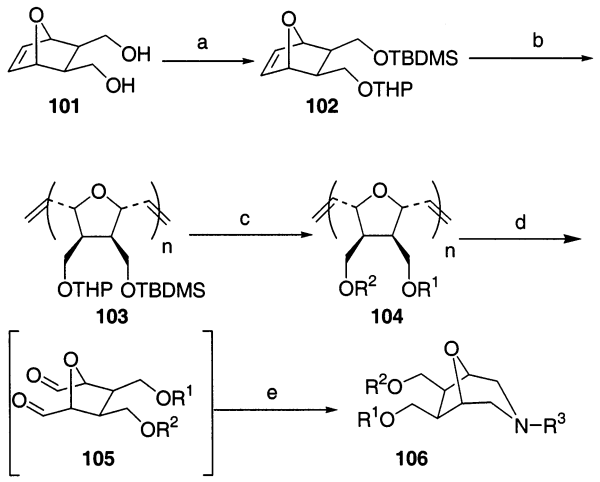
Barrett and co-workers[48] have devised an approach whereby monomeric building blocks **97** were initially utilized as both the polymer backbone and the templates for the target libraries (Figure 8). The solubility of the derived ROM polymers **98** varied depending on the solvent, thus allowing for analysis of the polymer to be routinely performed using NMR spectroscopy. Purification was achieved by precipitation and filtration. The library members of interest were revealed through an oxidative disassembly of the modified polymer backbone **99** on ozonolysis and reductive amination to afford the target molecules **100** in reasonable yields. This approach offered the advantage of allowing chemical modifications to be conducted in a homogeneous environment, thus avoiding the poor solvation typically experienced with solid supports. One limitation of this process is that all potential members of the libraries that could be synthesized would belong to a similar class of compounds. Second, because the soluble ROM polymers are heavily functionalized, the choice of solvents for dissolution and precipitation change with side-chain functionality (Scheme 26; Table 10).

Table 10. Yields of the Products Synthesized (over 5 Steps)

entry	R^1	R^2	R^3	yield[a] (%)
106a	Me	Me	Bn	20
106b	Me	Me	*n*-Bu	24
106c	Me	Me	CH_2−*c*-C_6H_{11}	22
106d	*p*-BrBn	Me	Bn	29
106e	*p*-BrBn	Me	*n*-Bu	32
106f	*p*-BrBn	Me	CH_2−*c*-C_6H_{11}	33
106g	*p*-BrBn	*p*-BrBn	Bn	28
106h	*p*-BrBn	*p*-BrBn	*n*-Bu	29
106j	*p*-BrBn	*p*-BrBn	CH_2−*c*-C_6H_{11}	25

[a] Isolated yields were determined after five steps.

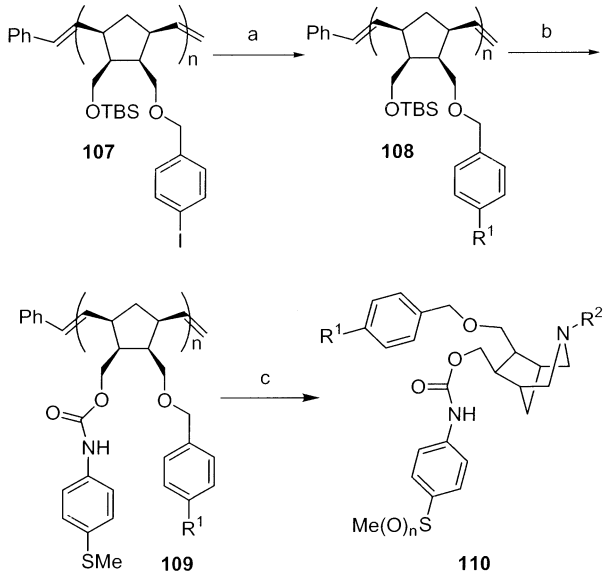
Scheme 26. Application of the Polymer Backbone Disassembly Methodology[a]



[a] Reagents and conditions: (a) (i) NaH, THF, TBDMSCl, 78%; (ii) dihydropyran, cat. PPTS, CH_2Cl_2, 92%; (b) (i) **1**, CH_2Cl_2, (ii) EtOCH=CH_2, 90%; (c) (i) *n*-Bu_4NF, THF; (ii) NaH, THF, R^1X; (iii) TsOH, MeOH−CH_2Cl_2 (1:2:1); (iv) NaH, THF, R^2X; (d) O_3, CH_2Cl_2, −78 °C, EtOH, Me_2S; (e) $NaBH(OAc)_3$, R^3NH_2.

To further demonstrate the applicability of ROMP-gels as immobilized supports, palladium-coupling reactions were attempted using aryl and alkyl zincates.[117] The polymers were desilylated and converted into the carbamates upon treatment with an isocyanate, which were purified by precipitation from solution. An oxidative disassembly of the polymer was achieved using ozone and subsequent reductive amination with *n*-butylamine and benzylamine gave amines **110** in reasonable yields as shown in Table 11 (Scheme 27).

Scheme 27. Zincate Couplings on Vanishing Supports[a]



[a] Reagents and conditions: (a) R^1MgX, $ZnCl_2$, $PdCl_2$(dppf), THF, DME; (b) (i) TBAF, THF; (ii) 4-$MeSC_6H_4NCO$, DMAP, $PhCH_3$, reflux; (c) (i) O_3, CH_2Cl_2, −78 °C, Me_2S, EtOH; (ii) $NaBH(OAc)_3$, R^2NH_2.

