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Polymer-supported reagents and catalysts: increasingly important tools for organic synthesis

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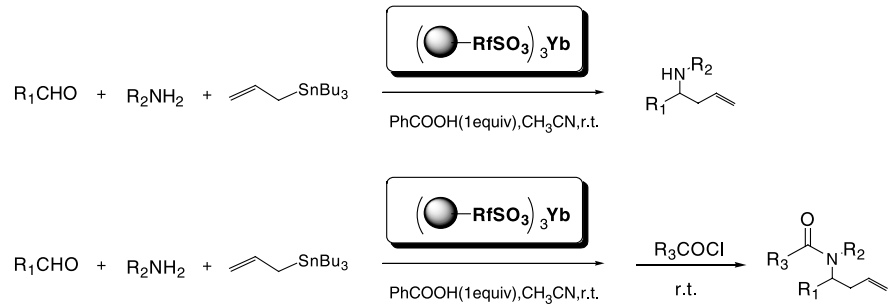
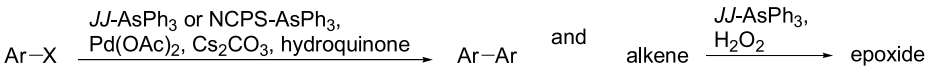
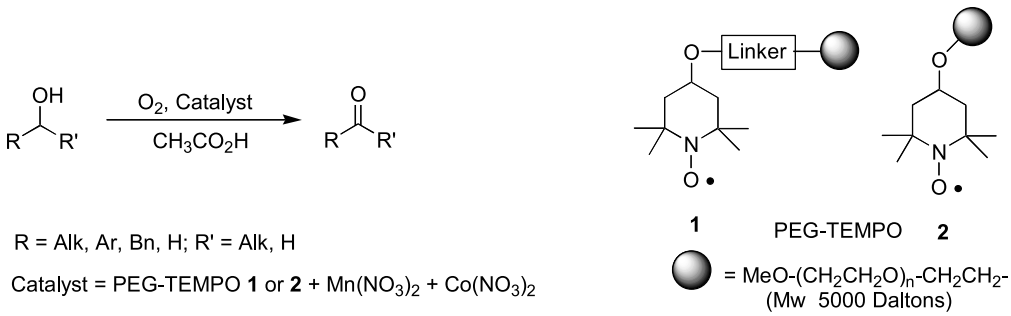
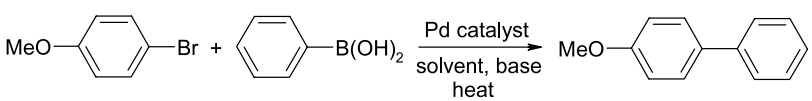
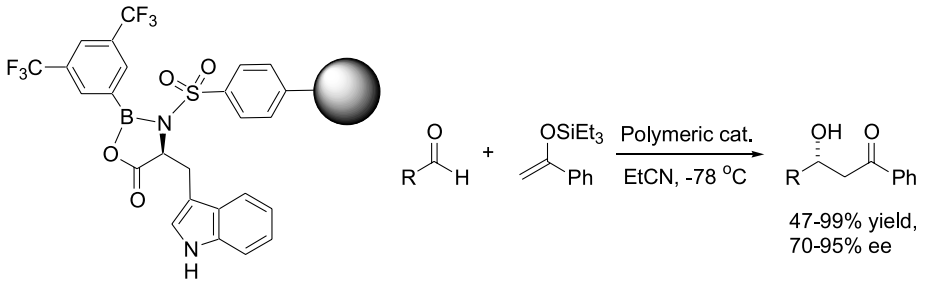
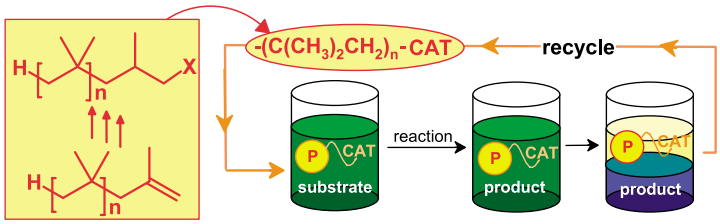




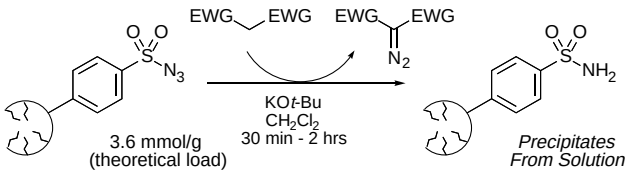




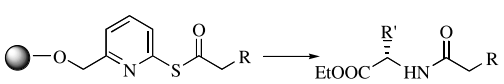




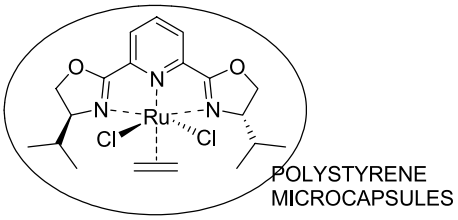
Polyisobutylene is a readily modified soluble polymeric support for use in synthesis and catalysis.

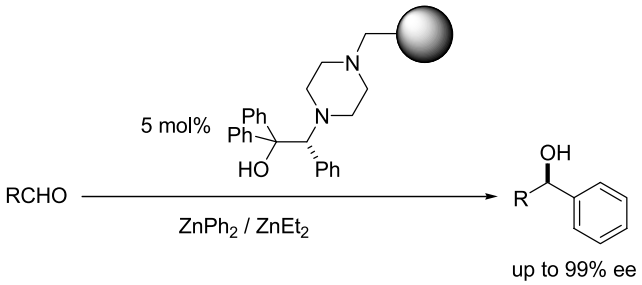


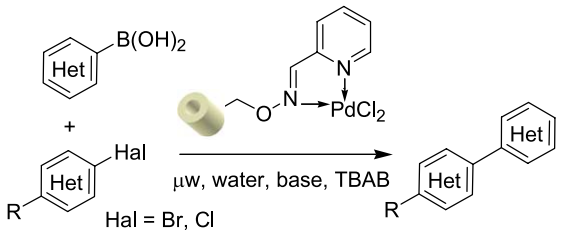
The development of a high-load, soluble oligomeric sulfonyl azide using ROM polymerization is reported. The utility in diazo transfer reactions with active methylene compounds is demonstrated using an efficient protocol, with most reactions showing completion in 30 minutes. The sulfonamide byproduct, being insoluble in the reaction solvent, can be completely removed by simple filtration through a silica gel SPE cartridge.

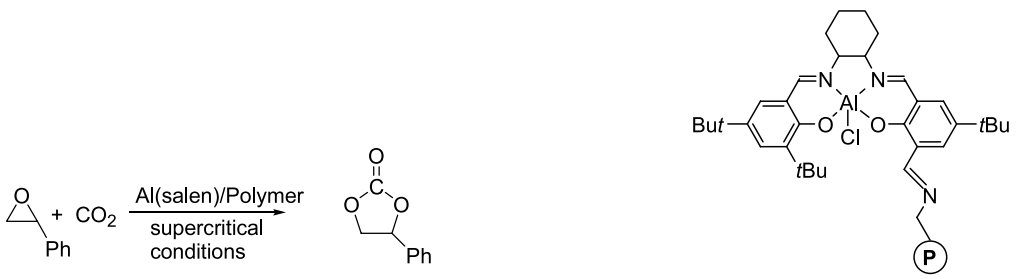


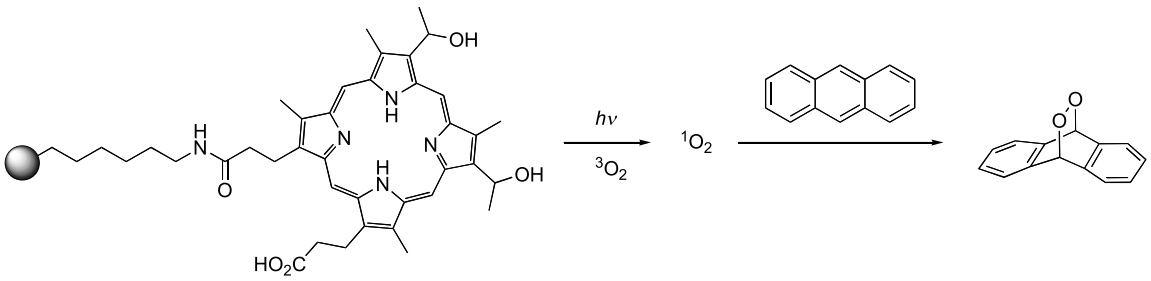
Pyridylthioesters anchored to a modified poly(ethylene glycol) of M_w 5000 have been prepared in high yields and employed as a convenient starting material in a new methodology that allowed to perform at the same time the reaction of the supported reagent and the traceless removal of the final product from the polymer support.



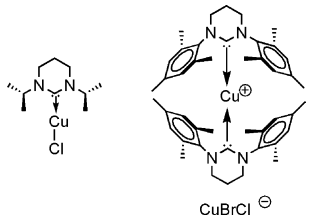


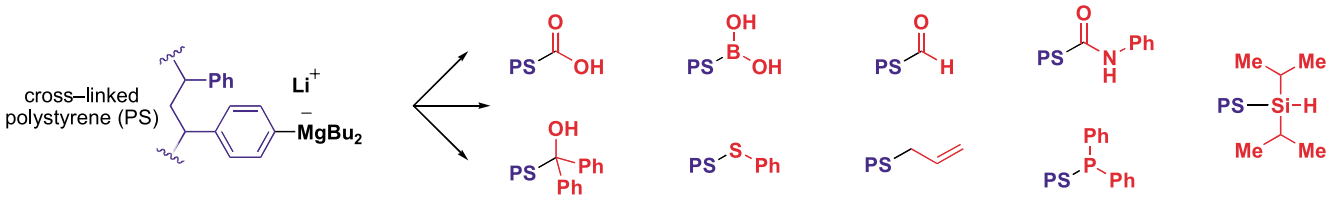


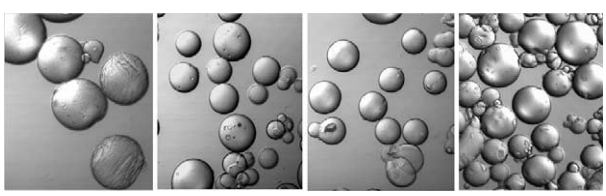


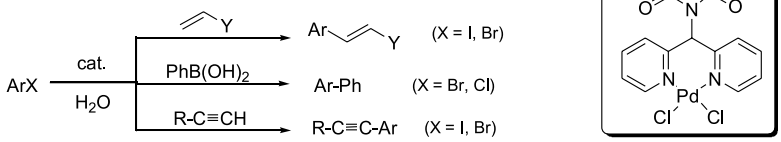


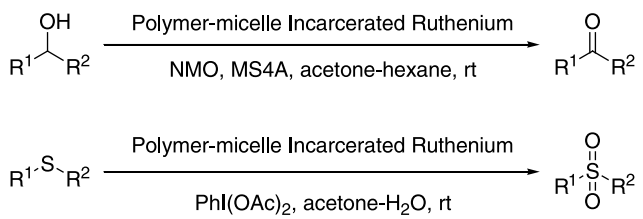
Novel Cu (I) N-heterocylic carbene complexes have been synthesized from CuX (X = Cl, Br) and 1,3-R_2-3,4,5,6-tetrahydropyrimidin-2-ylidenes (R = 2-Pr, mesityl). These were used in C=O hydrosilylation and C=O hydrocyanation reactions as well as in the ATRP of methyl methacrylate.

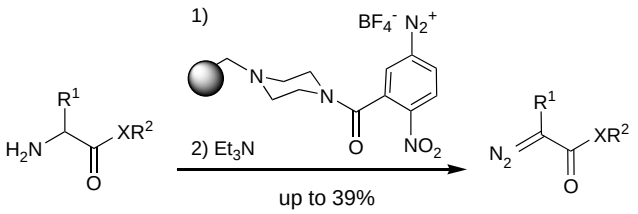












a: $R^1 = CH_2Ph$, XR^2= OEt
b: R^1 = p-$ClC_6H_4CH_2$, XR^2= OEt
c: R^1 = H, XR^2= OBn
d: $R^1 = CH_2iPr$, XR^2 = LeuOMe

OTHER CONTENTS

*Corresponding author
ⓘ+ Supplementary data available via ScienceDirect

COVER

The cover picture displays an extremely rare English 'ladder' scale by Degrave, Short, Fanner and Company, circa mid-19th century (from the collection of K. D. Janda). The scale is made up of three beams that can measure materials in units from 0.5 to 9 ounces. For polymer-supported reagents, one polymer does not fit all applications, and striking the proper *balance* between polymer structure and synthetic use is essential.

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Preface

Polymer-supported reagents and catalysts: increasingly important tools for organic synthesis

The use of polymer supports in organic synthesis began with solid-phase synthesis where the synthetic target is synthesized attached to the polymer. For a variety of reasons, including ease of reaction monitoring and product characterization, shorter method development time, etc., the role of the polymer has gradually shifted to supporting reagents for reacting with solution-phase substrates in what is sometimes referred to as polymer-assisted synthesis. Nowadays such use of polymer-supported reagents is as common, if not more so, than solid-phase synthesis, and a great number of such reagents have been reported in the literature and are commercially available. However, despite intensive research efforts over the past few years, the number of polymer-supported reagents known is still just a small fraction of the reagents commonly used in traditional solution-phase organic synthesis. Therefore, as the desire for faster production of compound collections with greater structural complexity increases, the need for polymer-supported reagents capable of effecting different reactions and those with greater efficiency grows as well. This Symposium-in-Print highlights some of the recent progress in developing new polymer-supported reagents and showcases some of the different strategies for enhancing their performance and improving methods for their preparation.

The cover picture displays an extremely rare English 'ladder' scale by Degrave, Short, Fanner and Company, circa mid-19th century (from the collection of Janda). The scale is made up of three beams that can measure materials in units from 0.5 to 9 oz. Upon each 'ladder step' are molecules that depict applications of polymer supports in organic synthesis. Each of these applications has specific requirements of the polymer regarding solvent compatibility, reactivity, porosity, etc. Thus, one polymer does not fit all applications, just as there is no universal solvent, and striking the proper balance between polymer structure and synthetic use is essential. To the lower left of picture are listed some of the polymer supports used in the research described in this issue. Judging by the number and variety of materials listed, it is quite clear that the research regarding polymer-supported reagents and catalysts the polymers used to support them is an active and dynamic field and that many important discoveries are still to be made.

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Optimization of polystyrene-supported triphenylphosphine catalysts for aza-Morita–Baylis–Hillman reactions

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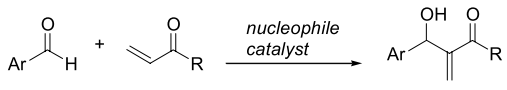
Abstract—A series of polar group functionalized polystyrene-supported phosphine reagents were examined as catalysts in the aza-Morita–Baylis–Hillman reactions of *N*-tosyl arylimines and a variety of Michael acceptors with the aim of identifying the optimal polymer/solvent combination. For these reactions *J*anda*J*el-PPh_3 (1 mmol PPh_3/g loading) resin containing methoxy groups (*JJ*-OMe-PPh_3) on the polystyrene backbone in THF solvent provided the highest yield of all the catalyst/solvent combinations examined. The methyl ether groups were incorporated into *JJ*-OMe-PPh_3 using commercially available 4-methoxystyrene, and thus such polar polystyrene resins are easily accessible and should find utility as nucleophilic catalyst supports.

1. Introduction

The Morita–Baylis–Hillman reaction (Scheme 1) is an important tool in organic synthesis that allows for the formation of carbon–carbon bonds in densely functionalized products under mild reaction conditions.[1] While early versions of this reaction were marked by some irreproducible results and long reaction times, recent years have seen much advancement in the understanding of its mechanism[2] and improvements in its efficiency and reliability. Nowadays the use of improved catalysts,[3] including chiral ones, and activated electrophiles have greatly improved the utility and scope of this reaction and variations of it have seen increasing use in the synthesis of complex, biologically active compounds.[4]



Scheme 1. The Morita–Baylis–Hillman reaction.

We have had a long standing interest in the development of this reaction,[5] and have reported on the use of not only nucleophilic amine Lewis base catalysts, but phosphines as well, in aza-Morita–Baylis–Hillman (AMBH) reactions where the electrophile is a *N*-sulfonated imine rather than a simple, less electrophilic aldehyde.[6,7] We have examined the scope of this reaction in terms of nucleophiles, electrophiles, and catalysts and have developed convenient methods for the synthesis of a large variety of β-amino carbonyl compounds.

Another area of research interest for us has been the development of polymer-supported reagents[8,9] for use in solution-phase organic synthesis. We have recently reported both soluble and insoluble amine,[10] arsine,[11] ketone,[12] nitroxyl,[13] phosphine,[14] sulfide,[15] sulfonamide,[16] and sulfoxide[17] reagents that are useful in a wide range of synthetic transformations. In a bridging of our areas of interest, we have examined the use of a soluble poly(ethylene glycol)-supported phosphine,[18] and insoluble polystyrene-supported DMAP[18,19] and PPh_3 (*J*anda*J*el-PPh_3, **1a**, Scheme 2)[20,21] reagents as nucleophilic catalysts in AMBH reactions[22] and observed results similar to those obtained using the analogous small molecule catalysts.[23]

In this later report, we examined the relationship between resin loading level and catalyst efficiency and observed that a loading level of 1.5 mmol PPh_3/g of resin was optimal. In order to further optimize catalyst efficiency by identifying the optimal polymer backbone, we sought to prepare a series of related polystyrene resins in which the non-phosphine bearing styrene aromatic rings were functionalized with polar groups. Herein we report the preparation of a variety

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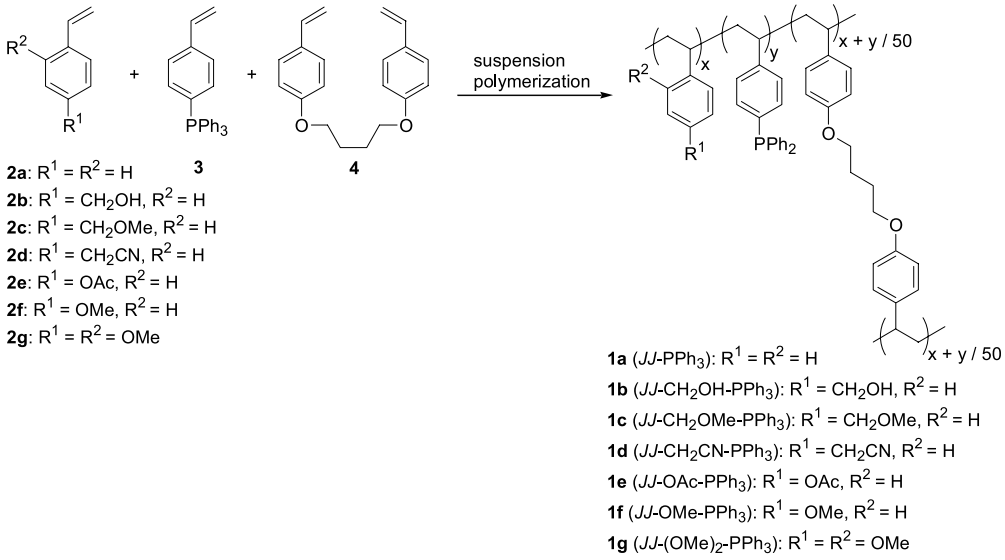


Scheme 2. Synthesis of *J*anda*J*el-Polar-PPh_3 reagents **1a**–**g**.

of such triphenylphosphine resins, **1b**–**g**, examination of their catalytic efficiency in AMBH reactions in a range of solvents and identification of the optimal polystyrene backbone for such catalyst.

2. Results and discussion

Various polar groups have been added to cross-linked polystyrene in order to increase resin polarity and compatibility with polar solvents such as DMF, MeOH and water. One of the most common and successful strategies for this is the introduction of long, polar poly(ethylene glycol) (PEG) grafts onto a polystyrene resin core and a variety of such polymers have been reported.[24] Additionally, the use of short PEG chains[25] and various ionic moieties[26] have been added to polystyrene resins with the aim of increasing resin polarity, with varying degrees of success. Thus, we wanted to determine if adding additional polar functional groups onto the polymer backbone would provide better phosphine catalysts[27,28] for AMBH reactions, with the idea of matching the polarity of the resin microenvironment[29] with that of the transition states and intermediates of the reaction.

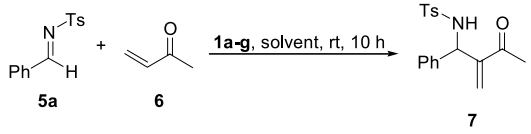
In keeping with our practice of using functional monomers to prepare the flexible cross-linker[30] containing *J*anda*J*el resins,[31] we selected styrene monomers **2b**–**g** for incorporation into the new phosphine polymers **1b**–**g** (Scheme 2). These monomers allow for the incorporation of alcohol, ether, ester, and nitrile functional groups. Styrenes **2b**,[32] **2c**,[33] and **2d**[34] were prepared according to literature procedures from 4-vinylbenzyl chloride and **2g** was prepared from 2,4-dimethoxybenzaldehyde by a Wittig reaction.[35] Monomers **2e** and **2f** are available commercially, while styryldiphenylphosphine (**3**)[14a] and cross-linker **4**[31c] were prepared as previously reported from 4-bromostyrene and 4-acetoxystyrene, respectively. With all of the required materials in hand, we prepared resins **1b**–**g** by suspension polymerization (Scheme 2).[36,37] The monomers were mixed such that for a 10 g batch of resin, 10 mmol of **3** was used and the balance of the monomer mixture was composed of **2b**–**g** and 2 mol% **4** (Table 1). This was done in order to obtain resins with loading levels of 1.0 mmol PPh_3/g. We chose to use this lower loading for resins **1b**–**g**, compared to a value of 1.5 mmol PPh_3/g for **1a**, because this results in resins that contain between 3.3 and 5.4 functionalized styrene units per PPh_3 group and resin **1a** has 3.3 styrene groups per PPh_3 group.[14a] Yields of the resins were good to excellent, and as in previous experiments,[14a] the observed P content was close to the theoretical value in all cases.

We next screened resins **1b**–**g** as catalysts in the AMBH reaction of **5a** with methyl vinyl ketone (**6**) to form **7** under identical reaction conditions (1.0 equiv **5a**, 1.5 equiv **6**, 0.1 equiv catalyst, room temperature, 10 h) using various solvents to examine if any catalyst/solvent combination would provide a higher yield than obtained with **1a** in THF (91%). The solvents chosen were acetonitrile (ACN), dichloromethane (DCM), DMF, DMSO, THF and toluene and the results of these reactions are summarized in Table 2. The only catalyst that afforded higher yield of **7** than **1a** in

Table 1. Synthesis of resins **1b**–**g**

Resin	**2** (mmol)	**3** (mmol)	**4** (mmol)	Yield (%)	P content (%)	
					Theor	Obsd
1b	53	10	1.3	90	3.10	3.06
1c	46	10	1.1	69	3.10	3.09
1d	42	10	1.0	93	3.10	3.31
1e	42	10	1.0	88	3.10	3.03
1f	54	10	1.2	91	3.10	3.15
1g	42	10	1.0	86	3.10	2.95

Table 2. Reactions of **5a** with **6** using **1a–g** as catalyst



Entry	Catalyst	Yield (%)[a]					
		ACN	DCM	DMF	DMSO	THF	Toluene
1	**1a**[b]	68	73	69	—	91	66
2	**1b**	47	30	55	60	51	34
3	**1c**	53	67	88	51	95	60
4	**1d**	37	54	60	44	90	42
5	**1e**	43	53	76	63	96	35
6	**1f**	74	88	75	63	97	64
7	**1g**	42	55	64	58	92	32

[a] Isolated yield.
[b] Results from Ref. 20.

Table 3. Resin swelling in various solvents[a]

Resin	ACN	DCM	DMF	DMSO	THF	Toluene	Dry vol.
1a[b]	1.6	6.6	4.4	—	6.2	5.4	1.6
1b	2.2	3.6	6.7	6.8	5.3	2.3	1.9
1c	3.1	10.3	7.5	3.9	9.8	9.0	1.8
1d	3.9	7.6	8.3	8.1	7.3	3.3	1.6
1e	3.4	8.0	6.4	5.4	6.3	5.3	1.5
1f	2.4	11.3	7.0	4.2	12.9	12.3	1.7
1g	2.6	8.4	7.4	4.0	7.8	7.4	1.7

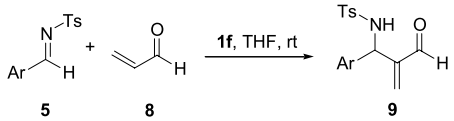
[a] Data is given in mL/g.
[b] Data is taken from Ref. 20.

all solvents examined except for toluene, in which the yields were almost the same, was methyl ether group functionalized **1f** and the highest obtained yield overall was with this catalyst in THF (97%). It is interesting to note the stark difference in performance between **1c** and **1f**, considering that they differ only by a methylene group. Resin **1c** was less effective as a catalyst than **1f** in all solvents except for DMF. Furthermore, the addition of a second methyl ether group, as in **1g**, also decreased catalyst efficiency. It also was somewhat surprising that **1b**, containing hydrogen bond donating hydroxyl groups, was the worst catalyst screened since such groups could stabilize intermediates of the AMBH reaction.[2]

In order to interpret the results in Table 2, we examined the swelling of resins **1b–g** in the same set of solvents used to perform the reactions, since this factor has been shown by both fluorescence[38] and NMR[39] spectroscopy to be a key factor in determining substrate accessibility to the interior, and thus the functional groups, of the resins. The swelling data for **1b–g** is summarized in Table 3. It is clear that there is a general correlation between the swelling of a resin in a particular solvent and yield obtained with that resin/solvent combination. All resins except **1b** swell well in THF and afford high yields of **7** in this solvent. Resin **1b** swells poorly in THF and affords the lowest yield of **7** in this solvent. On the other hand, the resins all swell very little or none at all in ACN and this proved to be one of the worst solvents for the reactions. A notable anomaly is the performance of **1d** in DMSO. This resin exhibits the highest level of swelling in DMSO, yet affords only a modest yield of **7**. Most importantly **1f** clearly swells the most in the relatively non-polar solvent examined (DCM, THF and toluene) and affords the highest yields of **7** in them.

Since we previously examined **1a** in AMBH reactions of a range of *N*-tosyl arylimines with only electrophile **6**,[20] we wanted to see if other Michael acceptors, such as acrolein (**8**) and phenyl acrylate (**10**), are also useful in this reaction system. The results of AMBH reactions catalyzed by **1f** of **8** and **10** with a variety of electrophiles **5** are summarized in Tables 4 and 5, respectively. Gratifyingly, in reactions of **8** to form **9**, complete disappearance of the electrophile **5** was observed within 3 h, except for when an electron-rich dimethylamino functionalized imine was used (Table 4, entry 5). Reactions of **10** catalyzed by **1f** were much more sluggish by comparison and thus were allowed to proceed for 36 h. However, reasonable yields of **11** were obtained in all cases despite the long reaction times.

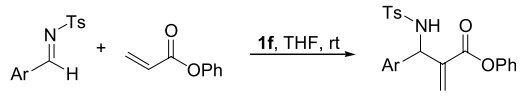
Table 4. AMBH reaction of **8** catalyzed by **1f**



Entry	Ar–	Time (h)	Yield (%)[a]
1	Ph–	3	75
2	4-Me–C_6H_4–	3	54
3	4-Et–C_6H_4–	3	75
4	4-MeO–$_6H_4$–	3	36
5	4-NMe_2–C_6H_4–	24	No reaction

[a] Isolated yield of **9** from reaction of **5** (1.0 equiv), **8** (2.0 equiv) and **1f** (0.1 equiv).

Table 5. AMBH reaction of **10** catalyzed by **1f**



5 **10** **11**

Entry	Ar–	Yield (%)[a]
1	Ph–	81
2	4-Me–C_6H_4–	58
3	4-Et–C_6H_4–	50
4	4-F–$_6H_4$–	63
5	4-Cl–C_6H_4–	74
6	4-Br–C_6H_4–	45
7	2,3-Cl_2–C_6H_3–	68
8	4-NO_2–C_6H_4–	67
9	3-NO_2–C_6H_4–	70

[a] Isolated yield of **11** from reaction of **5** (1.0 equiv), **10** (1.2 equiv) and **1f** (0.1 equiv).

3. Conclusions

In summary, we have examined a range of polar polystyrene resins as supports for PPh_3 groups in which the supported phosphine was used as a nucleophilic catalyst in AMBH reactions. To our knowledge, this is the first such comparative study and it was observed that incorporation of 4-methoxystyrene into the polymer afforded the best support in terms of catalyst efficiency in THF solvent. Thus, resin **1f** was found to be the best heterogeneous polymer-supported catalyst examined to date for the prototypical AMBH reaction of **5** and **6** to form **7**. Furthermore the scope of the reaction system was extended to the use of acrolein and phenyl acrylate as Michael acceptors with a wide range of *N*-tosyl arylimines. We believe that the enhanced performance of **1f** compared to **1a** is a result of its increased polarity since AMBH reactions are known to involve polar transition states and reaction intermediates.

4. Experimental

4.1. General

All reagents were obtained from the Aldrich, Lancaster or Acros chemical companies and were used without further purification. All moisture sensitive reactions were carried out in dried glassware under a N_2 atmosphere. Tetrahydrofuran was distilled under a N_2 atmosphere over sodium and benzophenone. Dichloromethane was distilled under a N_2 atmosphere over calcium hydride. Merck silica gel 60 (230–400 mesh) was used for chromatography. Thin-layer chromatography analysis was performed using glass plates coated with silica gel 60 F_{254}. NMR spectra were recorded using either a Bruker DRX 300 or an AV400 spectrometer. Chemical shift data is expressed in ppm with reference to TMS. HR EI-MS data was recorded on a Finnigan MAT 96 mass spectrometer.

4.1.1. 4-Vinylbenzyl alcohol (2b). A solution of 4-vinylbenzyl chloride (32.0 g, 213 mmol), sodium acetate (23.0 g, 280 mmol), Bu_4NI (7.9 g, 21.3 mmol) in dry THF (300 mL) was heated to reflux for 48 h. After cooling to room temperature, this was diluted with water (200 mL), extracted with $CHCl_3$ (3×300 mL). The organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo to afford 4-vinylbenzyl acetate as a orange oil (37.1 g, 99%). ^1H NMR ($CDCl_3$, TMS, 300 MHz): δ 2.09 (s, 3H), 5.08 (s, 2H), 5.26 (dd, 1H, $J=10.9$, 0.9 Hz), 5.75 (dd, 1H, $J=17.6$, 0.9 Hz), 6.71 (1H, dd, $J=17.6$, 10.9 Hz), 7.31 (d, 2H, $J=8.1$ Hz), 7.40 (d, 2H, $J=8.1$ Hz). ^{13}C NMR ($CDCl_3$, TMS, 75 MHz): δ 20.71, 65.83, 114.15, 126.26 (2C), 128.37 (2C), 135.44, 136.23, 137.41, 170.52. HR EI-MS: calcd for $C_{11}H_{12}O_2$, 176.0837; found, 176.0837.

To a EtOH solution (150 mL) of 4-vinylbenzyl acetate (37.1 g, 211 mmol) was added 6 N NaOH (50 mL). The reaction mixture was refluxed for 3 h. After cooling to room temperature, it was diluted with water (200 mL), extracted with $CHCl_3$ (3×300 mL). The organic layers were purified by distillation (100 °C, 20 mmHg) to afford **2b** as a colourless liquid (17.0 g, 60%). ^1H NMR ($CDCl_3$, TMS, 400 MHz): δ 4.64 (s, 2H), 5.24 (dd, 1H, $J=10.9$, 0.9 Hz), 5.75 (dd, 1H, $J=17.6$, 0.9 Hz), 6.71 (1H, dd, $J=17.6$, 10.9 Hz), 7.29 (d, 2H, $J=8.1$ Hz), 7.39 (d, 2H, $J=8.1$ Hz). ^{13}C NMR ($CDCl_3$, TMS, 75 MHz): δ 65.22, 114.03, 126.54 (2C), 127.36 (2C), 136.61, 137.13, 140.68. HR EI-MS: calcd for $C_9H_{10}O$, 134.0732; found, 134.0732.

4.1.2. 4-Vinylbenzyl methyl ether (2c). To a MeOH solution (100 mL) of 4-vinylbenzyl chloride (10.0 g, 6.6 mmol) sodium methoxide (7.1 g, 13.1 mmol) was added. The reaction mixture was heated to reflux for 24 h. After cooling to room temperature, it was then filtered and concentrated in vacuo. The crude product was diluted with diethyl ether (100 mL) and then washed with water (3× 100 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by silica gel chromatography (5% EtOAc/hexane) to afford as **2c** a colourless liquid (8.8 g, 91%). ^1H NMR ($CDCl_3$, TMS, 300 MHz): δ 3.39 (s, 3H), 4.45 (s, 2H), 5.24 (dd, 1H, $J=10.9$, 0.9 Hz), 5.74 (dd, 1H, $J=17.6$, 0.9 Hz), 6.71 (1H, dd, $J=17.6$, 10.9 Hz), 7.29 (d, 2H, $J=8.1$ Hz), 7.39 (d, 2H, $J=8.1$ Hz). ^{13}C NMR ($CDCl_3$, TMS, 75 MHz): δ 58.07, 74.42, 113.80, 126.25 (2C), 127.94 (2C), 136.55, 137.01, 137.79. HR EI-MS: calcd for $C_{10}H_{12}O$, 148.0888; found, 148.0813.

4.1.3. 4-Vinylphenylacetonitrile (2d). To an anhydrous CH_3CN solution (55 mL) of 18-crown-6 (0.7 g, 2.8 mmol), 4-vinylbenzyl chloride (10.0 g, 70.0 mmol) and powdered KCN (6.4 g, 100 mmol) were added. The reaction mixture was stirred at room temperature for 16 h and then concentrated in vacuo. The residue was diluted with water (100 mL) and extracted with diethyl ether (100 mL). The organic layer was sequentially washed with water (50 mL), brine (50 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by silica gel chromatography (10% EtOAc/hexane) to afford **2d** as a yellow liquid (8.9 g, 95%). ^1H NMR ($CDCl_3$, TMS, 300 MHz): δ 3.74 (s, 2H), 5.29 (dd, 1H, $J=10.9$, 0.9 Hz), 5.77 (dd, 1H, $J=17.6$, 0.9 Hz), 6.70 (1H, dd, $J=17.6$, 10.9 Hz), 7.28 (d, 2H, $J=8.1$ Hz), 7.42 (d, 2H, $J=8.1$ Hz). ^{13}C NMR ($CDCl_3$, TMS, 75 MHz): δ 23.72, 114.64, 117.77, 126.81 (2C), 128.59 (2C), 129.18, 135.87, 137.37. HR EI-MS: calcd for $C_{10}H_9N$, 143.0735; found, 143.0735.

4.1.4. 2,4-Dimethoxystyrene (2g). A solution of 2,4-dimethoxybenzaldehyde (10.0 g, 6.0 mmol), methyltriphenylphosphonium bromide (25.8 g, 7.2 mmol), K_2CO_3 (40.0 g, 30.0 mmol), 18-crown-6 (0.2 g, 0.1 mmol) in dry THF (180 mL) was heated to reflux for 24 h. After cooling to room temperature, it was then filtered through Celite and concentrated in vacuo. The crude product was purified by silica gel chromatography (20% EtOAc/hexane) to afford **2g** as a colourless liquid (7.8 g, 78%). ^{1}H NMR ($CDCl_3$, TMS, 400 MHz): δ 3.72 (s, 3H), 3.73 (s, 3H), 5.06 (dd, 1H, J= 11.2, 1.6 Hz), 5.54 (dd, 1H, J=17.8, 1.6 Hz), 6.35 (d, 1H, J=2.3 Hz), 6.39 (dd, 1H, J=8.4, 2.3 Hz), 6.87 (1H, dd, J= 17.8, 11.2 Hz), 7.30 (d, 1H, J=8.4 Hz). ^{13}C NMR ($CDCl_3$, TMS, 75 MHz): δ 55.34, 55.41, 98.34, 104.68, 112.24, 119.84, 127.23, 131.23, 157.82, 160.55. HR EI-MS: calcd for $C_{10}H_{12}O_2$, 164.0837; found, 164.0836.

4.2. General procedure for *J*anda*J*el-Polar-PPh_3 synthesis (Procedure A)

A solution of acacia gum (6.0 g) and NaCl (3.8 g) in warm deionized water (45 °C, 150 mL) was placed in a 150 mL flanged reaction vessel equipped with a mechanical stirrer and deoxygenated by purging with N_2 for 2 h.[37] A solution of polar styrene monomer **2a–g**, **3** (1.0 mmol/g of total monomer), **4** (2.0 mol%), and AIBN (0.2 g) in chlorobenzene (10 mL) was injected into the rapidly stirred aqueous solution. The resulting suspension was heated at 85 °C for 20 h. At this time the crude polymer was collected and washed with hot water (3×100 mL) and then placed in a Soxhlet extractor and further washed with THF for one day. The beads were recovered, washed sequentially with methanol, diethyl ether and hexanes, and dried in vacuo. Elemental analysis was used to determine phosphine content, and thus the PPh_3 loading level.

4.2.1. Poly(4-styryldiphenylphosphine-*co*-[4-vinylbenzyl alcohol]-*co*-1,4-bis[4-vinylphenoxy]butane) (*JJ*-CH_2OH-PPh_3, 1b). This was prepared by procedure A using of **2b** (7.1 g, 53.0 mmol), **3** (2.9 g, 10.0 mmol), **4** (0.4 g, 1.3 mmol), and AIBN (0.2 g) in chlorobenzene (10 mL) to afford **1b** (9.0 g, 90%). Elemental analysis was used to determine the phosphine content (3.1%), and thus a loading level of 1.0 mmol PPh_3/g.