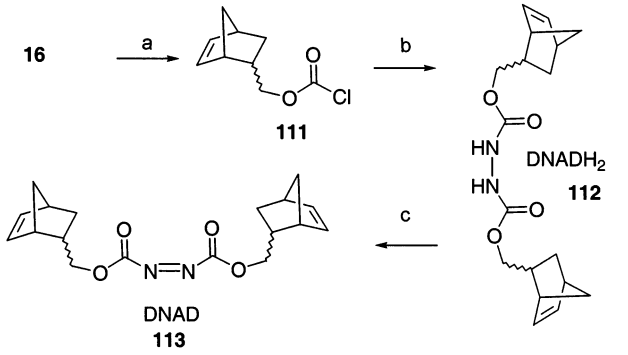
Table 11. Products of Zincate Coupling and Subsequent Backbone Disassembly

entry	R^1	R^2	*n*	yield (%)
110a	4-toluyl	*n*-butyl	1	32
110b	4-toluyl	Bn	2	56
110c	*n*-hexyl	Bn	1	36
110d	3-anisyl	Bn	1	38
110e	3-anisyl	Bn	2	49

B. Chromatography-Free Parallel Mitsunobu Reactions

In the Mitsunobu reaction two different reagents, triphenylphosphine and diethyl azodicarboxylate (DEAD), have to be employed at the same time.[121] The immobilization of both reagents on solid supports would clearly result in no reaction. Thus, the conventional approach to facilitate workup through the use of solid supports is ineffective. One approach is to tag both reagents with masked acidic groups, which later can be unmasked to scavenge the side products.[118]Another approach devised by Barrett et al.[119] was through the replacement of DEAD by di-(5-norbornenyl-2-methyl)azodicarboxylate (DNAD) **113** used in combination with polystyrene-supported triphenylphosphine[101,120] **114**, thereby facilitating a chromatography-free Mitsunobu reaction. The resulting $DNADH_2$ **112** was ROM polymerized, allowing for removal from the reaction mixture by precipitation and filtration (Scheme 28).

Scheme 28. Synthesis of Di(5-norbornenyl-2-methyl)azodicarboxylate (DNAD)[a]



[a] Reagents and conditions: (a) $COCl_2$, $PhNMe_2$, PhMe 83%; (b) H_2NNH_2, Na_2CO_3, EtOH 88%; (c) $PhI(OAc)_2$ CH_2Cl_2, 83%.

It was found that unreacted DNAD inhibited the ROM polymerization of the $DNADH_2$. By adding a slight excess of polymer-supported triphenylphosphine **114**, this problem could be circumvented because any remaining DNAD would be scavenged out of solution. With this methodology in hand, a small library of Mitsunobu products was prepared, with yields between 60 and 100% and purities between 86 and 97%, as shown in Table 12 (Scheme 29; Figure 9).

Scheme 29. Scavenging of Excess DNAD

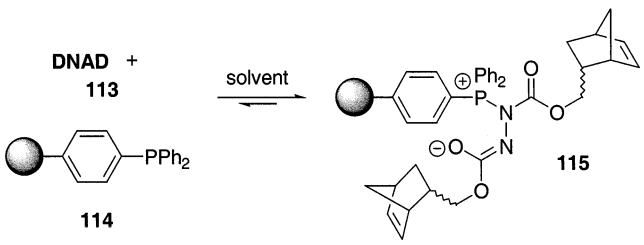


Table 12. Yields and Purities (Percent) of the Mitsunobu Products[a]

	alcohol		
nucleophile	**116a**	**116b**	**116c**
117a	100 (92)	94 (95)	73 (95)
117b	80 (91)	78 (95)[b]	81 (91)[b]
117c	100 (96)	73 (90)[c]	62 (89)[b]
117d	68 (96)[b]	43 (86)[b,d]	61 (97)[b,d]
117e	*e*	*e*	*e*

[a] The value refers to the isolated yield of the product RNu. Figures in parentheses are the purities of RNu as judged by ^1H NMR. Purities judged by GC-MS were ≥95% unless otherwise indicated. [b] DNAD **113** (2.5 equiv) and phosphine **114** (2.5 equiv) were used. [c] GC purity = 86%. [d] Short filtration through silica. [e] The Mitsunobu reaction worked but ROM polymerization using **1** did not.

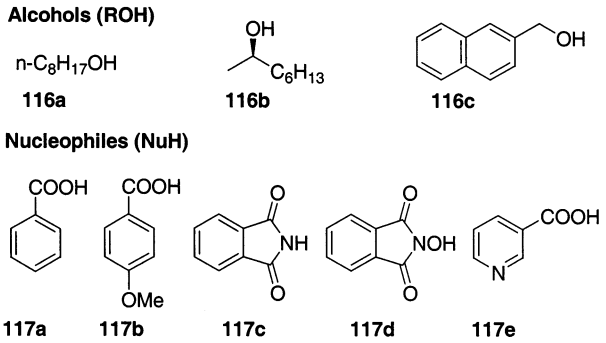
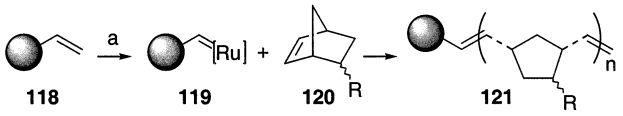


Figure 9. Starting material for the Mitsunobu reaction.

C. ROMPspheres

The major advantage of the ROM polymerization process is that the reactions are "living systems" allowing for the grafting of monomers onto different types of supports. As previously discussed, Buchmeiser[37] used this approach to synthesize grafted ROM polymers onto the surface of silica gel and polystyrene, which were employed in catalysis. For a different application Barrett utilized a similar strategy whereby the monomer was grafted onto a polystyrene support, thus affording high-loading polymer beads using a ROM polymerization reaction. In contrast to Buchmeiser's work, who immobilized only up to 10% of monomer by weight onto the supports, the Barrett group developed a methodology allowing them to increase the weight of the beads by up to a factor of 10. These ROM graft copolymers were prepared upon the treatment of vinyl polystyrene **118** with Grubbs catalyst **1** to afford the polymer-supported ruthenium "boomerang catalyst"[122] **119**, which was in turn allowed to react with an excess of monomer **120** to afford a ROMPsphere **121**.[123] These initial studies indicated that a substantial weight increase of the polymer particles was achievable. By using a 4-fold weight excess of monomer, 83% was incorporated onto the polystyrene core. Even with a 100-fold excess of monomer a maximum 12-fold weight increase of the beads was achieved. The amount of monomer incorporated onto the polymer was calculated by measuring the increase in weight, as well as a visible difference in the size of the ROMPsphere **121** compared to the polystyrene beads **118** (Scheme 30).

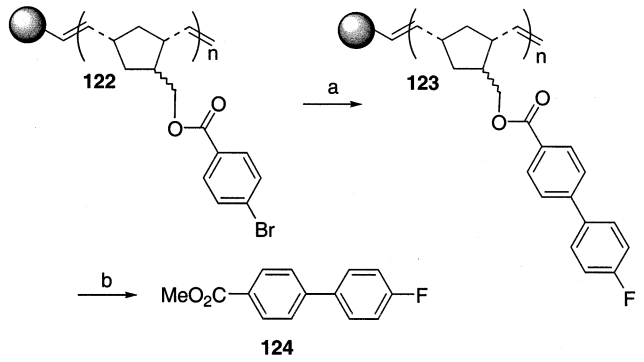
Scheme 30. Synthesis of ROMPspheres[a]



[a] Reagents and conditions: (a) (i) **1** (8 mol %), CH_2Cl_2; (ii) $EtOCH{=}CH_2$, 100%.