4.2.2. Poly(4-styryldiphenylphosphine-*co*-[4-vinylbenzyl methyl ether]-*co*-1,4-bis[4-vinylphenoxy]butane) (*JJ*-CH_2OMe-PPh_3, 1c). This was prepared by procedure A using of **2c** (7.0 g, 46.0 mmol), **3** (2.9 g, 10.0 mmol), **4** (0.4 g, 1.1 mmol), and AIBN (0.2 g) in chlorobenzene (10 mL) to afford **1c** (6.9 g, 69%). Elemental analysis was used to determine the phosphine content (3.1%), and thus a loading level of 1.0 mmol PPh_3/g.

4.2.3. Poly(4-styryldiphenylphosphine-*co*-[4-vinylphenylacetonitrile]-*co*-1,4-bis[4-vinylphenoxy]butane) (*JJ*-CH_2CN-PPh_3, 1d). This was prepared by procedure A using of **2d** (6.8 g, 42.0 mmol), **3** (2.9 g, 10.0 mmol), **4** (0.3 g, 1.1 mmol), and AIBN (0.2 g) in chlorobenzene (10 mL) to afford **1d** (9.3 g, 93%). Elemental analysis was used to determine the phosphine content (3.3%), and thus a loading level of 1.0 mmol PPh_3/g.

4.2.4. Poly(4-styryldiphenylphosphine-*co*-[4-acetoxystyrene]-*co*-1,4-bis[4-vinylphenoxy]butane) (*JJ*-CH_2OAc-PPh_3, 1e). This was prepared by procedure A using of **2e** (6.8 g, 42.0 mmol), **3** (2.9 g, 10.0 mmol), **4** (0.3 g, 1.0 mmol), and AIBN (0.2 g) in chlorobenzene (10 mL) to afford **1e** (8.8 g, 88%). Elemental analysis was used to determine the phosphine content (3.0%), and thus a loading level of 1.0 mmol PPh_3/g.

4.2.5. Poly(4-styryldiphenylphosphine-*co*-[4-methoxystyrene]-*co*-1,4-bis[4-vinylphenoxy]butane) (*JJ*-(OMe)-PPh_3, 1f). This was prepared by procedure A using **2f** (7.1 g, 54.0 mmol), **3** (2.9 g, 10.0 mmol), **4** (0.4 g, 1.2 mmol), and AIBN (0.2 g) in chlorobenzene (10 mL) to afford **1f** (9.1 g, 91%). Elemental analysis was used to determine the phosphine content (3.2%), and thus a loading level of 1.0 mmol PPh_3/g.

4.2.6. Poly(4-styryldiphenylphosphine-*co*-[2,4-dimethoxystyrene]-*co*-1,4-bis[4-vinylphenoxy]butane) (*JJ*-$(OMe)_2$-PPh_3, 1g). This was prepared by procedure A using of **2g** (6.8 g, 42.0 mmol), **3** (2.9 g, 10.0 mmol), **4** (0.3 g, 1.0 mmol), and AIBN (0.2 g) in chlorobenzene (10 mL) to afford **1g** (8.6 g, 86%). Elemental analysis was used to determine the phosphine content (3.0%), and thus a loading level of 1.0 mmol PPh_3/g.

4.3. Resin swelling measurements

The *J*anda*J*el-Polar-PPh_3 resin (50.0 mg) was placed in a syringe (1 mL) equipped with a polypropylene frit and the dry volume was measured. Solvents were injected into the syringe until resins were soaked thoroughly. After equilibrating for 1 h, the volume of the swollen resin was measured and the measured volume was normalized to mL/g.

4.4. General procedure for the *JJ*-Polar-PPh_3 catalyzed AMBH reactions of *N*-sulfonated imine (5) with methyl vinyl ketone (6)

The *JJ*-Polar-PPh_3 (0.05 mmol) was added to dry THF (1.0 mL) under an argon atmosphere and the suspension was stirred for 1 h at room temperature (swelling time). At this time, the *N*-sulfonated imine (**5**, 0.5 mmol) and **6** (63 μL, 0.75 mmol, 1.5 equiv) were added to the suspension. The reaction mixture was stirred at room temperature for the indicated time or until TLC analysis indicated the disappearance of **5**. The reaction mixture was then diluted with CH_2Cl_2 (7.0 mL) and the catalyst was filtered off and recovered. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography (25% EtOAc/petroleum ether) to afford the desired product **7**. Characterization data for **7** was consistent with the previously reported data.[6f]

4.5. General procedure for the *JJ*-OMe-PPh_3 (1f) catalyzed AMBH reactions of *N*-sulfonated imines (5) with acrolein (8)

JJ-OMe-PPh_3 (**1f**, 0.05 mmol) was added to dry THF (1.0 mL) under an argon atmosphere and the suspension was stirred for 1 h at room temperature (swelling time). At this time, the *N*-sulfonated imine (**5**, 0.5 mmol) and **8** (67 μL,

56 mg, 1.0 mmol, 2.0 equiv) were added to the suspension. The reaction mixture was stirred at room temperature for the indicated time or until TLC analysis indicated the disappearance of **5**. The reaction mixture was then diluted with CH_2Cl_2 (7.0 mL) and the catalyst was filtered off and recovered. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography (20% EtOAc/petroleum ether) to afford the desired product **9**. Characterization data for these products was consistent with previously reported data.[6m]

4.6. General procedure for the *JJ*-OMe-PPh_3 (1f) catalyzed AMBH reactions of *N*-sulfonated imines (5) with phenyl acrylate (10)

JJ-OMe-PPh_3 (**1f**, 0.05 mmol) was added to dry THF (1.0 mL) under an argon atmosphere and the suspension was stirred for 1 h at room temperature (swelling time). At this time, the *N*-sulfonated imine **5** (0.5 mmol) and **10** (89 mg, 0.6 mmol, 1.2 equiv) were added to the suspension. The reaction mixture was stirred at room temperature for the indicated time. The reaction mixture was then diluted with CH_2Cl_2 (7.0 mL) and the catalyst was filtered off and recovered. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography (12.5% EtOAc/petroleum ether) to afford the desired product **11**. Characterization data for these products was consistent with previously reported data.[6f]

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Facile and purification free synthesis of peptides utilizing ROMPgel- and ROMPsphere-supported coupling reagents

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Abstract—5-Norbornene-2-carboxaldehyde and norbornadiene were respectively converted into norbornene derivatives functionalized with fluoroformamidinium hexafluorophosphate and 2-bromo-*N*-methylpyridinium tetrafluoroborate residues. Both these norbornene monomers were ring opening metathesis polymerized or graft copolymerized onto polystyrene cores to produce ROMPgel and ROMPsphere peptide-coupling reagents. These were used to prepare hindered amides, dipeptides and tripeptides with minimal purification in parallel arrays.

1. Introduction

The synthesis of structurally diverse combinatorial oligopeptide libraries using purification free processes originated from the pioneering work of Merrifield and Letsinger.[1] Since the advent of this methodology, an array of techniques including parallel synthesis,[2] tagging,[3] split and mix,[4] and indexing[5] has been developed for the generation of peptide and non-peptide libraries on solid supports. The need to synthesize chemically diverse libraries of small drug-like entities through automation has resulted in a shift from the traditional solid support approach to the use of solid supported reagents.[6] This approach significantly facilitates the process of library synthesis for high throughput assay[7] since the undesired by-products are bound to the support facilitating purification through simple filtration. The use of polymer-supported reagents was conceived as a practical solution for simplifying tedious workup procedures associated with the removal of undesired by-products[8] such as phosphine oxides, sulfonamides and urea type reagents. Over the past three decades this approach has been further extended to include transformations such as oxidations,[9] reductions,[10] halogenations,[11] carbon–carbon bond formation[12] and also the use of polymer bound catalysts.[13] These supported reagents are normally synthesized on cross-linked polystyrene beads, macroporous ion exchange resins, or inorganic supports. The major focus of combinatorial chemistry and parallel synthesis has been the generalization of synthetic protocols to maximize functional group diversity through automation. We have sought to address this need by the introduction of new classes of high-loading polymer-supported reagents for purification-free (mix, filter and evaporate) parallel synthesis.

Recently, we have reported the use of ring opening metathesis (ROM) polymerization for the synthesis of high-loading, insoluble, polymer-gel supported reagents (ROMPgels). These reagents have several major advantages. Firstly, alkene metathesis catalysts are noted for tolerance of diverse functionalities thereby permitting the production of fully functionalized (reagent) monomers prior to the polymerization process. Secondly, such monomers are readily available from inexpensive precursors. Thirdly, ROMPgels are high-loading reagents, which have been employed for Horner–Emmons reactions,[14] in TOSMIC condensation reactions,[15] in acylation reactions including the preparation of Mosher amides,[16] and in reactions using triphenylphosphine,[17] *N*-hydroxysuccinimide,[18] naphthalene and biphenyl,[19] Wilkinson's catalyst,[20] allylboronate reagents,[21] and diazoketophosphonates,[22] in catalyzing the Stetter reaction[23] and as scavengers for amines and hydrazines.[24] Hanson and Flynn,[25] Roberts[26] and Janda[27] have described related ROMPolymer-supported reagents and supports and the area of ROMPolymer-supported reagents has been reviewed.[28] To further expand on our current methodologies, we now wish to provide details for the synthesis and application of immobilized fluoroformamidinium and immobilized 2-bromopyridinium ROMPgel and ROMPsphere reagents for peptide-coupling reactions and the synthesis of hindered amides.[28]

Keywords: Acylations; Combinatorial chemistry; Peptides; Parallel synthesis; Supported reagents.
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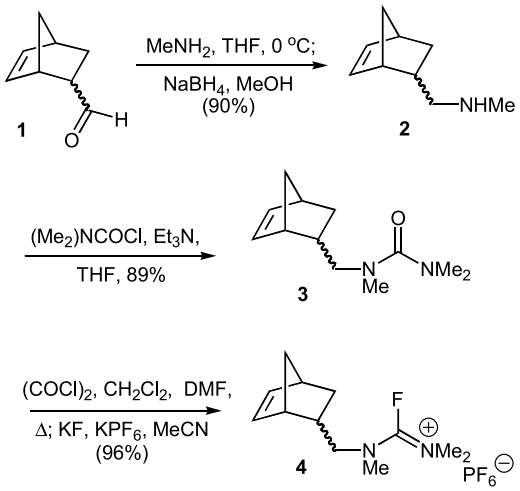
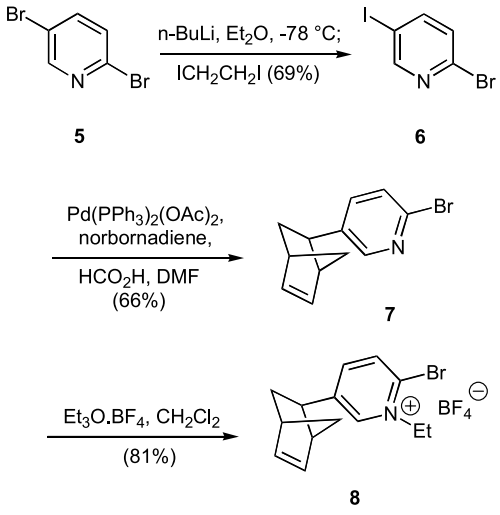
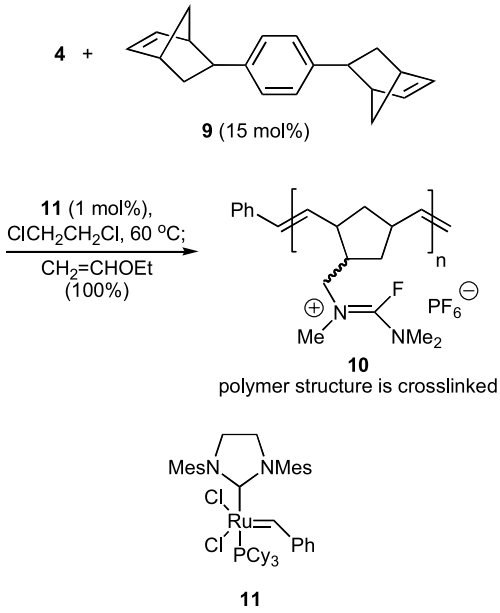
Gramicidin,[29] an antibiotic first isolated in 1941, was found to contain a $C^{\alpha\alpha}$ di-substituted amino acid residue. Since then such amino acid residues have been identified in a number of natural products[30] and their occurrence has led to significant interest in the development of efficient methods for their synthesis.[31] Traditional peptide-coupling protocols, using activated esters and anhydrides,[32] and carbodimides with *N*-hydroxybenzotriazole,[33] have been found to be inadequate for coupling such hindered moieties. The next real advancement in coupling activity came with the development of phosphonium salt based reagents such as (1-benzotriazolyoxy)tris(dimethylamino)-phosphonium hexafluorophosphate (BOP)[34] and (1-benzotriazolyoxy)tris(pyrrolidino)-phosphonium hexafluorophosphate (PyBOP).[35] Due to toxicity of their side products, they soon were replaced by uronium reagents such as *O*-(benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU)[36] and *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU).[37] Recently an immobilized version of as *O*-(benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU) based on a polystyrene bound benzotriazole was published.[38] These uronium reagents show a remarkable activity and low racemization in standard peptide-couplings but are still of limited use for the coupling of $C^{\alpha\alpha}$ di-substituted amino acid residues, due to the steric demand of the activating group. Other very active onium type coupling reagents for hindered amide bonds include thiazolium (2-bromo-3-ethyl-4-methylthiazolium tetrafluoroborate, BEMT)[39] and iminium (benzotriazol-1-yloxy-*N*,*N*-dimethylmethan-iminium hexachloroantimonate, BOMI)[40] type reagents. Recently, onium type coupling reagents, that generate acid fluorides or bromides, have been reported to be effective in the synthesis of amides derived from mono- and di-substituted amino acids in acceptable yields, with good reaction rates and with minimal racemization. The most promising and synthetically accessible candidates are fluoroformamidinium salts (tetramethylfluoro-formamidinium hexafluorophosphate, TFFH and bis(tetramethylenefluoroformam-idinium) hexafluorophosphate, BTFFH)[41] and 2-halopyridinium salts (2-bromo-1-ethylpyridinium tetrafluoroborate, BEP and 2-fluoro-1-ethylpyridinium tetrafluoroborate, FEP).[42] The inherent problem of all reagents mentioned, including the immobilized TBTU, is the formation of undesired by-product, which may be toxic[43] and that necessitate extensive work-up after peptide-couplings in solution. Consequently, we sought to prepare related polymer-supported reagents to simplify work-up and to minimize the need for chromatographic purification. Herein we report the synthesis of monomers **4** and **8** (Schemes 1 and 2), their polymerization and graft ROM-polymerization using starter divinylbenzene cross-linked polystyrene cores (Scheme 3) and their use in the elaboration of hindered peptides and amides in the solution phase with minimal purification (Scheme 4).



Scheme 1. Synthesis of the fluoroformamidinium monomer **4**.



Scheme 2. Synthesis of the 2-bromopyridinium monomer **8**.

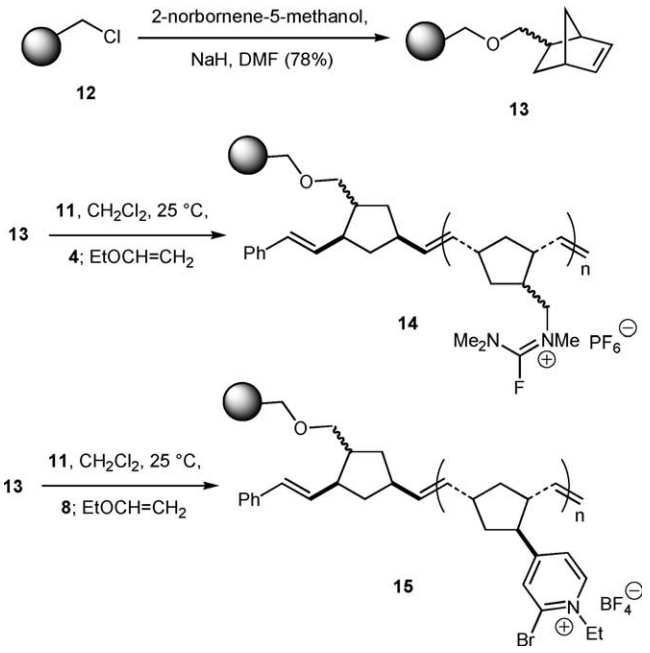


Scheme 3. Synthesis of the ROMPgel reagent **10**.

2. Results and discussion

2.1. Synthesis of monomers

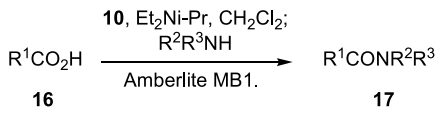
The fluoroformamidinium monomer **4** was synthesized in four steps from commercially available 5-norbornene-2-carboxaldehyde (**1**) (Scheme 1). Reductive amination of



Scheme 4. Synthesis of the ROMPsphere reagents **14** and **15**.

aldehyde **1** gave amine **2**[44] which was allowed to react with dimethylcarbamoyl chloride to afford the urea derivative **3** in 89% yield. Formation of the formamidinium salt **4** was achieved using a one-pot phosgene-free procedure described by Nájera et al.[45] Thus, reaction of the amide **3** with oxalyl chloride and DMF in dichloromethane afforded the formamidinium chloride salt. Subsequent treatment with potassium hexafluorophosphate and potassium fluoride in acetonitrile gave the formamidinium hexafluorophosphate **4** as a crystalline solid.

The second coupling reagent prepared was an immobilized variant of the 2-bromo-1-ethylpyridinium tetrafluoroborate (BEP) coupling reagent (Scheme 2). Monomer **8** was synthesized in 3 steps from the commercially available



Scheme 5. Parallel synthesis of hindered amides using the ROMPgel **10**.

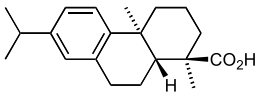
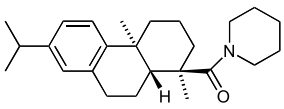
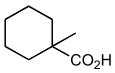
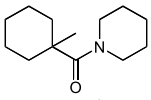
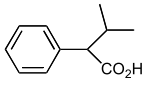
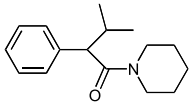
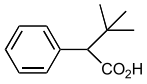
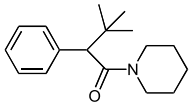
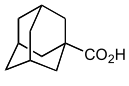
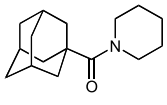
2,5-dibromopyridine. Selective bromine–lithium exchange,[46] upon treatment of the dibromide **5** with *n*-butyllithium at −78 °C and iodination using 1,2-diiodoethane gave 2-bromo-5-iodopyridine **6** (69%). Palladium catalyzed *exo*-hydroarylation[47] of iodide **6** gave the bromide **7** (66%). Subsequent ethylation using triethyloxonium tetrafluoroborate[48] gave the norbornene pyridinium salt **8** (81%).

2.2. Ring opening metathesis polymerization: synthesis of ROMPgel and ROMPsphere coupling reagents

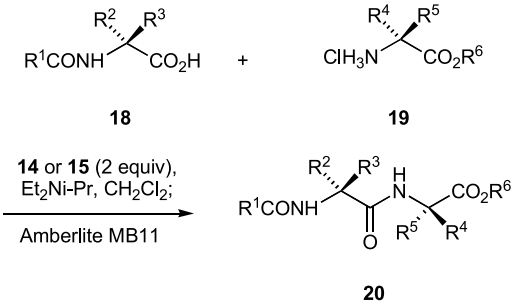
With monomers **4** and **8** in hand, the stage was set for both ROM-polymerization in the presence of a crosslink to provide the ROMPgel reagent **10** and graft ROM-polymerization reactions onto polystyrene beads to provide the corresponding ROMPsphere[49] reagents **14** and **15**. ROMPsphere reagents are analogous to functionalized Hodges Rasta resins[50] due to the fact that both types of polymers are derived from living polymerization reactions to increase the mass and loading of core divinylbenzene cross-linked polystyrene beads. ROM polymerization of monomer **4** in the presence of catalyst **11**[51] (1 mol%) and cross-linker **9**[22] gave the fluoroformamidinium ROMPgel **10** (Scheme 3). This was isolated in excellent yield (98%) after quenching with ethyl vinyl ether and extensive washing with dichloromethane and diethyl ether.

Secondly, Merrifield resin **12** (0.9 mmol/g^{-1}) was allowed to react with excess 2-norbornene-5-methanol in DMF under basic conditions for 24 h at reflux (Scheme 4). The polymer was sequentially washed with dichloromethane and methanol and dried. The loading of the norbornene **13** was

Table 1. Parallel synthesis of hindered amides using the ROMPgel **10**

Entry	R^1CO_2H (**16**)		$R^1CONR^2R^3$ (**17**)		Yield % (purity %)[a]
1	**16a**		**17a**		87 (88)
2	**16b**		**17b**		98 (97)
3	**16c**		**17c**		73 (88)
4	**16d**		**17d**		95 (90)
5	**16e**		**17e**		81 (88)

[a] Yields refer to isolated products; the purities were estimated by ^1H and ^{13}C NMR spectra and, for volatile acids and amides, also by GC–S analysis.



Scheme 6. Peptide—coupling reactions using ROMPsphere reagents **14** and **15**.

estimated by an increase in mass and by elemental analysis. The supported norbornene **13** (0.65 mmol/g^{-1}) was allowed to react with carbene **11** (3 mol%) in dichloromethane to afford a red colored polymer, which was subsequently washed with dichloromethane and 2-propanol. The resin was immediately treated separately with the monomers **4** or **8** for 2 h and the polymerization reactions terminated with ethyl vinyl ether, and the beads were washed with dichloromethane and diethyl ether. Both ROMPsphere reagents **14** and **15** were obtained with loadings of 1.45 and 1.80 mmol/g^{-1} respectively as determined by an increase in mass and by elemental analysis. We investigated the swelling properties of the ROMPsphere salts **14** and **15** in a range of solvents and observed significant swelling for both ROMPspheres in dichloromethane, THF and DMF. Dichloromethane, as the most volatile, was selected for amide and peptide synthesis.

2.3. Parallel synthesis of hindered amides and peptides

As previously discussed, both fluoroformamidinium and 2-bromopyridinium salts have proven to be effective coupling reagents for formation of peptides from α,α-dialkylated amino acids with minimal racemization. Thus we evaluated the effectiveness of the ROMPgel **10** (Scheme 5, Table 1) and the ROMPsphere reagents **14** and **15** (Scheme 6, Table 2) in the purification-minimized parallel synthesis of hindered amides and di-peptides containing the sterically hindered Aib (α-aminoisobutyric acid). In several examples of dipeptide synthesis, the degree of racemization was determined using both the Anteunis test[52] and Young's test.[53] ROMPgel reagent **10** was suspended in dichloromethane at room temperature and allowed to react with ethyldiisopropylamine and the acid component. After ten minutes, a secondary amine was added and the resulting mixture stirred at room temperature for 12 h. Pre-washed Amberlite MB1 ion exchange resin was added and the mixture shaken for a further 2 h. The suspension was filtered, and the ROMPgel washed alternatively with CH_2Cl_2 and MeOH. Evaporation of the solvent afforded the desired amides in reasonable yields and high purities (Table 1, entries 1–5).

The ROMPsphere reagents **14** and **15** were suspended in dichloromethane at −10 °C, and allowed to react with ethyldiisopropylamine (3 equiv), an *N*-protected amino acid **18** (0.5 equiv) and an amino ester hydrochloride **19** (0.5 equiv) at 25 °C for 12 h. Pre-washed Amberlite MB11 ion exchange resin was added and the mixture shaken for a further 2 h. The suspension was simply filtered, washed with dichloromethane and methanol to afford the corresponding di- and tri-peptides **20** (Scheme 6, Table 2). The reactions could also be very effectively performed in Bohdan Miniblocks: the peptide-coupling was performed in one block and afterwards the liquid reaction components were transferred in parallel into a second block containing the ion exchange resin. After agitating the resin for further 1 h, the solution was free of salt by-products and the pure dipeptides **20** were released into a deep well Miniblock and evaporated. The preparation of $C^{\alpha\alpha}$-disubstituted peptides was shown to be extremely effective in terms of reaction time, yields and purities, as exemplified in by **20b**, **20c**, **20d**, **20g** and **20h**. The results in Table 2 indicate that there is little difference in term of yield and purity when using the ROMPsphere reagents **14** or **15**. In several cases the Anteunis test was conducted at −78 °C using ethyldiisopropylamine as the base and samples were taken after 10 min, 1 h and finally 12 h and the DL values were determined by HPLC using a protocol described by Li and Xu.[42] Unfortunately, complete epimerization was observed after only 10 min reaction using the ROMPsphere reagents **14** and **15** (Table 2, entries 9 and 10). Changing the base for the peptide-coupling from ethyldiisopropylamine to a weaker base such as 2,6-lutidine or *N*-methylmorpholine failed to suppress complete epimerization. Our optical rotation values for the coupling of *Z*-Gly and PheOEt were shown to be zero (Table 2, entries 1 and 2). These unexpected results were possibly due to slow

Table 2. Yields and purities of dipeptides **20** synthesized using ROMPspheres **14** or **15**

Entry	Dipeptide	**18**	**19**	ROMPsphere	% Yield[a]	% Purity[b]
1	**20a**	Z-Gly	(L)-Phe-OEt ·HCl	**14**	96	95[c]
2	**20a**	Z-Gly	(L)-Phe-OEt ·HCl	**15**	86	87[c]
3	**20b**	Boc-Aib	Gly-OEt ·HCl	**14**	97	98
4	**20c**	Z-Gly	Aib-OMe·HCl	**14**	97	98
5	**20c**	Z-Gly	Aib-OMe·HCl	**15**	84	96
6	**20d**	Boc-Aib	Aib-OMe·HCl	**14**	90	98
7	**20e**	Z-(L)-Leu	Gly-OEt·HCl	**14**	89	92[d]
8	**20e**	Z-(L)-Leu	Gly-OEt·HCl	**15**	92	94[d]
9	**20f**	Z-Gly-(L)-Phe	(L)-Val-OMe·HCl	**14**	95	90[c]
10	**20f**	Z-Gly-(L)-Phe	(L)-Val-OMe·HCl	**15**	87	87[c]
11	**20g**	*N*-Fmoc-Aib	Gly-OEt·HCl	**15**	85	88
12	**20h**	*N*-Fmoc-Aib	(L)-Ala-OEt·HCl	**15**	80	89[d]

[a] Isolated yields.
[b] Purity as determined by ^{1}H NMR.[54]
[c] Product completely racemized (epimerized).
[d] Extent of racemization not determined.

diffusion of the amine to the ROMPsphere immobilized activated acid thereby facilitating racemization. In spite of this limitation, the ROMPsphere coupling reagents **14** and **15** are valuable in the parallel synthesis of hindered peptides containing α,α-disubstituted amino acid residues (Table 2, entries 3–6 and 11).

3. Conclusions

We have demonstrated the utility of a ROMPgel-supported fluoroformamidinium hexafluorophosphate, a ROMPsphere-supported fluoroformamidinium hexafluoro-phosphate and a ROMPsphere-supported *N*-ethylpyridinium tetrafluoroborate for the parallel synthesis of hindered amides with minimal purification. The approach, whilst useful for hindered peptides containing α,α-disubstituted amino acid residues, it is unsatisfactory for standard peptide-coupling reactions on account of racemization.

4. Experimental

4.1. General

All reactions were carried out in an atmosphere of dry nitrogen or argon at room temperature unless otherwise stated. Reaction temperatures other than room temperature were recorded as bath temperatures unless otherwise stated. Flash chromatography was carried out on BDH silica 60, 230–400 mesh ASTM (eluants are quoted in parenthesis). Analytical thin-layer chromatography (TLC) was performed on Merck precoated silica 60 F_{254} plates. Hexanes refers to redistilled alkanes with bp 40–60 °C. Dichloromethane (CH_2Cl_2) and tetrahydrofuran (THF) were purified by distillation under N_2 respectively from CaH_2 and Ph_2CO/K, All other organic solvents and reagents were obtained from commercial sources and used without further purification. Organic extracts were concentrated using a rotary evaporator at <40 °C bath temperature. Non volatile oils and solids were vacuum dried at <2 mm Hg. Bohdan miniblocks with 8 mL glass reactors with bottom filtration and the option for transfer from one block to the other were used for parallel reactions.

4.1.1. 5-(Methylaminomethyl)bicyclo[2.2.1]hept-2-ene (2).[55] $MeNH_2$ in THF (2.0 M; 65 mL, 132 mmol) was added to aldehyde **1** (8.0 g, 66 mmol), Et_2–O (50 mL) and 4 Å molecular sieves (8.0 g) at 0 °C. The mixture was stirred for 2 h, filtered and rotary evaporated to afford the imine as an oil, which was dissolved in MeOH (100 mL) and $NaBH_4$ (3.7 g, 99 mmol) was added in portions at 0 °C. After stirring at 25 °C for 4 h, the mixture was rotary evaporated to afford a residue, which was portioned between CH_2Cl_2 and hydrochloric acid (2 M; 66 mL). The aqueous solution was basified to a pH 8–9 and extracted with CH_2Cl_2. The combined organic phases were dried (Na_2SO_4) and rotary evaporated to afford **2** (8.1 g, 90%) as a pale yellow oil; IR (thin film) 3291, 1623, 1468, 1447, 1341, 1150, 718 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 6.08–5.88 (m, 2H), 2.80–2.74 (m, 2H), 2.57–2.54 (m, 1H), 2.41–2.36 (m, 3H), 2.34–2.14 (m, 2H), 1.85–1.77 (m, 1H), 1.28–1.10 (m, 3H), 0.50–0.46 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.2, 132.1, 56.7, 49.5, 44.3, 42.3, 39.1, 36.8, 30.6; MS (CI, NH_3) *m/z* 138 $(M+H)^+$; HRMS (CI, NH_3) calcd for $C_9H_{16}N$ $(M+H)^+$, 138.1283; found: $(M+H)^+$, 138.1280.

4.1.2. *N*-(Bicyclo[2.2.1]hept-5-en-2-ylmethyl)-*N*,*N*′,*N*′-trimethylurea (3). Dimethyl-carbamoyl chloride (4.7 g 44 mmol) was added slowly with stirring to amine **2** (6.0 g, 44 mmol) in THF (250 mL) and Et_3N (12.2 mL, 88 mmol) at 25 °C. After 3 h, the reaction mixture was filtered through Celite and silica gel and rotary evaporated to afford a residue. Chromatography (hexane/Et_2O 2:1) gave urea **3** (8.2 g, 89%) as a yellow oil: R_f 0.14 (EtOAc/hexanes 2:3); IR (thin film) 1644, 1495, 1461, 1382, 1343, 1260, 1123, 1112, 1063, 782, 719 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.09 (dd, $J=5.3$, 2.8 Hz, 1H), 5.84 (dd, $J=5.3$, 2.8 Hz, 1H), 3.20 (m, 1H), 2.85 (dd, $J=2.6$, 7.7 Hz, 2H), 2.75 (br s, 3H), 2.74 (br s, 6H), 2.36 (m, 1H), 1.76 (m, 1H), 1.36 (m, 1H), 1.29–1.18 (m, 2H), 0.48 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.4, 137.3, 132.3, 54.1, 49.5, 44.4, 42.2, 38.6, 37.4, 37.3, 30.0; MS (CI, NH_3) *m/z* 209 $(M+H)^+$; HRMS (CI, NH_3) calcd for $C_{12}H_{21}N_2O$ $(M+H)^+$209.1654; found: $(M+H)^+$, 209.1645. Anal. calcd for $C_{12}H_{20}N_2O$: C, 69.19; H, 9.68; N, 13.45. Found: C, 69.39; H, 9.84; N, 13.12.

4.1.3. *N*-(Bicyclo[2.2.1]hept-5-en-2-ylmethyl)-*N*,*N*′,*N*′-trimethylfluoroform-amidinium hexafluorophosphate (4). Oxalyl chloride (1.0 mL, 11.5 mmol) was added dropwise to the urea **3** (2.1 g, 10 mmol) and DMF (75 μL) in CH_2Cl_2 (10 mL) at 25 °C. After 1 h, the solution was heated to reflux for 4 h when rotary evaporation gave the crude chloroformamidinium salt. KPF_6 (2.2 g, 12.0 mmol) and KF (0.56 g, 10.0 mmol) in MeCN (10 mL) were added and the mixture was stirred for 48 h. The suspension was filtered and the filtrate was concentrated in vacuo to afford a residue. Recrystallization from CH_3CN and Et_2O gave the salt **4** (2.3 g, 64%) as a white solid: mp 91–93 °C; IR (solid) 1647, 1473, 1457, 1412, 1398, 1245, 1058, 833, 726 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.32 (m, 1H), 5.92 (m, 1H), 3.80–3.60 (m, 1H), 3.42 (br s, 3H), 3.41 (br s, 6H), 2.91 (br s, 1H), 2.84 (br s, 1H), 2.54 (m, 1H), 2.00–1.98 (m, 1H), 1.59–1.55 (m, 1H), 1.38–1.36 (m, 1H), 1.24–1.16 (m, 1H), 0.60–0.56 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.4, 139.5, 131.0, 61.1, 49.9, 44.6, 44.5, 43.2, 42.4, 37.4, 30.1; MS (FAB +) *m/z* 211 (M^+); HRMS (FAB +) *m/z* calcd for $C_{12}H_{20}FN_2$ (M^+), 211.1611; found: (M^+), 211.1614.

4.1.4. 2-Bromo-5-iodopyridine (6). *n*-BuLi in hexanes (2.5 M; 7.00 mL, 17.5 mmol) was added dropwise to 2,5-dibromopyridine **5** (3.76 g, 15.9 mmol) in THF (190 mL) at −78 °C and the mixture stirred for 40 min. ICH_2CH_2I (5.78 g, 20.5 mmol) in THF (25 mL) was added and the mixture was allowed to warm up to 25 °C over 12 h. The solution was diluted with H_2O and Et_2O (1:1, 300 mL) and the aqueous phase was extracted with additional $Et_{-2}O$ (4× 50 mL). The combined organic phases were washed with $Na_2S_2O_4$ (100 mL) and brine (100 mL), dried (Na_2SO_4) and rotary evaporated to afford a yellow solid. Chromatography (hexanes/CH_2Cl_2 4:1) gave iodide **6** (3.2 g, 69%) as a white solid: mp 119 °C (EtOH); IR (film) 1544, 1439, 1354, 1278, 1141, 1086, 994, 911, 828, 716, 666, 624 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.60 (d, $J=2.0$ Hz, 1H), 7.82 (dd, $J=$ 2.0, 8.3 Hz, 1H), 7.28 (d, $J=8.3$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.2, 146.6, 145.5, 130.0, 91.8; MS

(EI, *m/z*) 283 ($M^{\cdot+}$), 237, 204, 156, 127; calcd for C_5H_3BrIN: ($M^{+\cdot}$), 282.8494; found: ($M^{+\cdot}$), 282.8497. Anal. calcd for C_5H_3BrIN: C, 21.15; H, 1.06; N, 4.93. Found: C, 21.14; H, 0.95; N, 4.87.

4.1.5. 2-Bromo-5-(*exo*-bicyclo[2.2.1]hept-2-en-5-yl)pyridine (7). Norbornadiene (3.0 mL, 28 mmol), $(Ph_3P)_2$-$Pd(OAc)_2$ (266 mg, 0.35 mmol), piperidine (2.1 mL, 21 mmol) and HCO_2H (0.6 g, 0.5 mL, 14 mmol) were added to 2-bromo-5-iodopyridine **6** (2.0 g, 7.0 mmol) in DMF (5 mL) and the suspension was slowly heated to 55 °C and maintained at that temperature for 12 h. The solution was diluted with H_2O (100 mL) and extracted with Et_2O (3×50 mL). The combined organic phases were washed with brine (200 mL), dried (Na_2SO_4), rotary evaporated and chromatographed (hexane/EtOAc 97:3) to afford **7** (1.84 g, 66%) as a clear oil; IR (film) 1573, 1555, 1451, 1384, 1331, 1316, 1285, 1251, 1200, 1133, 1088, 1020, 1003, 947, 904, 827, 776, 733, 714, 650 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.29 (s, 1H), 7.44 (m, 2H), 6.23 (m, 2H), 3.02 (s, 1H), 2.89 (s, 1H), 2.67 (t, $J=6.7$ Hz, 1H), 1.68 (dd, $J=1.8$. 6.7 Hz, 2H), 1.48 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.8, 140.8, 139.0, 137.6, 136.8, 127.5, 47.9, 45.6, 42.4, 40.9, 33.6; MS (EI) *m/z* 250 ($M^{\cdot+}$), 184, 104. Anal. calcd for $C_{12}H_{12}BrN$: C, 57.63; H, 4.83, N, 5.60. Found: C, 57.71, H, 4.71, N, 5.58.

4.1.6. 2-Bromo-5-(*exo*-bicyclo[2.2.1]hept-2-en-5-yl)-1-ethylpyridinium tetrafluoroborate (8). Et_3OBF_4 (874 mg, 4.60 mmol) in CH_2Cl_2 (3 mL) was added dropwise to pyridine **7** (1.1 g, 4.4 mmol) in CH_2Cl_2 (3 mL) at 0 °C. After 3 h at 25 °C, the solution was heated to reflux for 30 min. The salt was precipitated upon the addition of Et_2O (12 mL) at 0 °C, filtered and dried to afford salt **8** (1,36 g, 81%) as a white solid: mp 174–176 °C (Et_2O); IR (film) 1617, 1571, 1507, 1468, 1391, 1332, 1287, 1213, 1163, 1053, 903, 836, 797, 734, 713, 664 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.94 (s, 1H), 8.22 (m, 2H), 6.22 (m, 2H), 4.87 (q, $J=7.2$ Hz, 2H), 3.04 (s, 2H), 2.89 (t, $J=6.7$ Hz, 1H), 1.77 (m, 2H), 1.64 (t, $J=7.2$ Hz, 3H), 1.46 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.0, 147.1, 145.4, 138.1, 136.7, 133.7, 133.3, 59.4, 47.9, 45.6, 42.7, 41.5, 33.7, 15.5; MS (FAB$^+$) *m/z* 278 (M^+), 212, 89, 77; calcd for $C_{14}H_{17}BrN$: (M^+), 278.0554; found: (M^+), 278.0544. Anal. calcd for $C_{14}H_{17}BBrF_4N$: C, 45.94; H, 4.68; N, 3.83. Found: C, 45.87, H, 4.68; N, 3.78.