ROMPspheres have a number of advantages: for one, they are of uniform particle size, which appears to replicate the particle size distribution of the polystyrene core. Second, the active sites of the ROM polymer are well accessible because there is no cross-linking in the tentacle-like polymer chains growing from the initial bead. These supports thus have similarities with the Rasta resins developed by Hodges et al.[44−47] The physical properties of the ROMPspheres were investigated; the beads were found to swell in solvents such as CH_2Cl_2, DMF, and THF, but not as much as polystyrene. The polymer matrix **122** was also found to be chemically inert, as palladium coupling and cleavage of the substrates were possible to afford the products **124** in good yields and purities (Scheme 31).

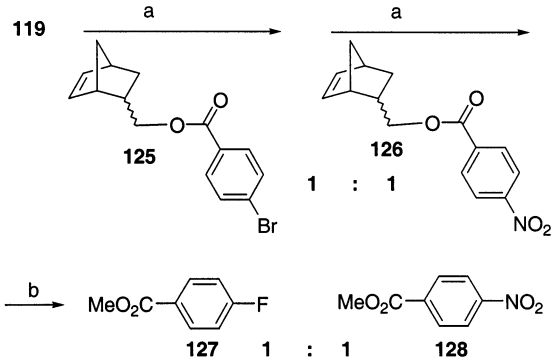
Scheme 31. Zincate Coupling on ROMPspheres[a]



[a] Reagents and conditions: (a) 4-F−C_6H_4MgBr, $ZnCl_2$, $PdCl_2$-(dppf) (10 mol %), THF−DME (8:1); (b) NaOMe (1 equiv), THF−MeOH (4:1).

ROMP is a living polymerization and as such ideal for the formation of block copolymers. Thus, supported catalyst **119** was sequentially treated with two different monomers (ester **125**, CH_2Cl_2, filtration of the intermediate and the ester **126**, CH_2Cl_2, and termination) to give the desired block copolymer, which was cleaved with 0.2 equiv of NaOMe in THF−MeOH. When the reaction time for the couplings was kept below 2 h, the polymer was still living after the first step and equal amounts of the two polymers were incorporated, clearly demonstating the potential of this approach to generate bifunctional solid supports (Scheme 32).

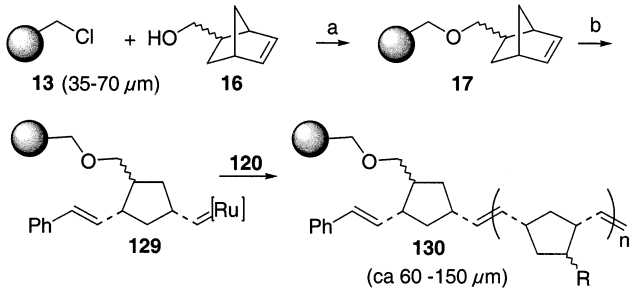
Scheme 32. Block Polymer Formation[a]



[a] Reagents and conditions: (a) (i) CH_2Cl_2; (ii) filter after 2 h; (b) NaOMe (0.21 equiv), THF−MeOH (4:1).

More recently, a second strategy has been adopted whereby a norbornene moiety is attached to the polystyrene **17** and subsequently allowed to react with Grubbs catalyst **1** to afford a ruthenium-functionalized polymer **129** from which monomers can be grafted by ROM polymerization. The advantage of this second approach is that, unlike the vinyl polystyrene, there is less chance of polymer back-biting. This has been successfully employed in the development of the ROMPsphere-supported peptide-coupling reagent[72] as discussed in section II.G (Scheme 33).

Scheme 33. Alternative Approach toward ROMPspheres[a]



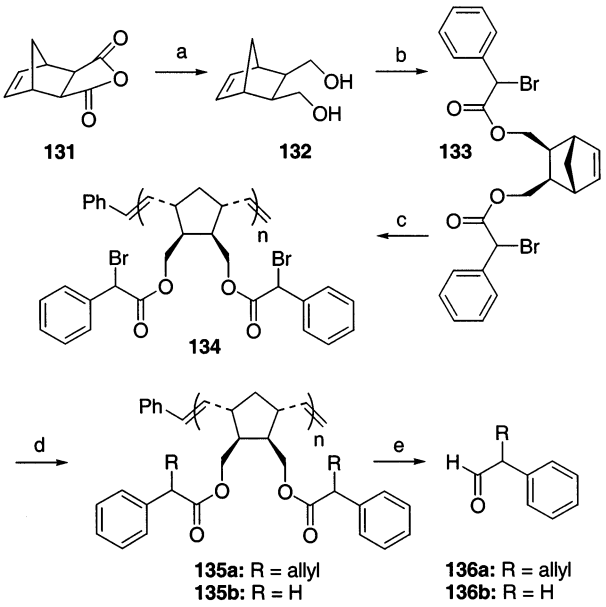
[a] Reagents and conditions: (a) KH, DMF, 60 °C; (b) **4**, CH_2Cl_2.

D. Recyclable Soluble Supports

Recently, Enholm and co-workers[124,125] have reported the use of a soluble ROM polymer for the synthesis of α-substituted acids and as a scaffold for the incorporation of a chiral auxiliary onto the polymer to facilitate diastereoselective radical cyclization reactions. As previously discussed, the usage of soluble polymer avoids the problems normally encountered with solid supports, such as rates of diffusion and monitoring of the reactions. As an additional advantage this permits the usage of a phase switch through precipitation of the support to remove tin. The soluble polymer **134** was prepared from the dibromide **133** by treatment with Grubbs catalyst, followed by termination of the polymerization with ethyl vinyl ether. The resulting polymer **134** was allylated under free radical conditions to afford diester **135a**, which was cleaved from the support via saponification to afford **136a** in 31% yield over five steps. A further extension of the free radical reaction resulted in a tin hydride reduction of bromoester **134** to afford **136b** in a yield of 28% over five steps. Surprisingly, the alkene units in the polymer backbone showed remarkable tolerance to these free radical conditions (Scheme 34).

To further demonstrate the applicability of soluble ROM polymers in radical reactions, the polymerizable chiral auxiliary **137**, based on (+)-isosorbide, was developed (Scheme 35). After attachment of a suitable template by DCC coupling, the auxiliary **138** was polymerized using Grubbs catalyst **1**, yielding the oligomers **139** that were soluble in CH_2Cl_2 but

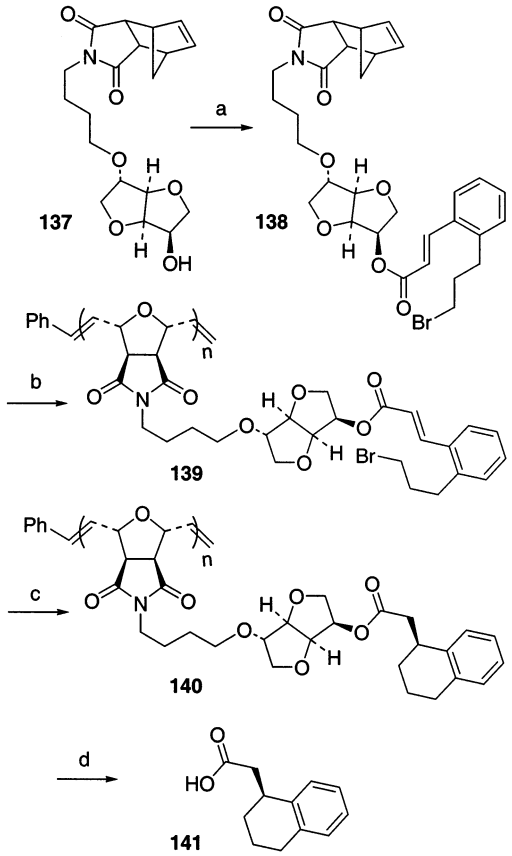
Scheme 34. Synthesis and Application of the Soluble Polymers[a]



[a] Reagents and conditions: (a) $LiAlH_4$, THF, 82%; (b) PhCH(Br)CO_2H, DCC, CH_2Cl_2, 80%; (c) (i) **1** (1.5 mol %), CH_2Cl_2; (ii) $EtOCH{=}CH_2$, 79%; (d) *n*-Bu_3SnR, AIBN, PhH; (e) LiOH, THF−H_2O. Yield after five steps R= allyl, 31%; R = H, 28% yield.

insoluble in MeOH. Radical cyclization, employing tri-*n*-butylstannane under Lewis acid-catalyzed conditions, yielded products **141** with enantiomeric purities of up to 90% ee after cleavage from the support by saponification (Scheme 35; Table 13). The structures in Schemes 34 and 35 are drawn as in the Enholm papers. It is, however, likely the starting monomers **131** and **137** are predominantly endo not exo.

Scheme 35. Enantioselective Radical Cyclization on a Soluble ROM Polymer[a]



[a] Reagents and conditions: (a) DCC, 4-DMAP, 2-(Br$(CH_2)_3$)-$C_6H_4CH{=}CHCO_2H$, CH_2Cl_2, 86%; (b) **1**, CH_2Cl_2, 90%; (c) *n*-Bu_3SnH, Lewis acid, Et_3B, O_2, CH_2Cl_2, −78 °C; (d) LiOH, MeOH.

Table 13. Yield and Enantioselectivities of Acid 141 Utilizing Different Lewis Acids

entry	Lewis acid	*T* (°C)	solvent	yield (%)	ee (%)
1	none	0	CH_2Cl_2	87	0
2	none	−78	CH_2Cl_2	84	40
3	$MgBr_2(OEt_2)$	−78	CH_2Cl_2/ether (1:1)	84	86
4	$ZnCl_2$	−78	CH_2Cl_2/THF (1:1)	80	>90
5	$Yb(OTf)_3$	−78	CH_2Cl_2/ether (1:1)	72	75

E. Capture ROMP Release

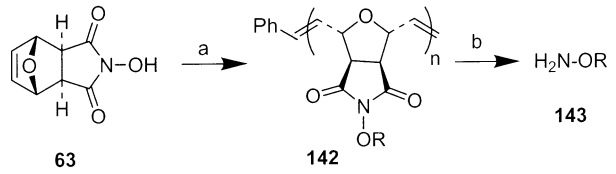
An alternative mode of application for ROM polymers has been used by Hanson et al. in the synthesis of *O*-alkylhydroxylamines via hydrazinolysis of soluble polymer-bound *N*-hydroxysuccinimides.[126] In this concept alcohols are coupled to commercially available *N*-hydroxysuccinimide **63** via a Mitsunobu reaction. The product is then polymerized using 5 mol % of the Ru catalyst **3**, yielding a soluble polymer **142** that could be precipitated with MeOH and washed free of any side products. Cleavage with anhydrous hydrazine in THF at ambient temperature for 1 h followed by a biphasic extraction (ether/H_2O), to remove the now water soluble polymer, gave rise to the desired *O*-alkylhydroxylamines **143** in good yields and purities without the need for chromatography. This approach therefore exemplifies the applicability of ROM polymers to a capture and release strategy in parallel synthesis. The main advantage is that capture through polymerization is very straightforward compared to linking small organic molecule onto preformed supports (Scheme 36; Table 14).

Table 14. Yield and Purities of the *O*-alkylhydroxylamines 143[a]

entry	alcohol	yield of **142** (%)	yield of **143**[b] (%)	purity[c] (%)	residual N_2H_4 (%)
1	benzyl alcohol	95	72	84	6
2	2-octanol	83[d]	59	69	12
3	2-octanol	97[d,e]	89[e]	73[e]	n/a
4	1,2,3,4-tetrahydro-1-naphthalenol	99	95	91	6
5	1,2,3,4-tetrahydro-1-naphthalenol	93[c]	77[c]	67[c]	n/a
6	3-phenyl-1-propanol	>99	97	82	5
7	(*E*)-3-phenyl-2-propen-1-ol	99	79	84	8
8	1-naphthalene-methanol	>99	96	63	9
9	(2*E*)-3,7-dimethyl-2,6-octadien-1-ol	63[d]	61	73	7
10	(4-methoxyphenyl)-methanol	>99	58	79	9

[a] Reactions performed as outlined in Scheme 36. [b] Based on original amount of alcohol. [c] Determined by GC before azeotropic removal of hydrazine. [d] Polymerization conducted with 2 mol % of 4. [e] Cleavage with $MeNH_2$/MeOH.