4.1.7. *N,N′,N′*-Trimethylfluoroformamidinium hexafluorophosphate functionalized ROMPgel (10). Catalyst **11** (2.7 mg, 3.17 μmol) in $ClCH_2CH_2Cl$ (0.25 mL) was added to monomer **4** (225.8 mg, 0.63 mmol) and cross-linker **9** (24.9 mg, 0.09 mmol) in $ClCH_2CH_2Cl$ (1 mL). The mixture was heated at 50 °C for 0.5 h and allowed to cool to 25 °C. After 16 h, CH_2Cl_2 (1 mL), CH_3CN (0.5 mL) and ethyl vinyl ether (0.5 mL) were added and the mixture heated to 50 °C for 1.5 h. After cooling, the mixture was cooled to 25 °C, filtered and the ROMPgel extracted with CH_2Cl_2 (3×20 mL), THF (2×20 mL) and Et_2O (3×20 mL) followed by concentration in vacuo to give ROMPgel **10** (252.4 mg, 100%) as a white solid; IR (solid) 1640, 1457, 1407, 1250, 1099, 834 cm^{-1}. Anal. calcd for $C_{13.04}H_{20.26}P_{0.87}F_{6.09}N_{1.74}$: C, 45.53; H, 5.94; N, 7.08. Found: C, 45.43; H, 5.80; N, 6.95.

4.1.8. Polystyrene-supported norbornene (13). *endo*/*exo*-Bicyclo[2.2.1]hept-5-en-2-ylmethanol (**12**) (2.5 g, 20 mmol) and KH (0.8 g, 20 mmol) were added to Merrifield resin (Polymer Labs, 75–150 μm, 0.9 mmol/g^{-1}; 10 g) in DMF (100 mL). The mixture was heated at 60 °C for 16 h, quenched with MeOH and filtered, washed with DMF (3× 30 mL), CH_2Cl_2 (3×30 mL) and MeOH (3×30 mL) and dried to afford resin beads **13** (10.6 g, 76%, 0.65 mmol/g^{-1}); IR (film) 1094, 1017, 857, 819 cm^{-1}. Anal. calcd: C, 89.96, H; 7.82. Found C, 89.99; H, 7.98.

4.1.9. ROMPsphere-supported fluoroformamidium hexafluorophosphate (14). Resin **13** (1.00 g) was suspended in CH_2Cl_2 (9 mL) and agitated for 15 min, the solvent was removed by decantation and catalyst **11** (255 mg, 3 mmol) in CH_2Cl_2 (1.5 mL) was added and agitation continued for 45 min. The resin was thoroughly washed with CH_2Cl_2 and 2-PrOH, suspended in CH_2Cl_2 (10 mL) and monomer **4** (3.00 g, 14 mmol) in CH_2Cl_2 (15 mL) was added. After agitating for 3 h, the resin was washed with CH_2Cl_2 and Et_2O (3×3 mL) and dried to yield the ROMPsphere supported reagent **14** (2.0 g, 1.45 mmol). Anal. calcd C, 62.36; H, 6.70, N, 3.93. Found C, 62.7; H, 6.86; N, 3.52.

4.1.10. ROMPsphere-supported 2-Bromo-1-ethylpyridinium tetrafluoroborate (15). The resin 13 (200 mg) was suspended in CH_2Cl_2 (6 mL) and agitated for 15 min, the solvent was removed by decantation and catalyst **11** (60 mg, 0.6 mmol) in CH_2Cl_2 (1.5 mL) was added and agitation continued. After 15 min, the resin was further diluted with CH_2Cl_2 (6 mL) and agitated for an additional 1 h, and thoroughly washed with CH_2Cl_2. Monomer **8** (600 mg, 1.6 mmol) in CH_2Cl_2 (3 mL) was added to the resin and agitation continued for 12 h. The resin was washed with CH_2Cl_2 and Et_2O (3×3 mL) and dried to yield the ROMPsphere reagent 15 (636 mg, 1.8 mmol/g^{-1}); IR (film) 1733, 1499, 1288, 1052, 864 cm^{-1}. Anal. calcd C, 57.95; H, 5.54; N, 2.75. Found C, 58.37; H, 5.93; N, 2.31.

4.2. General procedure for amide synthesis using ROMPgel reagent 10

i-Pr_2NEt (3 equiv) was added to acid 16 (0.07–0.11 mmol) and ROMPgel 10 (2 equiv) in CH_2Cl_2 (0.5 mL). After 0.5 h, piperidine (6.9–11.0 μL; 1 equiv) was added and the mixture shaken for 12 h. Amberlite MB1 ion exchange resin was added and the mixture shaken for a further 3.5 h. Filtration and rotary evaporation gave amide **17e**[56] (22.2 mg, 81% yield, 88% purity): mp 85.5–87.5.0 °C; lit[56] 86–87 °C.

4.2.1. 12-Isopropyl-2,6-dimethyltricyclo[8.4.0.0]tetradeca-1(14),10,12-trien-6-yl-piperidinomethanone (17a). (24.0 mg, 87% yield, 88% purity) as a clear yellow oil: R_f 0.60 (EtOAc/hexanes 1:1); IR ($CHCl_3$) 1625, 1457, 1409, 1247, 1120, 1012, 910 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.17 (d, $J=8.0$ Hz, 1H), 7.00 (d, $J=7.6$ Hz, 1H), 6.91 (s, 1H), 3.66–3.52 (m, 4H), 3.03–2.94 (m, 1H), 2.91–2.79 (m, 2H), 2.35–2.26 (m, 2H), 1.84–1.30 (m, 13H), 1.33 (s, 3H), 1.24 (s, 3H), 1.23 (s, 3H), 1.21 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.9, 147.1, 145.5, 135.2, 127.0, 124.1, 123.6, 47.0, 46.7, 45.2, 44.7, 37.6, 37.5, 35.2, 33.4, 30.7, 26.2, 25.5, 24.7, 23.9, 22.1, 18.9, 15.7; MS (CI, NH_3) *m/z* 368

$(M+H)^+$; HRMS (CI, NH_3) calcd for $C_{25}H_{38}NO$ $(M+H)^+$, 368.2953; found: $(M+H)^+$, 368.2952.

4.2.2. 1-[(1-Methylcyclohexyl)carbonyl]piperidine (17b). (14.9 mg, 98% yield, 97% purity) as a clear colorless oil: R_f 0.50 (EtOAc/hexanes 1:1); IR ($CHCl_3$) 1696, 1629, 1592, 1448, 1127, 1104, 1014 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.56 (m, 4H), 2.04–2.01 (m, 2H), 1.64–1.16 (m, 14H), 1.23 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.4, 46.4, 44.6, 37.1, 35.1, 26.3, 26.0, 25.6, 24.8, 24.2, 23.1, 22.9, 15.7; MS (CI, NH_3) *m/z* 210 $(M+H)^+$; HRMS (CI, NH_3) calcd for $C_{13}H_{24}NO$ $(M+H)^+$210.1858; found: $(M+H)^+$, 210.1859.

4.2.3. 1-(3-Methyl-2-phenylbutanoyl)piperidine (17c). (12.5 mg, 73% yield, 88% purity) as a clear yellow oil; R_f 0.50 (EtOAc/hexanes 1:1); IR ($CHCl_3$) 1639, 1442, 1247, 1221, 1138, 1108, 1016, 772, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.33–7.18 (m, 5H), 3.53–3.37 (m, 4H), 3.31 (d, $J=10.0$ Hz, 1H), 2.51–2.41 (m, 1H), 1.58–1.35 (m, 5H), 1.10–1.07 (m, 1H), 1.01 (d, $J=6.4$ Hz, 3H), 0.66 (d, $J=6.8$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3, 139.5, 128.5, 128.4, 126.7, 56.2, 46.8, 43.2, 31.9, 26.3, 25.5, 24.6, 22.3, 20.4; MS (CI, NH_3) *m/z* 263 $(M+NH_4)^+$246 $(M+H)^+$; HRMS (CI, NH_3) calcd for $C_{16}H_{24}NO$ $(M+H)^+$246.1858; found: $(M+H)^+$, 246.1850.

4.2.4. 1-(3,3-Dimethyl-2-phenylbutanoyl)piperidine (17d). (17.5 mg, 95% yield, 90% purity) as a white solid: R_f 0.80 (EtOAc/hexanes, 1:1); mp 73.0–75.0 °C; IR ($CHCl_3$) 1620, 1456, 1437, 1264, 1136, 1016, 850, 737 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35–7.21 (m, 5H), 3.64–3.58 (m, 1H), 3.56 (s, 1H), 3.43–3.32 (m, 3H), 1.58–1.35 (m, 6H), 1.04 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0, 137.4, 130.2, 127.8, 126.6, 57.1, 47.3, 42.8, 34.8, 28.3, 26.1, 25.6, 24.6; MS (CI, NH_3) *m/z* 260 $(M+H)^+$; HRMS (CI, NH_3) calcd for $C_{17}H_{26}NO$ $(M+H)^+$260.2014; found: $(M+H)^+$, 260.2014.

4.3. General procedure for dipeptide synthesis using ROMPsphere reagents 14 and 15

ROMPspheres **14** or **15** (0.4 mmol) and $^{iso}Pr_2NEt$ (104 μL, 0.6 mmol) were added to the *N*-protected α-aminoacid **18** (0.2 mmol) and the hydrochloric salt of the α-aminoester **19** (0.2 mmol) in CH_2Cl_2 (1 mL) and the mixture was shaken for 12 h at 25 °C. Amberlite MB11 (ion exchange resin, 0.5 g) was added and shaking continued for 1 h. The suspension was filtered and the remaining solid was subsequently washed with CH_2Cl_2 (2×2 mL) and MeOH (2×2 mL) and rotary evaporated to afford the desired peptide **20**: *N*-Cbz-Gly-L-Phe-OEt (**20a**)[57] (71 mg, 96%); Boc-Aib-Gly-OEt (**20b**)[58] (56 mg, 97%); Boc-Aib-Aib-OMe (**20d**)[59] (54 mg, 90%); *N*-Cbz-L-Leu-Gly-OEt (**20e**)[60] (15 mg, 89%); *N*-Cbz-Gly-L-Phe-L-Val-OMe (**20f**)[42] (89 mg, 95%).

4.3.1. Z-Gly-Aib-OMe (20c). (60 mg, 97%); IR (film) 3331, 1731, 1670, 1533, 1457, 1387, 1274, 1153, 1051, 978, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.31 (br s, 5H), 6.71 (br s, 1H), 5.55 (br s, 1H), 5.11 (s, 2H), 3.84 (d, $J=5.2$ Hz, 2H), 3.71 (s, 3H), 1.52 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.8, 168.2, 156.6, 136.1, 128.6, 128.2, 128.0, 67.3, 56.6, 52.7, 44.6, 24.7; HRMS (CI^+, NH_4) calcd for $C_{15}H_{21}N_2O_5$: $(M+H)^+$, 309.1458; found: $(M+H)^+$, 309.1451.

4.3.2. *N*-Fmoc-Aib-Gly-OEt (20g). (67 mg, 85%); IR (film) 3343, 1715, 1669, 1524, 1449, 1254, 1191, 1091, 909, 824, 736 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.80 (br d, $J=7.2$ Hz, 2H), 7.62 (d, $J=7.2$ Hz, 2H), 7.41 (t, $J=7.2$ Hz, 2H), 7.32 (t, $J=7.2$ Hz, 2H), 6.10 (br s, 1H), 5.31 (br s, 1H), 4.23 (m, 3H), 4.13 (q, $J=7.1$ Hz, 2H), 3.89 (m, 2H), 1.54 (s, 6H), 1.29 (t, $J=7.1$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.8, 170.2, 156.2, 143.7, 140.5, 128.1, 127.4, 123.2, 120.1, 66.9, 61.9, 56.8, 47.6, 42.9, 25.8, 25.5, 14.5; HRMS (CI^+, NH_4) calcd for $C_{23}H_{26}N_2O_5$: $(M^{\cdot+})$, 410.1842; found: $(M^{\cdot+})$, 410.1844.

4.3.3. *N*-Fmoc-Aib-L-Ala-OEt (20h). (65 mg, 80%); IR (film) 3343, 1731, 1655, 1522, 1449, 1254, 1153, 1090, 910, 735 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.80 (br d, $J=7.2$ Hz, 2H), 7.62 (d, $J=7.2$ Hz, 2H), 7.41 (t, $J=7.2$ Hz, 2H), 7.32 (t, $J=7.2$ Hz, 2H), 6.72 (br s, 1H), 5.34 (br s, 1H), 4.55 (m, 1H), 4.43 (m, 2H), 4.23 (m, 3H), 1.55 (s, 6H), 1.41 (d, $J=6.57$ Hz, 3H), 1.28 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.2, 173.3, 155.4, 144.3, 141.7, 128.1, 127.4, 125.4, 120.1, 66.9, 61.9, 57.2, 47.6, 42.9, 25.5, 18.7, 14.5; MS (CI^+, NH_4) 58 (32), 118 (86), 179 (78), 198 (89), 203 (40), 229 (15), 299 (14), 340 (340), 357 (94), 425 (6) HRMS (CI^+, NH_4) calcd for $C_{24}H_{28}N_2O_5$: $(M^{\cdot*******+})$, 424.1998; found: $(M^{\cdot+})$, 424.2001.

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Synthesis of polystyrene-bound perfluoroalkyl sulfonic acids and the application of their ytterbium salts in multicomponent reactions (MCRs)

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Abstract—New polystyrene-bound perfluoroalkyl sulfonic acids and their ytterbium salts have been prepared. Multicomponent reactions (MCRs) for the efficient synthesis of homoallylic amines or amides catalyzed by the polystyrene-bound perfluoroalkyl sulfonic ytterbium salts are reported.

1. Introduction

Polymer-bound catalysts and reagents have attracted much attention of researchers in the development of economically and environmentally benign organic synthesis.[1] Up to now, several polymer-bound super Brønsted acids and Lewis acids (such as **1**,[2a–c] **2**,[2d] **3**,[2e] **4**,[2f] **5**[2g]) have been reported to be useful in organic reactions (Scheme 1). Other ways similar to polymer attachment such as microencapsulated and perfluorous chain 'immobilized' Lewis acids (**6** and **7**) were also reported.[3] Perfluororesinsulfonic acid such as Nafion is one of the most famous immobilized super acids superior to conventional resin sulfonic acids such as sulfonated polystyrenes in its catalytic activity, thermal stability and chemical resistance.[2a,b] However, its low swelling in non-protic organic solvents leads to its compromised reactivity in some cases.[4] On the other hand, the commercially available polystyrene can be efficiently swollen by both polar and non-polar organic solvents.[5] Merrifield type resins, the cross-linked chloromethyl polystyrenes, are widely developed for polymer-bound catalysts.[6] Up to now, polystyrene-bound super Brønsted acid **5** is believed to be the strongest acid among the known solid acids.[2g,7] In light of the Brønsted acidity order reported in AcOH ($TfOH > Tf_2NH > Tf_3CH$),[8] therefore, development of new polymer-bound super Brønsted acids and Lewis acids is still desirable.

Recently, multicomponent reactions (MCRs) have received increasing attention due to their diversity-oriented synthetic methodology for the rapid generation of small molecules libraries.[9] MCRs have been also considered as one of the most efficient methods to construct complex molecules from simple starting materials in a single operation. Multicomponent coupling reactions to produce homoallylic amines has attracted much attention because they are as key structural moieties in a variety of important naturally occurring compounds and pharmaceuticals. Addition of allylstannane reagents to imines catalyzed by Lewis acids has been widely investigated. The first addition of allylstannane with imine catalyzed by $Ln(OTf)_3$ in organic solvents was reported in 1995, which afforded moderate yield in 24 h.[10a] In 1998, both Kobayashi's and Akiyama's groups reported one-pot reaction catalyzed by 20 mol% of scandium triflate.[10b,11] In the same year, Greeves et al. reported $Yb(OTf)_3$ catalyzed allylation of aldehydes with the accelerating co-catalyst of benzoic acid using only 2 mol% of $Yb(OTf)_3$ in CH_3CN in much shorter time.[10c] They also reported the synthesis of homoallylic alcohols and amines catalyzed by $La(OTf)_3$/benzoic acid in 2002.[10d] The authors suggested that the Brønsted acid of PhCOOH was not only simply regenerating the catalyst but also the Brønsted acid and the Lewis acid working together as a combined catalyst to produce a 'double activation'. Recent developments in this area deal with imines activation by

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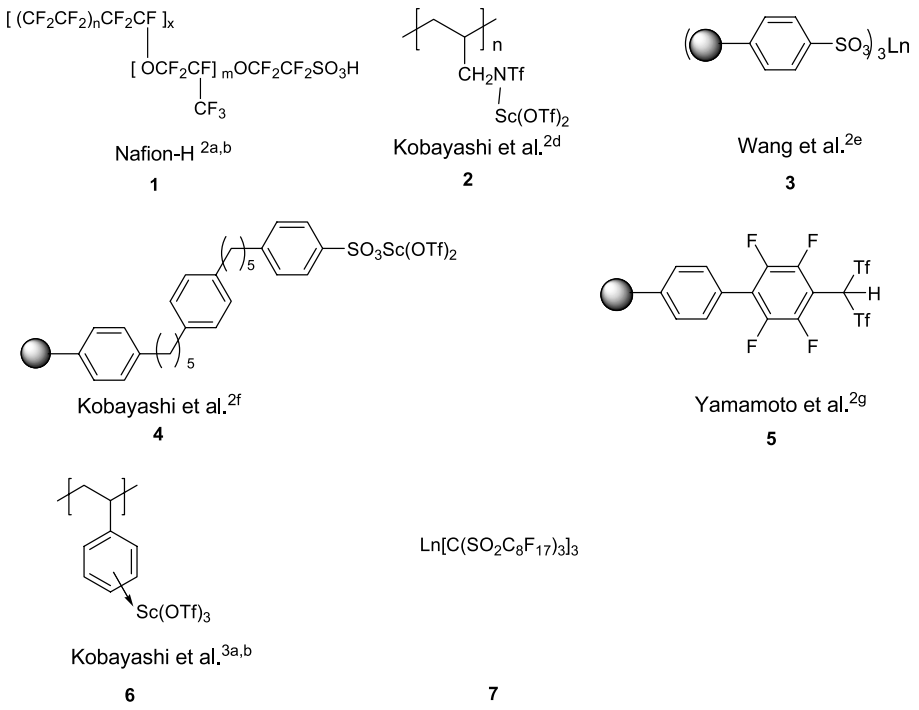
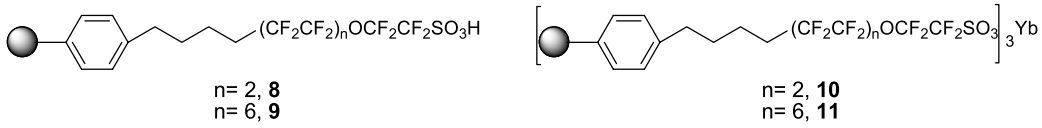


Scheme 1. Typical immobilized super Brønsted acids and their metal salts.