Scheme 36. Capture ROMP Release in the Synthesis[a]



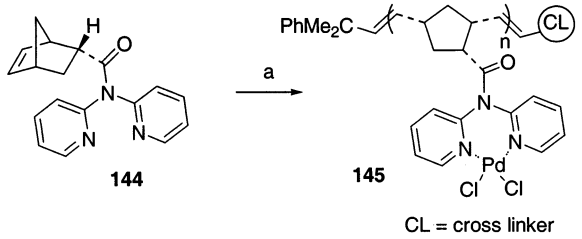
[a] Reagents and conditions: (a) (i) ROH, PPh_3, DIAD, THF, 25 °C; (ii) 5 mol % **4**, CH_2Cl_2, reflux; (iii) $EtOCH{=}CH_2$; (iv) MeOH then filtration; (b) (i) $H_2N{-}NH_2$, THF, 25 °C; (ii) extraction of water soluble oligomers.

IV. Immobilized Catalysts on ROM Polymer Supports

A. Dipyridinyl Catalysts for Pd-Coupling Reactions

Several different dipyridyl-based ligands have been developed by Buchmeiser et al. and shown to be efficient in stabilizing palladium(0) in cross-coupling reactions.[14,19,39,56,64,66] Monomeric dipyridine ligands were shown to be very active in palladium-catalyzed coupling reactions. The analogous system **144** with a norbornene unit in the ligand backbone was subjected to ROM polymerization to give polymeric particles. In this case first the active monomer was polymerized to give "living" oligomers, which were precipitated by cross-linking with **7** yielding small polymer particles. The polymeric ligands were subsequently derivatized with chloroplatinic acid to provide a supported homogeneous catalyst **145**, which was air, moisture, and temperature stable up to 150 °C and highly active (94−99% yields) for the vinylation of aryl iodides and aryl bromides (Heck-type couplings) with turn-over numbers (TONs) of up to 210000. Even higher TONs (up to 430,000) were achieved in the arylation of alkynes. Moderate yields (<65%) and TONs (<4000) were observed in the amination reactions of aryl bromides. The activity of the polymeric catalyst was significantly higher than that of the soluble analogue, thus suggesting well-defined ligand-bound catalytic sites rather than polymer-supported palladium colloids[56] (Scheme 37).

Scheme 37. Synthesis of an Immobilized Pd−Dipyridinyl Catalyst[a]



[a] Reagents and conditions: (i) **2**, CH_2Cl_2; (ii) cross-linker **7**; (iii) H_2PdCl_4.

The catalytic system subsequently was further elaborated by introducing structural changes to the dipyridinyl moiety **146**−**149**. Unfortunately, all changes lead to a less favored coordination of the ligand to palladium due to a more distorted square planar ligand sphere. Nonetheless these catalysts were still quite active.[66] In summary, novel bis-

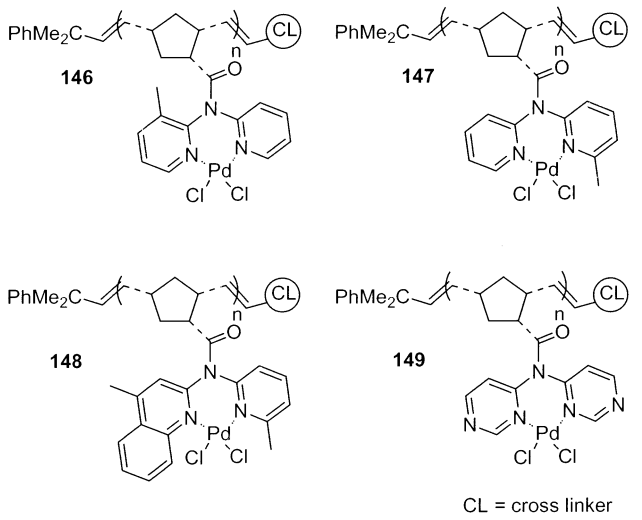


Figure 10. Structural variations on the immobilized Pd-dipyridinyl catalyst.

(pyridine)-based polymeric catalysts were shown to be active in Heck, Suzuki, and Sonogashira couplings as well as amination reactions using aryl iodides, bromides, and chlorides[64] (Figure 10; Table 15).

B. Catalysts for Atom-Transfer Radical Polymerization Reactions

On the basis of the above-mentioned dipyridyl-amide ligands **144**, a novel class of terpyridine monomers **150** was synthesized. Both monomers were subsequently graft polymerized onto norbornene-derivatized silica and used to complex a number of different metal salts, preferably copper(II) and iron-(II). In the case of the tripyridine monomer, a dimeric iron complex **151** was also prepared as a crystalline solid that was polymerized.[65] All of the immobilized catalysts prepared were tested in heterogeneous atom-transfer radical polymerizations of styrene in benzene or toluene. Yields of up to 35% were obtained in the polymerization of styrene.[19] The polymer was virtually metal free and had molecular weights of up to 80000. The low conversions probably are thus not due to deactivation or degradation of the catalysts but rather due to unfavorable rate constants that are involved with the half-life of the radical species[65] (Figure 11; Table 16).

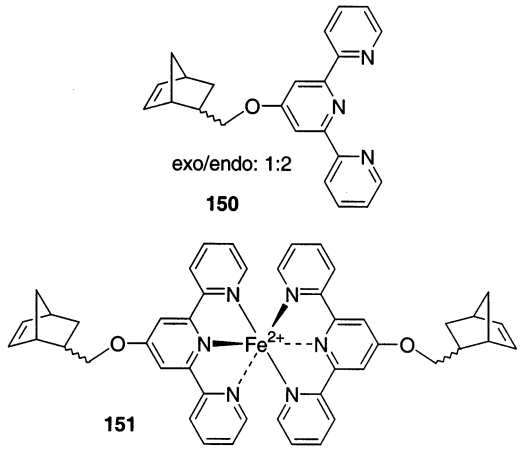


Figure 11. Monomers for the synthesis of polymer ATRP catalysts.