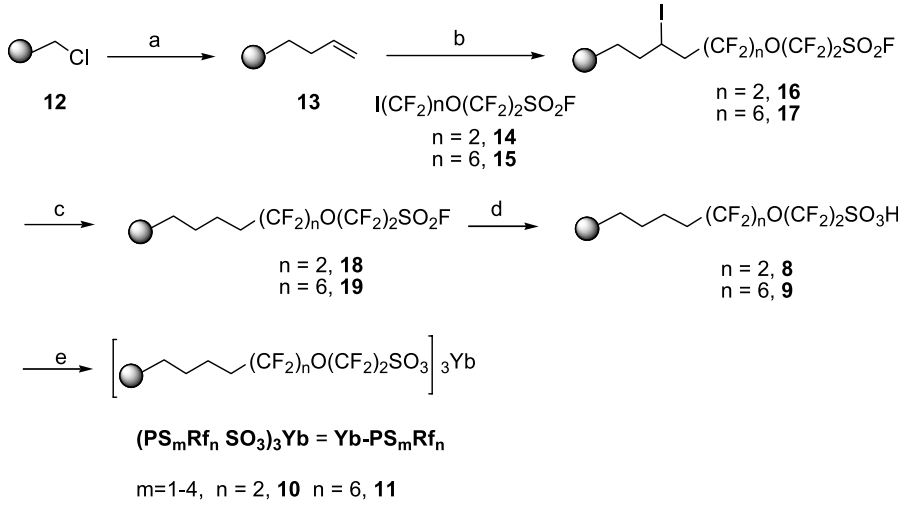
Scheme 2.

chlorotrimethylsilane or acid chloride, catalytic Pd(II) or Pt(II) complex, $NdCl_5$, montmorillonite and other Lewis acids.[12] Herein, we would like to report the synthesis of polystyrene-bound super Brønsted acids **8**, **9** and their ytterbium salts, **10** and **11** (Scheme 2), and the highly efficient one-pot multicomponent coupling reactions for the synthesis of homoallylic amines and amides catalyzed by polystyrene-bound perfluoroalkyl sulfonic ytterbium.

2. Results and discussion

2.1. Synthesis of polystyrene-bound perfluoroalkyl sulfonic acids and their ytterbium salts

We began our synthesis with addition reaction of perfluoroalkyl iodide **14** or **15** to the Merrifield resin allyl-PS **13**[13] accomplished by sodium dithionite and radical

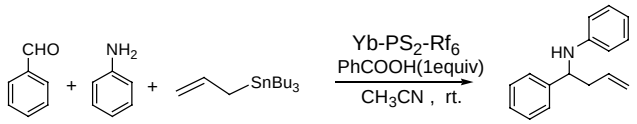


Scheme 3. Reaction conditions: (a) Ref. 7, Merrifield resin, 100–200 mesh (or 200–400 mesh), 1 or 2% DVB cross-linker; (b) BPO, toluene, 110–120 °C; (c) Bu_3SnH, AIBN (cat.), THF, reflux, 24 h; (d) (i) NaOH, 1N, THF/H_2O, room temperature, overnight; (ii) 1 N HNO_3, rt, 8 h; (e) (i) Na_2SO_4 (satd); (ii) $YbCl_3$ (aq), room temperature, overnight.

initiators.[14] Sulfinatodehalogenation reaction was first investigated because of its high efficiency for various alkenes had been reported.[13a,15] The addition reaction of polyfluoro sulfonyl fluoride **14** (or **15**) (3 equiv) with **13** was carried out in CH_3CN/H_2O (v/v:1:1) monitored by IR spectrometry and ^{19}F NMR in the presence of $Na_2S_2O_4$ and $NaHCO_3$ under reflux. Unfortunately, no addition reaction occurred even with prolonged reaction time. Poor swelling of the Merrifield resin in the aqueous solvent might account for this result (Scheme 3).

So, we tried to carry out the radical addition using the initiator of AIBN or BPO. The radical initiators most commonly used dissolve easily in CH_2Cl_2, THF and toluene, which swell the Merrifield resin well. In 1993, Burton et al. reported the synthesis of partially fluorinated phosphonic/sulfonic acids using addition of $I(CF_2)_4OCF_2CF_2SO_2F$ or $I(CF_2)_2OCF_2CF_2SO_2$ to $(EtO)_2P(O)CH_2OCH_2CH{=}CH_2$ initiated by BPO.[14b] Using this method, we employed 1–20 mol% of freshly recrystallized BPO, **13**(1 or 2% DVB cross-linker) and 3 equiv of **14** or **15** in dry toluene. After gas exchange for three times with nitrogen, the mixture was heated in oil bath at 110–120 °C. IR spectrum indicated that the more BPO (1, 5, 10 and 20 mol%) used, the weaker the absorption of the C–C double bond, but far from complete conversion yet. Using100 or 200 mol% of BPO, the C–C double bond of resin almost disappeared completely in 24 h in toluene. However, this was unpractical method. To find the optimized conditions, we focused on carefully degassing of the reaction mixture because radical reaction is sensitive to oxygen. After dry nitrogen is bubbled through the mixture of 20 mol% of BPO and 3 equiv of perfluoroakyl iodide in toluene for 1 h, the mixture was stirred at 110–120 °C for 6 h, a second portion of BPO (20 mol%) was added to complete the reaction during another 20 h at 120 °C. The next step was to remove the iodide of the polymer. Although zinc powder is cheap and widely used for the reduction,[14b,15] the reduction of polymer **16** (or **17**) was run in the mixture of THF/*i*-PrOH using activated zinc powder with or without adding AcOH for longer reaction time, only a slight amount of the iodide was reduced to be indicated by elemental analysis. Bu_3SnH as a candidate was employed to perform the reduction according literature.[16] As a result, polymer **16** (or **17**) was completely reduced by 3 equiv of Bu_3SnH in the presence of catalytic amount of AIBN in THF under reflux (elemental analysis, $I<0.5$ wt%). The resulting polymer was filtrated and washed, and dried polymer **18** (or **19**) gave comparable loading of F and S. **18** (or **19**) was dispersed in THF, and NaOH solution was then added slowly. It is noteworthy that the resin could not be completely wetted by water. The mixture was stirred overnight. After filtration, the polymer was redispersed in water and acidified by HNO_3.[17] After washing and drying, elemental analysis of PS–$_fSO_3H$ **8** (or **9**) and IEC(H^+ exchange capacity determined by titration according to Ref. 2e). Then, **8** (or **9**) was dispersed in saturated Na_2SO_4 and several drops of THF to exchange all of the H^+. Washed till the filtrate was neutral then redispersed in $YbCl_3$ solution and stirred overnight. Loading of **10** (or **11**) was determined by titration (Table 1).[2e]

Table 2. Three-component coupling reaction of benzaldehyde, aninline and tributylallylstannane catalyzed by different Yb-resins[a]



20a **21a** **22a**

Entry	Yb–PS$_m$–Rf$_n$ (mol%)	Time (h)	Yield (%)[b]
1	Yb–PS$_1$–Rf$_2$ (2.0)	0.5	93
2	Yb–PS$_1$–Rf$_2$ (1.0)	1.0	91
3	Yb–PS$_1$–Rf$_2$ (0.5)	2.5	92
4	Yb–PS$_1$–Rf$_2$ (0.3)	3.0	93
5	Yb–PS$_1$–Rf$_2$ (0.1)	5.0	93
5	Yb–PS$_1$–Rf$_2$ (0.05)	8.0	84
6	Yb–PS$_1$–Rf$_6$ (0.1)	5.0	94
7	Yb–PS$_2$–Rf$_2$ (0.1)	5.0	93
7	Yb–PS$_2$–Rf$_6$ (0.1)	5.0	95
8	Yb–PS$_3$–Rf$_2$ (0.1)	5.0	89
9	Yb–PS$_3$–Rf$_2$ (0.1)	5.0	90
10	Yb–PS$_4$–Rf$_2$ (0.1)	5.0	88
11	Yb–PS$_4$–Rf$_6$ (0.1)	5.0	91

[a] Molar ratio: **20a**:**21a**: allyltribuylstannane: PhCOOH: Yb–PS$_m$–Rf$_n$(**10** or **11**)=1.0:1.0:1.1:1.0:0.1.
[b] Isolated yield.

2.2. One-pot multi-component reaction for synthesis of homoallylic amines and amides catalyzed by polymer-bound perfluoroalkyl sulfonic ytterbium

To evaluate the catalytic activity of the Yb-resins, we first conducted the three-component coupling reaction of benzaldehyde, aniline and tributylallylstannane in the presence of 1 equiv of benzoic acid (with respect to benzaldehyde) at room temperature using the different Yb-resins in CH_3CN. The results are shown in Table 1. It was found that the reaction underwent smoothly in the presence

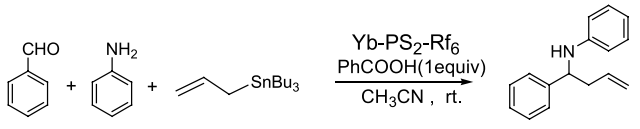
Table 1. Yb-resins prepared from different resins and ytterbium chloride

Entry	Yb resin (PS$_m$–Rf$_n$SO$_3$)$_3$Yb	Merrifield resin used	H^+ exchange capacity (**8** or **9**, IEC: mmol/g)[a]	Loading of Yb (mmol/g)[b]
1	**10a** (Yb–PS$_1$–Rf$_2$)	1% DVB, 0.95–1.05 mmol/g Cl^-, 100–200 mesh	0.69	0.21
2	**11a** (Yb–PS$_1$–Rf$_6$)	1% DVB, 0.95–1.05 mmol/g Cl^-, 100–200 mesh	0.46	0.13
3	**10b** (Yb–PS$_2$–Rf$_2$)	1% DVB, 2.8–3.0 mmol/g Cl^-, 200–300 mesh	1.22	0.38
4	**11b** (Yb–PS$_2$–Rf$_6$)	1% DVB, 2.8–3.0 mmol/g Cl^-, 200–300 mesh	0.92	0.28
5	**10c** (Yb–PS$_3$–Rf$_6$)	2% DVB, 0.98–1.02 mmol/g Cl^-, 100–200 mesh	0.67	0.21
6	**11c** (Yb–PS$_3$–Rf$_6$)	2% DVB, 0.98–1.02 mmol/g Cl^-, 100–200 mesh	0.57	0.16
7	**10d** (Yb–PS$_4$–Rf$_2$)	2% DVB, 2.8–3.0 mmol/g Cl^-, 200–400 mesh	1.20	0.36
8	**10d** (Yb–PS$_4$–Rf$_6$)	2% DVB, 2.8–3.0 mmol/g Cl^-, 200–400 mesh	0.86	0.26

[a] Determined by acid base titration.
[b] Determined by titration using EDTA (according to Ref. 2e).

of 0.1 mol% of Yb–PS_m–Rf_n in CH_3CN at room temperature. No big differences in the reaction yield were observed for these Yb-resins (Table 2). The Yb–PS_2–Rf_6 (**11b**) with a cross-linked degree of 1% and a longer perfluoroalkyl chain was the most effective to catalyze this reaction. Complete conversion of the substrates could be achieved in 5 h in CH_3CN. Further, we examined the reaction in other solvents listed in Table 3. Reactions in other organic solvents other than acetonitrile needed much longer time to complete. A slight decrease in the yield was observed in the solvents of DMF, CH_2Cl_2, and THF (Table 3, entries 1–3). Toluene, water or ethanol gave good yield. We presume that these Yb-resins have amphiphilic property. Moreover, a number of substrates were subjected to the optimized reaction conditions to examine scope and limitation of this reaction. Aromatic, aliphatic or α,β-unsaturated aldehydes were found to undergo highly efficient conversions in high yields. Substituted aromatic aldehydes and anilines with electron-withdrawing substituents reacted somewhat faster (Table 4, entries 2, 3, 6 and 12); cyclohexyl aldehyde reacted even faster (Table 2).

Table 3. Effect of solvents on the reaction catalyzed by Yb–PS_2–R_{f6} (**11b**)[a]



20a **21a** **22a**

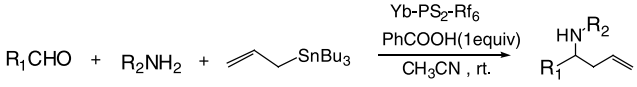
Entry	Solvent	Time (h)	Yield (%)[b]
1	DMF	18	65
2	THF	18	81
3	CH_2Cl_2	18	72
4	Tulene	18	92
5	EtOH	10	94
5	H_2O	8.0	90

[a] Molar ratio: **20a**:**21a**: allyltribuylstannane: PhCOOH: Yb–PS_2–Rf_6 (**11b**) = 1.0:1.0:1.1:1.0:0.1.
[b] Isolated yield.

The polymer bound catalysts could be recovered by simple filtration. For example, Yb–PS_2–R_{f6} (**11b**) was reused for 10 times in the reaction of benzaldehyde, aniline and tributylallylstannane in the presence of 1 equiv of benzoic acid in CH_3CN (Table 5). No lost of activity was observed for the recovered catalyst.

Then, we chose the one-pot four-component coupling reaction of benzaldehyde, aniline, tributylallylstannane and acrylic chloride in the presence of 1 equiv of benzoic acid (with respect to benzaldehyde) at room temperature using 0.1–1 mol% Yb–PS_2–R_{f6} (**11b**) Yb-resins in CH_3CN. Thus, the three-component coupling of benzaldehyde, aniline, tributylallylstannane is fast under the above reaction conditions. When the aldehyde disappeared, 1.2 equiv of acrylic chloride (with respect to aldehyde) was added. However, the homoallylic amine did not

Table 4. Three-component coupling reaction catalyzed by Yb–PS_2–Rf_6 (**11b**) in CH_3CN[a]

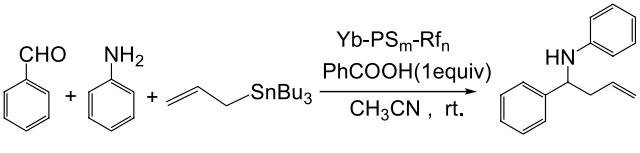


20 **21** **22**

Entry	R_1	R_2	Time (h)	Product	Yield (%)[b]
1	Ph	Ph	5.0	**22a**	95
2	*p*-F-Ph	Ph	3.5	**22b**	93
3	*p*-Cl-Ph	Ph	3.0	**22c**	90
4	*p*-Br-Ph	Ph	4.0	**22d**	92
5	*p*-MeO-Ph	Ph	6.5	**22e**	87
6	*p*-O_2N-Ph	Ph	3.0	**22f**	90
7	*m*-MeO-Ph	Ph	5.5	**22g**	90
8	2-Furyl	Ph	3.0	**22h**	86
9	*c*-Hexane	Ph	2.0	**22i**	85
10	*trans*-PhCH=CH	Ph	4.5	**22j**	89
11	Ph	*p*-F-Ph	4.0	**22k**	90
12	Ph	*p*-O_2N-Ph	3.0	**22l**	86
13	Ph	*p*-MeO-Ph	6.0	**22k**	95

[a] Molar ratio: **20**:**21** : allyltribuylstannane: PhCOOH: Yb–PS_2– Rf_6(**11b**) = 1.0:1.0:1.1:1.0:0.1.
[b] Isolated yield.

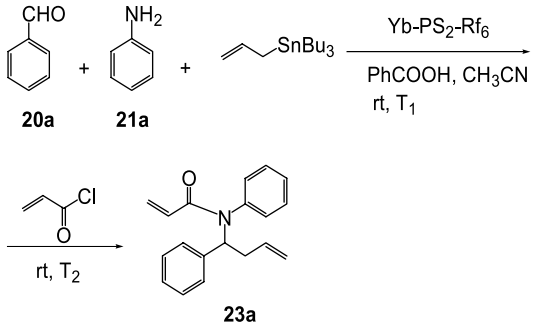
Table 5. Recycling of Yb–PS_2–R_{f6} (**11b**)



20a **21a** **22a**

	Run									
	1	2	3	4	5	6	7	8	9	10
Yield (%)	95	95	94	94	94	93	93	92	93	93

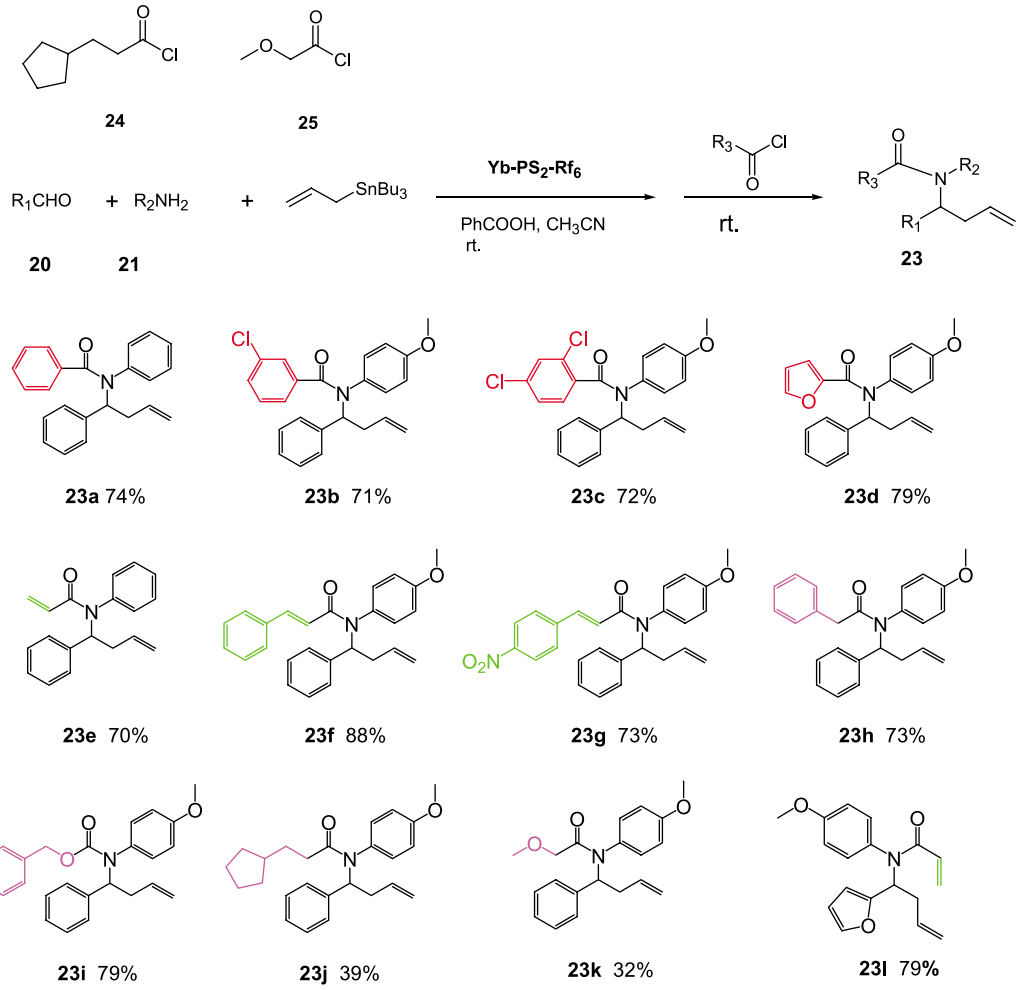
Table 6. One-pot four component tandem reaction for synthesis of acrylic amide



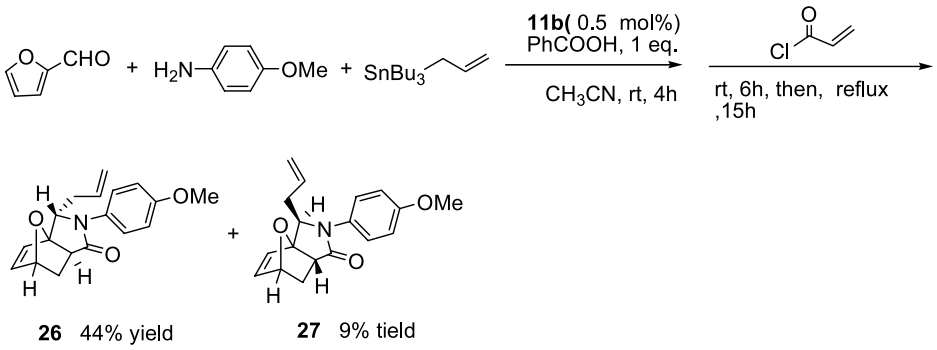
Entry	Yb–PS_2–Rf_6 (mmol%)	T_1 (h)	T_2 (h)	Acrylic chloride (equiv)	Yield (%)[a]
1	0.1	5	6	1.2	Trace
2	0.1	5	6	2.2	54
3	0.3	5	6	2.2	60
4	0.5	4	6	2.2	77
5	1.0	2	6	2.2	78
6	2.0	1	6	2.2	76

[a] Isolated yield.

disappear even after a long time. Only trace amide was isolated (Table 6, entry 1). Water generated from the imine in situ to destroy the acrylic chloride. So 2.2 equiv of acrylic chloride was used and the yield increased to 54% (Table 6, entry 2). With the increasing amount of catalyst used, the allylation reaction finished in shorter time as expected. Yield of the acylated product also improved a little. Further increase of the catalyst loading to 2 mol%



Scheme 4. Structures and yields of one-pot four-component reaction.



Scheme 5.

gave no better result than 0.5 mol% of catalyst used (Table 6, entries 4 and 6).

Having in hand the optimized conditions, a number of acid chlorides were subjected to examine the scope and limitation of the one-pot four-component reaction in the presence of 0.5 mol% of Yb–PS_2–R_{f6} (**11b**). In view of the synthetic usefulness of this reaction, *para*-methoxy aniline was used as an amine component. The reactions were carried out; the allylation step was a little slower when *para*-methoxy aniline was used instead of aniline. To ensure the complete conversion of reaction, acid chlorides were added after 4 h and the acylation reaction proceeded for 6 h. It turned out that aryl, heteroaryl or α,β-unsaturated aryl substituted acid chlorides produced the α-substituted amides in good yield, while aliphatic chlorides such as **24** and **25** reacted slowly to give the poor yield (Scheme 4).

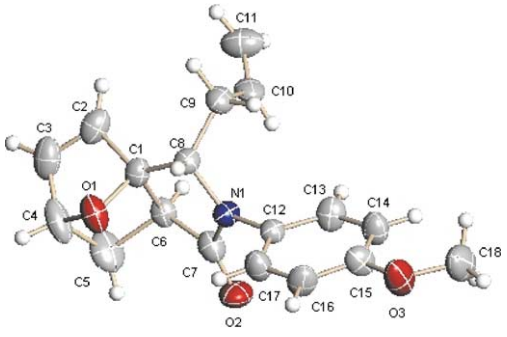


Figure 1. X-ray structure of compound **26**.

We finally investigated the product **23l** of four-component domino reaction in one operation for preparation of polycyclic compound by raising the reaction temperature through intramolecular Diels–Alder reactions to produce compounds **26** and **27** in moderate yield (Scheme 5). An X-ray diffraction analysis confirmed the structure and stereochemistry of **26** in Figure 1. It is well known that both Lewis acid and heating can promote Diels–Alder reactions. To investigate either or both are playing in this reaction, in the absence of Yb–PS_2–Rf_6 (**11b**), pure **23l** was subjected to Diels–Alder reaction. Without heating, no intramolecular Diels–Alder reaction took place (Scheme 5).

3. Conclusion

In summary, we have developed the synthesis of new polymer-bound polyfluoroalkyl super Brønsted acids and their ytterbium salts. In addition, the polymer-bound-Yb salts as Lewis acids catalyzed multicomponent reaction for the synthesis of homoallylic amines and amides. These heterogeneous catalysts are highly efficient, recyclable and reusable.

4. Experimental

4.1. General

Melting point was recorded on a METTLER FP62 capillary melting point apparatus and is uncorrected. The ^{1}H NMR (300 MHz), ^{13}C NMR (75 MHz) and ^{19}F NMR spectra (282 MHz) were recorded on a Bruker AMX-300 spectrometer. Chemical shifts are reported in δ-units (ppm) and J-values (Hz) with Me_4Si and CF_3COOH as the internal standard. IR spectra were recorded with a Nicolet AV-360 spectrometer by films and disks. Mass spectra (EI) were taken on an HP5898-A. Elemental analyses were performed on a Carlo-Erba 1106. Merrifield resins were received from Acros. Polyfluoroalkyl sulfonyl fluorides were obtained from SIOC. All starting materials were used as received unless otherwise stated. Column chromatography was performed on silica gel 300–400 mesh (Yantai Chemical Co. Ltd.).

4.1.1. Preparation of polystyrene-bound olefin 13 in quantitative yield according to the literature.[13] To a dry 500 mL three-necked flask, dry Merrifield resin PS_4 10.0 g (estimated as 30.0 mmol, 2% DVB, 200–400 mesh, 2.8–3.0 mmol/g Cl) was suspended in dry THF 100 mL under nitrogen. Ally magnesium chloride (0.80 M in Et_2O, 160 mL, 128 mmol) was slowly added at 0–25 °C in 1 h. The reaction mixture was stirred at 50 °C for 20 h. After cooling to room temperature, the mixture was quenched with 100 mL of THF: 1 N HCl, the mixture was filtered. The resin was washed successively with water, THF and MeOH and dried in vacuo to give the polymer-bound olefin 9.83 g (yield %: 98.3%) IR (cm^{-1}, KBr) 3079, 2920, 1941, 1639, 1601, 1493, 1451, 994, 758, 698. Elemental analysis: Cl < 0.1%.

4.1.2. Typical procedure for synthesis of polymer bound super acid: addition of perfluoroalkyl chain. To a 250 mL three-necked flask, dry allyl-PS_4 **13** 5.0 g (estimated as 15 mmol, Cl<0.5% by elemental analysis, derived from Merrifield resin 2% DVB, 200–400 mesh, 2.8–3.0 mmol/g Cl), BPO 725 mg (3 mmol, 20 mol%) and I $(CF_2)_6O(CF_2)_2SO_2F$ (**15**) 28.2 g (45 mmol, 3 equiv) were added in dry toluene 100 mL under dry nitrogen. The mixture was bulbed for 1 h and then stirred at 110–120 °C for 6 h. The off-white dispersion turned to dark brown within 2 h. Another portion of BPO (725 mg, 20 mol%) was added, and the reaction mixture was stirred at 120 °C for another 20 h. After cooling to room temperature, the mixture was filtered and washed successively with water, EtOAc and THF till the filtrate was colorless. Then filter cake was dispersed in THF standing overnight, wash by THF, dried (P_2O_5) at 30 °C till no loss of weight was observed. **17**(12.1 g, 85% conversion) of yellowish power was obtained. Almost complete consumption of the allylic C–C double bond was indicated by IR spectrum. IR (cm^{-1}, KBr) 3084, 2926, 1603, 1513, 1465, 1360, 1330, 1248, 1215, 1148, 1118, 991, 822, 699.

4.1.3. Reduction of iodide. To a 250 mL three-necked flask, dry **17** 10.3 g (estimated as 8.8 mmol), Bu_3SnH 23.6 g (31 mmol, 3.5 equiv) and AIBN 48 mg (0.3 mmol, 3 mol%) were added in dry THF 60 mL under nitrogen. The mixture was heated to reflux for 24 h; another portion of AIBN (48 mg, 0.3 mmol) was added under reflux for another 24 h. The reaction mixture was cooled to room temperature, the mixture was filtered and the polymer was washed successively with THF, THF/petroleum ether (1:1), EtOAc and petroleum ether. Then, it was dried at 30 °C till no loss of weight. 9.3 g of **19** was obtained as yellowish power. IR (cm^{-1}, KBr) 3084, 2926, 1602, 1512, 1494, 1466, 1360, 1215, 1147, 1021, 822, 699; ^{19}F NMR (282 MHz, $CDCl_3$) δ −121.5 (s, 1F), −4.0 to −10.0 (m, 4F), −35 to −55 (m, 12F). Elemental analysis: I<0.5 wt%, F: 28.6 wt% (loading=0.8 mmol/g).

4.1.4. Preparation of sulfonic acid. To a 250 mL flask, dry **19** 8.5 g (10.6 mmol, 0.8 mmol/g) was dispersed in 60 mL of THF. And 12 mL of 1 N NaOH aq was added. The mixture was stirred at room temperature for 4 h. Then, it was filtered and washed by water till neutral. Redispersed in 15 mL of HNO_3 (1 N), and stirred overnight. After filtration, it was washed again by water till neutral. 8.0 g of yellowish power was obtained. IR (cm^{-1}, KBr) 3650, 3027, 2928, 1513, 1454, 1215, 1146, 760, 699. Elemental analysis: F: 28.52 wt%, S, 2.76 wt% (loading=0.86 mmol/g).

4.1.5. Preparation of ytterbium salt. Sodium salt of **8** (2.0 g, S, 2.76 wt%) was dispersed in 10 mL of $YbCl_3$ soln (0.132 mmol/mL, titrated by EDTA) and H_2O 10 mL, and the mixture was stirred room temperature overnight. After filtration, the resin was washed by water and EtOH, respectively. The resin was dried overnight in vacuo at 65 °C in the presence of P_2O_5 to afford 2.0 g. The combined filtrated was diluted to 100, 5 mL of the diluted solution was taken out and titrated by 0.004 M EDTA for three times. 9.9 mL of EDTA soln. was consumed by average. Thus, loading of the polymer bound perfluoroalkyl sulfonic ytterbium was calculated to be 0.264 mmol/g.

$9.9\times0.004\times100/5=0.792$ mmol. $0.132\times10-0.792=0.528$ mmol. Loading of Yb=0.528/2=0.264 mmol/g

4.1.6. General procedure for three-component coupling reaction. Aldehyde (10.0 mmol), amine (10.0 mmol), benzoic acid (367 mg, 10.0 mmol) and $[PS_2\text{-}R_{f6}SO_3]_3Yb$ (**11b**) 2.8 mg (0.28 mmol/g, 0.1 mol%) and allyltributylstannane (1.2 mL, 3.3 mmol) were mixed in CH_3CN (15 mL), and it was stirred at room temperature. TLC monitored the reaction. After filtration, the filtrate was washed with saturated $NaHCO_3$ solution, extracted with Et_2O (3×10 mL). The combined extracts were dried over Na_2SO_4. After removal of solvent at reduced pressure, the residue was purified by flash chromatography to give product **22**.

N-(1-Phenylbut-3-enyl)aniline (**22a**).[18] Yellow oil; ^1H NMR (300 MHz, $CDCl_3$) δ 7.22–7.38 (m, 4H), 7.16–7.22 (m, 1H), 7.05 (t, J=7.5 Hz, 2H), 6.61 (t, J=7.4 Hz, 1H), 6.46 (d, J=7.5 Hz, 2H), 5.63–5.80 (m, 1H), 5.08–5.18 (m, 2H), 4.36 (dd, J=5.4, 8.1 Hz, 1H), 4.12 (s, 1H), 2.40–2.61 (m, 2H); IR (cm^{-1}, film) 3412, 3054, 2965, 1639, 1602, 1504, 1316, 748, 700.

N-[1-(4-Fluorophenylbut-3-enyl)] aniline (**22b**). Yellow oil; ^1H NMR (300 MHz, $CDCl_3$) δ 7.30 (dd, J=5.7, 8.7 Hz, 2H), 7.04 (t, J=7.5 Hz, 2H), 6.96 (t, J=9.0 Hz, 2H), 6.62 (t, J=6.9 Hz, 1H), 6.44 (d, J=7.8 Hz, 2H), 5.62–5.80 (m, 1H), 5.10–5.20 (m, 2H), 4.36 (dd, J=5.4, 7.8 Hz, 1H), 4.12 (br s, 1H), 2.38–2.60 (m, 2H); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 163.6, 160.4, 147.3, 139.4, 139.3, 134.5, 129.3, 128.0, 127.9, 118.7, 177.7, 115.7, 115.4, 113.7, 56.7, 43.5; ^{19}F NMR (282 MHz, $CDCl_3$) δ −38.3; IR (cm^{-1}, film) 3413, 3052, 3020, 2979, 1639, 1603, 1505, 1429, 1315, 1221, 1155, 882, 750, 692; MS (*m/z*, %): 241, (M^+, 3.36), 200 (100), 77 (17.14). Anal. Calcd for $C_{16}H_{16}FN$: C 79.64, H 6.68, F 7.87, N 5.80; found C 79.40, H 6.77, F 7.85, N 6.13.

N-[1-(4-Chlorophenylbut-3-enyl)]aniline (**22c**).[19] Yellow oil; ^1H NMR (300 MHz, $CDCl_3$) δ 7.28 (s, 4H), 7.06 (t, J=7.5 Hz, 2H), 6.64 (t, J=7.5 Hz, 1H), 6.42 (d, J=7.5 Hz, 2H), 5.64–5.80 (m, 1H), 5.12–5.20 (m, 2H), 4.36 (dd, J=5.7, 8.1 Hz, 1H), 4.14 (br s, 1H), 2.36–2.60 (m, 2H); IR (cm^{-1}, film) 3415, 3079, 3052, 2925, 1639, 1603, 1504, 1316, 1190, 921, 824, 750, 692.

N-[1-(4-Bromophenylbut-3-enyl)]aniline (**22d**).[20] Yellow oil; ^1H NMR (300 MHz, $CDCl_3$) δ 7.42 (d, J=8.4 Hz, 2H), 7.20 (d, J=8.4 Hz, 2H), 7.03 (dd, J=7.2, 7.8 Hz, 2H), 6.62 (t, J=7.2 Hz, 1H), 6.41 (d, J=7.8 Hz, 2H), 5.61–5.79 (m, 1H), 5.12–5.20 (m, 2H), 4.32 (dd, J=5.1, 7.8 Hz, 1H), 4.12 (br s, 1H), 2.37–2.60 (m, 2H); IR (cm^{-1}, film) 3412, 3077, 3019, 1639, 1603, 1504, 1316, 1009.

N-[1-(4-Methoxyphenylbut-3-enyl)]aniline (**22e**).[19] Yellow oil; ^1H NMR (300 MHz, $CDCl_3$) δ 7.22 (d, J=9.0 Hz, 2H), 7.04–7.08 (m, 2H), 6.80 (d, J=9.0 Hz, 2H), 6.62 (t, J=7.5 Hz, 1H), 6.48 (d, J=7.8 Hz, 2H), 5.66–5.82 (m, 1H), 5.08–5.20 (m, 2H), 4.32 (dd, J=5.7, 7.8 Hz, 1H), 4.10 (br s, 1H), 3.74 (s, 3H), 2.40–2.60 (m, 2H); IR (cm^{-1}, film) 3410, 3075, 1638, 1603, 1510, 1246, 1035, 750, 692.

N-[1-(4-Nitrophenylbut-3-enyl)] aniline (**22f**).[19] Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12 (d, J=8.7 Hz, 2H), 7.50 (d, J=8.7 Hz, 2H), 7.04 (dt, J=7.5, 8.7 Hz, 2H), 6.64 (t, J=7.5 Hz, 1H), 6.42 (d, J=8.7 Hz, 2H), 5.62–5.80 (m, 1H), 5.10–5.22 (m, 2H), 4.42 (dd, J=5.7, 7.5 Hz, 1H), 4.12 (br s, 1H), 2.40–2.62 (m, 2H); IR (cm^{-1}, film) 3411, 3078, 3020, 1640, 1603, 1521, 1345, 910, 751.

N-[1-(3-Methoxyphenylbut-3-enyl)] aniline (**22g**). Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 (t, J=7.8 Hz, 1H), 7.02–7.10 (m, 2H), 6.88–6.92 (m, 2H), 6.74 (dd, J=2.4, 8.1 Hz, 1H), 6.62 (t, J=7.5 Hz, 1H), 6.50 (d, J=7.5 Hz, 2H), 5.66–5.80 (m, 1H), 5.08–5.20 (m, 2H), 4.32 (dd, J=5.7, 7.8 Hz, 1H), 4.12 (br s, 1H), 3.70 (s, 3H), 2.40–2.60 (m, 2H); IR (cm^{-1}, film) 3409, 3076, 3004, 1639, 1602, 1504, 1263, 1155, 1047, 920, 750, 693.

N-[1-(2-Furyl)but-3-enyl]aniline (**22h**).[19] Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (s, 1H), 7.08–7.16 (m, 2H), 6.66 (t, J=7.5 Hz, 1H), 6.58 (d, J=8.7 Hz, 2H), 6.22 (s, 1H), 6.12 (s, 1H), 5.64–5.80 (m, 1H), 5.08–5.18 (m, 2H), 4.52 (t, J=6.0 Hz, 1H), 3.96 (br s, 1H), 3.72 (t, J=6.6 Hz, 2H); IR (cm^{-1}, film) 3410, 3077, 3021, 1640, 1602, 1504, 1314, 1150, 921, 748, 692.

N-(1-Cyclohexylbut-3-enyl)aniline (**22i**).[18] Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.12 (dt, J=7.2, 8.7 Hz, 2H), 6.62 (t, J=7.2 Hz, 1H), 6.56 (d, J=8.7 Hz, 2H), 5.72–5.84 (m, 1H), 5.00–5.08 (m, 2H), 3.50 (br s, 1H), 3.22 (dd, J=5.1, 12.9 Hz, 1H), 2.12–2.38 (m, 2H), 1.40–1.56 (m, 1H), 1.00–1.28 (m, 5H); IR (cm^{-1}, film) 3409, 3075, 3018, 2924, 1639, 1601, 1505, 1321, 992, 912, 747, 691.

N-{1-[(E)-2-Phenylethenyl]but-3-enyl}aniline (**22j**).[19] Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10–7.38 (m, 7H), 6.58–6.72 (m, 4H), 6.22 (dd, J=6.0, 16.5 Hz, 1H), 5.76–5.80 (m, 1H), 5.10–5.22 (m, 2H), 4.02 (dd, J=5.4, 8.4 Hz), 3.80 (br s, 1H), 2.38–2.52 (m, 2H); IR (cm^{-1}, film) 3409, 3054, 3018, 1639, 1601, 1502, 1316, 968, 749, 693.