Table 15. Summary of Heck-Couplings, Polymerizations, and Pd-Mediated Aminations[l]

no.	Ar−I	g	H_2=CHR	g	product	resin[d] (mg)	Pd (μmol)	yield[e] (%)	solvent	10^3 TON
1	iodobenzene	5.0	styrene	2.8	*trans*-stilbene	100	210	87	DMF[b]	1.0
2		34.8		16.8		1	1.6[f]	69	DMF[c]	73.9
3		11.3		5.7		1	0.2	78	DMF[c]	206.5
4		9.0		4.6		3	1	90	DMAC[c]	40.2
5		9.0		4.6		1.2	0.4	99	DMAC[k]	111.0
6	iodobenzene/TBAB[a]	3 × 1.5/0.5	styrene	3 × 0.77	*trans*-stilbene	1	0.2	98	DMF[b]	93.2
7	iodobenzene	5.5	ethyl acrylate	2.7	ethyl *trans*-cinnamate	20	4.2	79	DMF[b]	5.1
8		9.1		4.5		20	6.7	<10	DMAC[k]	-
9		20.0		9.8		2	0.4	75	DMF[b]	175.1
10		17.0		8.1		1	1.6[f]	27	DMF[b]	14.1
11	iodobenzene	0.92	vinyl ferrocene	0.94	1-ferrocenyl-2-phenylethene	1	0.2	81	DMF[b]	17.4
12	iodobenzene	14.8	TMS-acetylene	3.55	tolan/TMS-ethynylbenzene	1	0.2	75 (2:1)	DMF	432

no.	Ar−Br	g	H_2=CHR	g	product	resin[d] (mg)	Pd (μmol)	yield[e] (%)	solvent	10^3 TON
13	bromobenzene	7.0	styrene	4.7	*trans*-stilbene	11[j]	3.9	72	DMF[c]	9.4
14		7.0		4.6		3	1	90	DMAC[k]	40.0
15	4-bromobenzonitrile	4.5	styrene	2.55	4-cyano-*trans*-stilbene	18	3.8	94	DMF[b]	6.1
16		6.7		3.8		5	1.1	62	DMF[b]	20.6
17		6.7		3.8		1	1.6[f]	51	DMF[b]	11.7
18		12.3		8.5		1	0.35	83	DMF[b]	157.7
19	4-bromo-1-fluorobenzene	15.3	styrene	9.1	4-fluoro-*trans*-stilbene	2	0.4	26	DMF[c]	54.1
20		7.8		4.6		2	0.7	59	DMAC[k]	34.4
21	4-methoxybromobenzene	8.3	styrene	4.6	4-methoxy-*trans*-stilbene	105	36	70	DMAC[k]	0.9

no.	Ar−Cl	g	H_2=CHR	g	product	resin[d] (mg)	Pd (μmol)	yield[e] (%)	solvent	10^3 TON
22	chlorobenzene	5.0	styrene	4.7	*trans*-stilbene	10[j]	3.5	0	DMF[c]	0.0
23	chlorobenzene/TBAB	5.0/3.0	styrene	4.7	*trans*-stilbene	10[j]	3.5	60	DMF[c]	8.2
24		5.0/3.0		4.6		10[j]	1.5	89	DMAC[k]	23.6
25		5.0/3.0		4.6		5	1.7	16	DMF, 70°	4.1
26	4-chloroacetophenone	13.5	styrene	9.1	4-acetyl-*trans*-stilbene	10	0.2	<10	DMF[c]	–
27	4-chloroacetophenone/TBAB	7.5/3.0	styrene	5.0	4-acetyl-*trans*-stilbene	20	6.9	19	DMF[c]	1.4
28		6.9/3.0		4.6		20	6.9	95	DMAC[k]	6.1

no.	Ar−Br	g	H_2=CHR	g	product	resin[d] (mg)	Pd (μmol)	yield[e] (%)	solvent	10^3 TON
29	dibromobenzene	2.0	divinylbenzene	1.14	polyphenylenevinylene (M_w, 1970; PDI, 1.63)	2	0.7	>99	DMAC[k]	18

no.	Ar−Br	g	amine	g	product	resin[d] (mg)	Pd (μmol)	yield[e] (%)	solvent	10^3 TON
30	bromobenzene/KO-*t*-Bu	4.2/3.5	*N*-methylaniline	2.8	*N*-methyldiphenylamine	15	3.2	45	THF[g]	3.8
31		4.2/3.5		2.8		22[h]	5.5	63	toluene	3.7
32	bromobenzene/KO-*t*-Bu[h]	5.0/4.0	piperidine	2.7	*N*-phenylpiperidine	22[j]	7.7	18	toluene	0.8
33	bromoanisole/KO-*t*-Bu	2.2/3.0	diphenylamine	2.0	4-methoxytriphenylamine	15	3.2	10	THF[g]	0.4

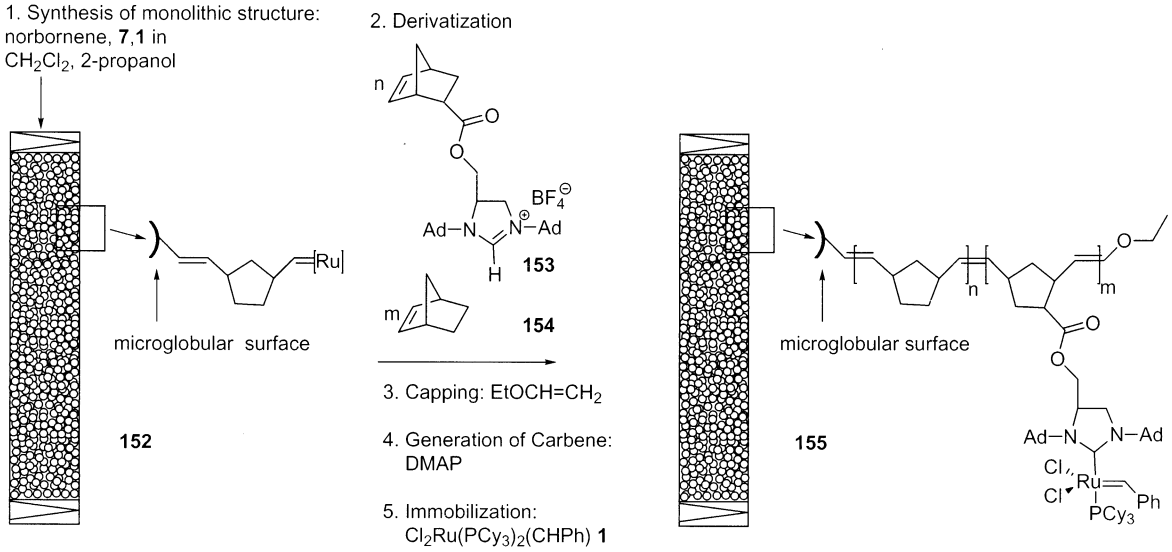
[a] TBAB = tetra-*n*-butylammonium bromide. [b] 30 mL of tri-*n*-butylamine. [c] 50 mL of tri-*n*-butylamine. [d] Containing 0.21 mmol/g immobilized Pd^{2+} (+0.4 mmol of free ligand). [e] Isolated yields. [f] Soluble, homogeneous analogue, Cl_2PdL_2. [g] 65 °C. [h] 2 h at 110 °C. [i] By NMR. [j] Containing 0.35 mmol/g of immobilized Pd (0) (+0.65 mmol of free ligand). [k] K_2CO_3/Na_2CO_3. [l] Unless stated otherwise, Heck couplings were carried out at T = 140 °C, t = 90 h.

Table 16. Summary of Polymerization Results for Styrene[a,c]

no.	ligand system	metal/cocatalyst	T (°C)	yield (%)	PDI	M_w (kDa)
1	poly-**144**	Cu(I)	110	14	1.78	30.9
2		Cu(II)/Al(i-OPr)$_3$	110	10	2.70	71.0
3	poly-**150**	Cu(I)	110	19	1.79	30.9
4	poly-**144**-coated NBE silica	Cu(I)	110	18	3.4	77.0
5		Cu(II)/Al(i-OPr)$_3$	110	7	1.67	30.6
6		Hg(II)/Al(i-OPr)$_3$	110	10	1.92	82.7
7	poly-**150**-coated NBE silica	Cu(I)	110	24	1.97	22.8
8		Cu(I)	70	31	1.57	48.1
9		Cu(I)	40	3	1.81	68.4
10		Cu(I)/Al(i-OPr)$_3$	110	22	3.3	45.5
11		Cu(I)/Al(i-OPr)$_3$	40	3	2.79	134.9
12	poly-**144**-coated NBE silica	Cu(II)/Al(i-OPr)$_3$	110	16	1.61	41.9
13		Cu(II)/MAO	110	22	1.55	23.1
14		Fe(II)/Al(i-OPr)$_3$	110	23	1.90	84.1
15	poly-**144**-grafted NBE silica	Cu(I)	110	24	1.77	42.5
16		Cu(II)/Al(i-OPr)$_3$	110	5	1.55	30.2
17	poly-**150**-grafted NBE silica	Cu(I)	110	15	1.65	27.7
18		Cu(II)/Al(i-OPr)$_3$	110	8	1.59	38.5
19	poly-**144**-grafted PS-DVB	Cu(I)	–	tr[b]	–	–
20		Cu(II)/Al(i-OPr)$_3$	–	tr	–	–
21	poly-**150**-grafted PS-DVB	Cu(I)	110	tr	1.42	35.6
22	poly-**151**-grafted silica	Fe(II)	70	3	1.74	56.5
23	poly-**151**-coated silica	Fe(II)	70	3	1.37	95.3

[a] Salts used: Cu(i), CuBr·Me_2S; Cu(II), $Cu(OAc)_2·H_2O$; Fe(II), $Fe(OAc)_2$; Hg(II), $Hg(OAc)_2$. [b] Traces. [c] Ref 132.

Scheme 38. Synthesis of the Monolithic Metathesis Catalyst[a]



[a] Ref 65. Copyright 2001 John Wiley & Sons.

Table 17. Results from RCM (No. 1−4) and ROMP (No. 5−13)[a,d]

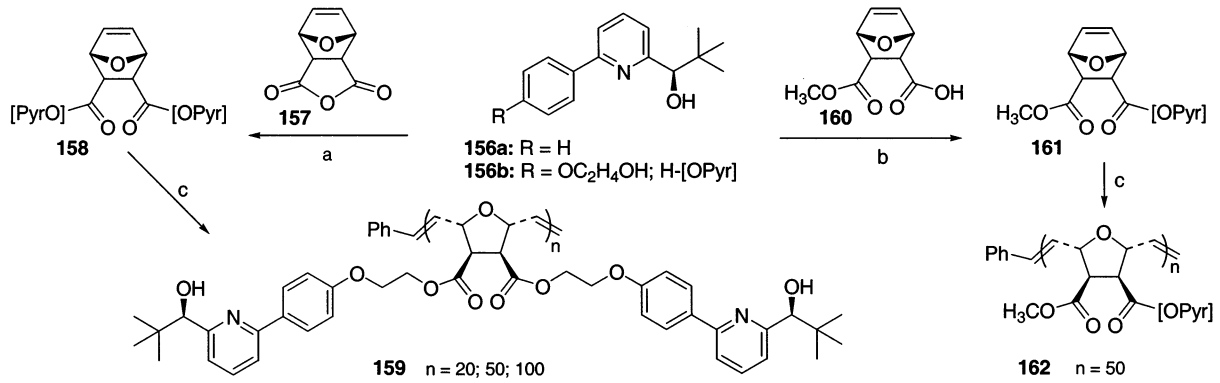
no.	compound	product	CTA	M:CTA	T (°C)	t (min)	yield (%)	TON_{max}[b] (min^{-1})	TOF[b]	M_n	PDI[c]
1	diethyl 2,2-diallyl-	diethyl 3-cyclopentene-			43	3	71	62	25		
2	malonate	1,1-dicarboxylate	**I**		56	50	100	63	–		
3			**I**		56	5	92	55	–		
4	1,7-octadiene	cyclohexene	**I**		56	30	41	56	1.9		
5	norbornene	$\neq CH\text{-}^cC_5H_8\text{-}3\text{-}CH\neq_n$	**II**	21:1	40	3				24000	2.4
6			**II**	21:1	40	3				34000	2.2
7			**II**	21:1	40	3				40000	2.1
8			**II**	21:1	40	3				45000	2.0
9	1-cyclooctene	$\neq CH\text{-}(CH_2)_6CH\neq_n$	**III**	18:1	40	3				2500	1.2
10			**III**	18:1	40	3				1100	2.6
11			**III**	18:1	40	3				1500	1.9
12			**III**	18:1	40	3				1500	1.7
13	norbornene	$\neq CH\text{-}^cC_5H_8\text{-}3\text{-}CH\neq_n$	**I**	5:1	56	30				12000	1.4

[a] The experiments obtained were obtained by flow-through (1, 5−8, and 9−12; these experiments were carried out consecutively with the same monolith) and cartridge experiments (2−4 and 13). CTA = chain transfer agent; **I** = *cis*-1,4-diacetoxybut-2-ene; **II** = diethyl 2,2-diallylmalonate; **III** = *cis*-2-hexene. [b] Heterogeneous conditions. [c] Polydispersity index. [d] Ref 65.

C. Immobilized Metathesis Catalysts

Due to their importance in modern organic synthesis, there has been considerable interest in immobilizing alkene metathesis catalysts. This has been achieved by Barrett through linking the carbenoid ligand, yielding "boomerang" catalysts that reversibly detach from the support.[122,127] This concept has been utilized by Nolan[52] on macroporous supports and by Yao,[128] Hoveyda,[129] and Blechert[130] using the bidentate ligand introduced by Hoveyda.[129] An alternative is the irreversible immobilization of the catalyst on a grafted *N*-heterocyclic carbene as first realized by Blechert.[131] On the basis of the technology developed by Buchmeiser et al. to generate monolithic polymer-based HPLC columns,[38,39] the group recently reported the synthesis of an immobilized metathesis catalyst **155**. It is based on a polymer-bound *N*-heterocyclic carbene ligand onto which a ruthenium catalyst was permanently immobilized through ligand exchange with one of its phosphine ligands.[132] A 1:1 mixture (by weight) of norbornene and **7** in 2-propanol (the porogenic solvent) was mixed at 0 °C with a solution of Grubbs catalyst **1** (0.4%) in CH_2Cl_2 and quickly transferred into a borosilicate glass MPLC column. After 15 min at 0 °C, the mixture was allowed to polymerize for 1 h, yielding a microglobular porous monolithic polymer **152** with active ruthenium catalyst on its chain ends. This polymer was washed with a solution of the norbornene-based precursor of the carbene ligand, which was thereby immobilized onto the surface of the polymer. After termination of the polymerization with ethyl vinyl ether, the ligand precursor was deprotonated with a base such as *N*,*N*-(dimethylamino)pyridine (DMAP) to generate the carbene. Washing the monolith with a solution of catalyst **1** gave rise to the immobilized catalyst **155** by ligand exchange to the more stable carbene ligand. With this immobilized catalyst on the surface of a nonswelling polymeric material, the stage was set for the use in a flow-through synthesis mode. The immobilized catalyst shows excellent activity in ring-closing metathesis (RCM) reactions (four examples, yields between 100 and 41%) and also ROM polymerizations (nine examples, molecular

Scheme 39. Synthesis of Enantiopure Oligomeric Hydroxypyridyl Catalysts[a]



[a] Reagents and conditions: (a) 2-chloro-1-methylpyridinium iodide, Et_3N, DMAP; (b) DCC, DMAP; (c) **1**, CH_2Cl_2.

weights obtained up to 45000) (Scheme 38; Table 17).

D. Catalysts for Asymmetric Diethylzinc Addition Reactions

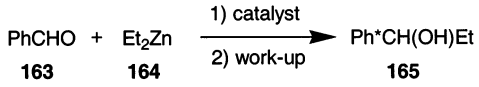
One of the biggest advantages of using ROM polymerization to generate catalytically active polymers is that the number of repetition units is easily controllable by the molar ratio of monomer to catalyst (section I.B). It is thus possible to generate fine-tuned polymers, which are homogeneously soluble in solvents such as CH_2Cl_2 and can be precipitated by the addition of ether or methanol. Another interesting option is that these oligomers of 30−100 repetition units can easily be retained by ultrafiltration membranes, thus enabling their continuous use in membrane reactors.[133] Bolm et al. have developed novel chiral polymers based upon enantiopure hydroxypyridyl units **156** that were chain elongated by a glycol spacer and coupled through esterification onto an *exo*-7-oxanorbornene derviative.[134,135] The disubstituted monomer **158** was generated through Mukaiyama-type esterification of the anhydride **157** with 2-chloro-1-methylpyridinium iodide, triethylamine, and DMAP. The monofunctionalized building block **161** was generated from the ester derivative **160** through DCC coupling. The oxanorbornene derivatives were polymerized, yielding soluble oligomers **159** and **162** of 20−100 repetition units. With these polymers, the addition of diethylzinc to benzaldehyde was catalyzed to provide products with enantiomeric purities of up to 73% ee, whereas the corresponding monomers yielded adducts with up to 87% ee. The polymers were also slightly less active in catalyzing the addition reactions, but it has been demonstrated that ROM polymer-supported catalysts can be used efficiently in enantioselective catalysis (Schemes 39 and 40; Table 18).

Table 18. Reaction of Benzaldehyde and Diethylzinc Catalyzed by Various Pyridinyl Alcohols

pyridinyl alcohol/ polymer	M_w/M_n	amount of pyridinyl alcohol[a] (mg/μmol)	t (h)	yield of **165** (%)	ee of **165** (%)[d]
156a		15.0/62.1	4[b]	91	87
156b		15.0/49.8	24[c]	86	83
158		16.8/44.6	24[b]	72	79
161		38.1/79.1	24[c]	89	80
159, $n = 20$	1.2	22.6/60.2	48[b]	88	73
159, $n = 50$	1.4	23.1/61.5	48[b]	83	73
159, $n = 100$	1.7	48.7/130.0	48[b]	77	73
162, $n = 50$	1.1	35.3/73.0	48[c]	78	71

[a] With respect to catalytically active subunits. [b] Reaction was performed at 0 °C. [c] Reaction was performed at room temperature. [d] Determined by HPLC using a chiral stationary phase.

Scheme 40



V. Conclusions

We have shown that ROM polymers including ROMPgels are very useful supports for the immobilization of reagents and scavengers. Their main advantage is versatility: many functional groups can be incorporated, either before polymerization or, if they are incompatible with the catalyst, postpolymerization from inexpensive monomers. ROMPgels swell significantly in a variety of solvents, and their physical properties can be finely tuned by the use of cross-linkers in their polymerization. Because there are several attractive synthetic routes to norbornene and oxanorbornene derivatives as precursors for ROM polymers, they are very inexpensive immobilized reagents. It is reasonable to expect several other useful ROM polymer-supported reagents to be introduced soon.

VI. Acknowledgment

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