4-Fluoro-N-(1-phenylbut-3-enyl)aniline (**22k**).[19] Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20–7.36 (m, 5H), 6.76 (t, J=8.7 Hz, 2H), 6.40 (m, 2H), 5.66–5.82 (m, 1H), 5.10–5.22 (m, 2H), 4.30 (dd, J=5.4, 8.7 Hz, 1H), 3.88 (br s, 1H), 2.40–2.62 (m, 2H); IR (cm^{-1}, film) 3415, 3077, 3029, 1639, 1601, 1513, 1221, 921, 819, 701.

4-Nitro-N-(1-phenylbut-3-enyl)aniline (**22l**).[18] Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (d, J=9.3 Hz, 2H), 7.36 (m, 5H), 6.45 (d, J=9.3 Hz, 2H), 5.64–5.80 (m, 1H), 5.12–5.40 (m, 2H), 4.50 (dd, J=5.4, 12.6 Hz, 1H), 2.50–2.70 (m, 2H); IR (cm^{-1}, film) 3371, 3080, 3029, 1641, 1601, 1525, 1504, 1321, 1112, 833, 754, 701.

4-Methoxyl-N-(1-phenylbut-3-enyl)aniline (**22m**).[21] Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16–7.46 (m, 5H), 6.76 (d, J=9.0 Hz, 2H), 6.54 (d, J=9.0 Hz, 2H), 5.76–5.92 (m, 1H), 5.18–5.30 (m, 2H), 4.40 (dd, J=3.6, 7.8 Hz, 1H), 4.00 (br s, 1H), 3.72 (s, 3H), 2.49–2.70 (m, 2H); IR (cm^{-1}, film) 3405, 3061, 3020, 1638, 1601, 1511, 1238, 1036, 818, 701.

4.1.7. General procedure of one-pot four-component reaction for synthesis of compound 23. Aldehyde (10 mmol), amine (10 mmol), benzoic acid (10 mmol), $[PS_2$-$R_{f6}SO_3]_3Yb$ (**11b**) 14 mg (0.5 mol%, 0.280 mmol/g) and allyltributylstannane (1.1 mmol) were added in CH_3CN 15 mL. The resulting mixture was stirred at room temperature till TLC inferred disappearance of the aldehyde within 4 h. Then acid chloride (2.2 mmol, 2.2 equiv) was added and stirred for another 6 h. The mixture was filtrated. The resin was washed by 20 mL of ethyl acetate. The combined organic layer was washed by saturated $NaHCO_3$ solution (2×10 mL), H_2O (10 mL), then dried over Na_2SO_4. Flash chromatography (ethyl acetate: hexane = 1:10–1:4) gave the product **23**.

N-Phenyl-N-(1-phenylbut-3-enyl) benzamide (**23a**). Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22–7.36 (m, 10H), 6.32–6.42 (m, 2H), 5.72–5.94 (m, 2H), 5.43 (m, 1H), 5.08–5.12 (m, 2H), 2.56–2.76 (m, 2H); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 165.5, 139.3, 137.9, 134.8, 130.6, 129.0, 128.7, 128.2, 128.0, 127.6, 117.4, 56.8, 35.1; IR (cm^{-1}, film) 3063, 3031, 2929, 1656, 1616, 1594, 1493, 1452, 1405, 1321, 1255, 702; MS (*m*/*z*, %): 277 (M^+, 3.86), 236 (55.52), 182 (100), 77 (28.73). Anal. Calcd for $C_{19}H_{19}NO$: C 82.28, H 6.90, N 5.05; found C 82.04, H 7.12, N 4.96.

3-Chloro-N-(4-methoxyphenyl)-N-(1-phenylbut-3-enyl) benzamide (**23b**). Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20–7.36 (m, 6H), 7.08 (d, J=4.2 Hz, 1H), 7.00 (d, J=4.2 Hz, 1H), 6.46–6.60 (m, 4H), 6.30 (t, J=7.8 Hz, 1H), 5.82–6.00 (m, 1H), 5.10–5.24 (m, 2H), 3.64 (s, 3H), 2.58–2.74 (m, 2H); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 169.8, 158.5, 139.4, 138.7, 134.9, 131.5, 129.0, 128.9, 128.7, 128.2, 128.1, 128.0, 127.7, 126.0, 117.6, 113.7, 113.4, 55.1, 35.0; IR (cm^{-1}, film) 3064, 3005, 2934, 1643, 1510, 1333, 1249, 1035, 734, 700; MS (*m*/*z*, %): 391 (M^+, 32.63), 350 (33.18), 261 (34.52), 139 (100), 77 (53.96). Anal. Calcd for $C_{24}H_{21}NO_2Cl$: C 73.56, H 5.66, N 3.57; found C 74.33, H 5.96, N 3.55.

3,5-Dichloro-N-(4-methoxyphenyl)-N-(1-phenylbut-3-enyl) benzamide (**23c**). Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (s, 1H), 7.20–7.32 (m, 5H), 7.06 (d, J=8.4 Hz, 1H), 6.94 (d, J=8.4 Hz, 1H), 6.60 (br s, 1H), 6.30 (t, J=7.2 Hz, 1H), 5.84–6.00 (m, 1H), 5.12–5.23 (m, 2H), 3.64 (s, 3H), 2.60–2.82 (m, 2H); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 168.8, 158.8, 139.3, 137.0, 134.9, 133.1, 132.0, 131.6, 131.3, 130.3, 129.6, 128.8, 128.3, 127.9, 127.4, 117.7, 113.7, 57.9, 55.3, 35.1; IR (cm^{-1}, film) 3065, 2934, 1634, 1510, 1454, 1389, 1333, 1296, 1250, 1033, 834, 788, 700; MS (*m*/*z*, %): 425 (M^+, 6.26), 384 (70.34), 295 (49.16), 173 (100). Anal. Calcd for $C_{24}H_{20}NO_2Cl_2$: C 67.61, H 4.96, N 3.29, Cl, 16.63; found C 67.75, H 5.09, N 3.05, 16.86.

N-(4-Methoxyphenyl)-N-(1-phenylbut-3-enyl) furan-2-carboxamide (**23d**). Colorless solid; mp 110 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (s, 1H), 7.12–7.30 (m, 5H), 6.50–6.98 (m, 4H), 6.42 (t, J=7.9 Hz, 1H), 6.14 (s, 1H), 5.70–5.94 (m, 1H), 5.08–5.36 (m, 3H), 3.76 (s, 3H), 2.56–2.78 (m, 2H); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ159.5, 159.4, 147.1, 144.4, 139.2, 135.0, 132.0, 130.7, 129.0, 128.1, 127.7, 117.6, 116.0, 113.9, 110.9, 57.2, 55.4, 34.8; IR (cm^{-1}, film) 3063, 3032, 1638, 1510, 1470; MS (*m*/*z*, %): 347 (M^+, 10.35), 306 (70.44), 237 (10.86), 131 (14.76), 95 (100).

Anal. Calcd for $C_{22}H_{21}NO_3$: C 76.06, H 6.09, N 4.03; found C 75.95, H 6.05, N 3.80.

N-Phenyl-N-(1-phenylbut-3-enyl) acryl amide (**23e**). Yellowish oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (s, 5H), 7.18–7.22 (m, 2H), 6.98–7.16 (m, 6H), 6.60 (m, 1H), 6.38 (m, 1H), 5.86–6.04 (m, 1H), 5.14–5.26 (m, 2H), 2.64–2.86 (m, 2H); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 171.0, 139.7, 139.6, 136.8, 135.0, 130.4, 128.9, 128.6, 128.2, 128.1, 127.6, 127.4, 127.2, 117.5, 57.7, 35.1; IR (cm^{-1}, film) 3062, 3032, 2929, 1719, 1693, 1644, 1593, 1493, 1451, 1381, 1333, 1286, 1231, 1026, 919, 699; MS (*m/z*, %): 327 (M^+, 1.41), 286 (32.28), 105 (100), 77 (46.02). Anal. Calcd for $C_{23}H_{21}NO$: C 84.37, H 6.46, N 4.28; found C 84.51, H 6.79, N 4.52.

N-(4-Methoxyphenyl)-N-(1-phenylbut-3-enyl) cinnamamide (**23f**). Yellowish oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (s, 5H), 7.18–7.22 (m, 2H), 6.98–7.16 (m, 6H), 6.60 (m, 1H), 6.38 (t, J=7.2 Hz, 1H), 5.86–6.04 (m, 1H), 5.14–5.26 (m, 2H), 2.64–2.86 (m, 2H); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 171.0, 139.7, 139.6, 136.8, 135.0, 130.4, 128.9, 128.6, 128.2, 128.1, 127.6, 127.4, 127.2, 117.5, 57.7, 35.1; IR (cm^{-1}, film) 3062, 3032, 2929, 1719, 1693, 1644, 1593, 1493, 1451, 1381, 1333, 1286, 1231, 1026, 919, 699; MS (*m/z*, %): 327 (M^+, 1.41), 286 (32.28), 105 (100), 77 (46.02). Anal. Calcd for $C_{23}H_{21}NO$: C 84.37, H 6.46, N 4.28; found C 84.51, H 6.79, N 4.52.

(E)-N-(4-Methoxyphenyl)-3-(4-nitrophenyl)-N-(1-phenylbut-3-enyl) acryl amide (**23g**). Colorless solid; mp143.2 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12 (d, J=8.7 Hz, 2H), 7.74 (d, J=15.6 Hz, 1H), 7.46 (d, J=9.3 Hz, 1H), 7.12–7.34 (m, 5H), 6.90 (m, 1H), 6.62 (m, 1H), 6.34 (t, J=7.5 Hz, 1H), 6.20 (d, J=15.6 Hz, 1H), 6.16 (m, 1H), 5.76–5.84 (m, 1H), 5.06–5.24 (m, 2H), 3.70 (s, 3H, OMe), 2.54–2.66 (m, 2H); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 165.3, 159.3, 147.8, 141.4, 139.2, 139.0, 134.8, 130.0, 128.7, 128.2, 128.1, 127.7, 123.8, 117.5, 114.0, 56.9, 55.3, 35.0; IR (cm^{-1}, film) 3076, 2933, 2246, 1651, 1621, 1596, 1510, 1342, 1294, 1249, 1108, 913, 841, 732, 701; MS (*m/z*, %): 428 (M^+, 11.20), 387 (40.10), 298 (10.86), 216 (100), 176 (30.58), 123 (34.44), 77 (9.30). Anal. Calcd for $C_{26}H_{24}N_2O_4$: C 72.90, H 5.61, N 6.54; found C 72.97, H 5.66, N 6.52.

N-(4-Methoxyphenyl)-2-phenyl-N-(1-phenylbut-3-enyl) acetamide (**23h**). Yellowish oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.00–7.26 (m, 11H), 6.82 (d, J=7.5 Hz, 1H), 6.58 (d, J=8.1 Hz, 1H), 6.24 (t, J=7.8 Hz, 1H), 5.96 (d, J=8.1 Hz, 1H), 5.76–5.92 (m, 1H), 5.04–5.20 (m, 2H) 3.78 (s, 3H), 3.34 (s, 2H), 2.50–2.64 (m, 2H); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 172.8, 160.6, 140.9, 137.0, 136.5, 132.1, 130.5, 130.2, 129.6, 129.5, 129.0, 127.8, 118.8, 115.2, 57.9, 56.8, 43.3, 36.5; IR (cm^{-1}, film) 3064, 3030, 2928, 1649, 1510, 1249, 700; MS (*m/z*, %): 371 (M^+, 10.64), 330 (42.19), 212 (100), 91 (30.92). Anal. Calcd for $C_{25}H_{25}NO_2$: C 80.83, H 6.78, N 3.77; found C 80.60, H 6.72, N 3.64.

N-Benzyl-N-4-methoxyphenyl (1-phenylbut-3-enyl) carbamate (**23i**). Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.02–7.56 (m, 10H), 6.58–6.76 (m, 4H), 5.68–5.84 (m, 2H), 5.02–5.08 (m, 4H), 3.70 (s, 3H), 2.50–2.74 (m, 2H); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 158.7, 156.3, 140.0, 135.1, 131.1, 128.9, 128.6, 128.3, 128.2, 127.7, 127.1, 117.5, 113.6, 67.0, 60.0, 55.3, 35.6; IR (cm^{-1}, film) 3064, 3032, 2955, 1698, 1643, 1512, 1454, 1397, 1295, 1248, 1041, 700; MS (*m/z*, %): 387 (M^+, 8.80), 306 (50.84), 131 (14.22), 91 (100). Anal. Calcd for $C_{25}H_{25}NO_3$: C 77.52, H 6.46, N 3.62; found C 77.37, H 6.50, N 3.44.

3-Cyclopentyl-N-(4-methoxyphenyl)-N-(1-phenylbut-3-enyl) propanamide (**23j**). Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.04–7.26 (m, 6H), 6.90 (m, 1H), 6.60 (m, 1H), 6.36 (t, J=8.1 Hz, 1H), 6.02 (m, 1H), 5.76–5.84 (m, 1H), 5.06–5.20 (m, 2H), 3.78 (s, 3H), 2.46–2.64 (m, 2H), 1.78–2.00 (m, 2H), 1.34–1.64 (m, 9H), 0.78–0.99 (m, 2H); MS (*m/z*, %): 377 (M^+, 8.39), 336 (20.70), 212 (100), 131 (7.46), 91 (6.13). Anal. Calcd for $C_{25}H_{31}NO_2$: C 79.54, H 8.38, N 3.71; found C 79.39, H 8.42, N 3.63.

2-Methoxy-N-(4-methoxyphenyl)-N-(1-phenylbut-3-enyl) acetamide (**23k**). Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.08–7.24 (m, 6H), 6.86 (m, 1H), 6.58 (m, 1H), 6.24 (t, J=7.8 Hz, 1H), 6.00 (m, 1H), 5.76–5.82 (m, 1H), 5.04–5.20 (m, 2H), 3.78 (s, 3H), 3.58 (q, J=15.0 Hz, 2H), 3.30 (s, 3H), 2.48–2.54 (m, 2H); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 169.3, 159.5, 139.2, 135.1, 128.9, 128.8, 128.1, 127.7, 117.5, 114.1, 70.9, 59.1, 56.4, 55.4, 34.8; IR (cm^{-1}, film) 3064, 3032, 2931, 2838, 1670, 1510, 1415, 1394, 1251, 1130, 1031, 702; MS (*m/z*, %): 325 (M^+, 14.30), 284 (100), 256 (56.79), 195 (53.09), 131 (45.91). Anal. Calcd for $C_{20}H_{23}NO_3$: C 73.28, H 7.12, N 4.30 O 14.75; found C 73.88, H 7.57, N 4.16.

N-(1-(Furan-2-yl) but-3-enyl)-N-(4-methoxyphenyl) acryl amide (**23l**). White solid; mp 78 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.08 (s, 1H), 7.06 (m, 1H), 6.64–6.88 (m, 2H), 6.20–6.40 (m, 4H), 5.68–5.82 (m, 1H), 5.10–5.18 (m, 2H), 4.46 (t, J=6.3 Hz, 1H), 3.72 (s, 3H), 2.62 (m, 2H); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 168.6, 162.0, 155.6, 144.4, 137.0, 133.2, 131.6, 130.5, 120.4, 112.9, 111.5, 58.1, 54.2, 37.2; IR (cm^{-1}, film) 3077 2933, 2246, 1652 1620 1596 1500; MS (*m/z*, %) 297, (M^+, 31.87), 256 (69.61), 202 (92.10), 177 (100), 91 (24.54), 7728.27). Anal. Calcd for $C_{18}H_{19}NO_3$: C 72.73, H 6.40, N 4.71; found C 72.53, H 6.56, N 4.56.

4.1.8. Procedure of the one-pot four-component intramolecular Diels–Alder reaction of 23l. In a 25 mL three-necked flask, furfuraldehyde 166 mL (2 mmol), *p*-methyoxyaniline 246 mg (2 mmol), benzoic acid 244 mg (2 mmol), $[PS_2–R_{f6}SO_3]_3Yb$(**11b**) 28 mg (0.5 mol%, 0.28 mmol/g) and allyltributylstannane 0.68 mL (2.2 mmol) were dissolved in 4 mL of CH_3CN. The mixture was stirred at room temperature for 4 h. 0.36 mL (4.4 mmol, 2.2 equiv) of acrylic chloride was then added and reacted at room temperature for another 6 h. The mixture was heated to reflux for 15 h. Then, the mixture was cooled to room temperature. After filtration, the polymer was washed by 20 mL of ethyl acetate. The combined organic layer was washed by saturated $NaHCO_3$ solution (2×10 mL), H_2O (10 mL), then dried over Na_2SO_4. Flash chromatography (ethyl acetate: hexane=1:1) gave 259 mg of compound **26** and 58 mg of compound **27** (4.5:1, total yield 53%), respectively.

2-Allyl-3-(4-methyoxyphenyl)-4-oxo-10-oxa-3-azo-tricyclo [5.2.1.0^{1,5}] dec-8-en-4-one (**26**). White solid; mp 82 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, J=9.0 Hz, 2H), 6.96 (d, J=9.0 Hz, 2H), 6.58 (d, J=5.9 Hz, 1H), 6.42 (dd, J=1.7, 5.9 Hz), 5.76–5.84 (m, 1H), 5.14–5.24 (m, 2H), 5.06 (dd, J=1.7, 4.5 Hz, 1H), 4.42 (t, J=5.2 Hz, 1H), 3.80 (s, 3H), 2.58–2.66 (m, 3H), 2.25 (ddd, J=3.6, 4.5, 11.8 Hz, 1H), 1.62 (dd, J=8.9, 11.8 Hz, 1H); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 173.7, 157.8, 137.4, 132.3, 132.1, 130.5, 126.1, 119.4, 114.5, 91.7, 78.6, 62.1, 55.5, 47.4, 34.2, 28.9; IR (cm^{-1}, film) 3077, 3002, 2952, 2837, 2244, 1697, 1640, 1513, 1247, 1035, 918, 831, 731, 699; MS (*m*/*z*, %): 297 (M^+, 37.59), 256 (21.44), 202 (100), 177 (16.16), 91 (7.19), 77 (12.67). Anal. Calcd for $C_{18}H_{19}NO_3$: C 72.73, H 6.40, N 4.71; found C 72.72, H 6.34, N 4.50. Crystal system, space group: monoclinic, $P2(1)/c$. Unit cell dimensions: a=6.4883(5) Å, b=31.818(3) Å, c=14.7894(12) Å, α=90°, β=94.0950(10)°, γ=90°; volume: 3045.4(4) Å^3; Z=8; calculated density: 1.297 mg/m^3; absorption coefficient: 0.088 mm^{-1}; F(000): 1264; crystal size: 0.478×0.453×0.412 mm^3; theta range for data collection: 1.38–27.00°; completeness to θ=27.00, 99.9%; data/restraints/parameters: 11191/23/925; goodness-of-fit on F^2: 0.930; final R indices[$I>2\sigma(I)$]: $R1$=0.0552, $wR2$=0.1251; R indices (all data): $R1$=0.0816, $wR2$=0.1368; absolute structure parameter: −0.7(14); largest diff. peak and hole: 0.184 and −0.246 e Å^3.

Compound **27**. White solid; mp 100 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 (d, J=9.0 Hz, 2H), 6.96 (d, J=9.0 Hz, 2H), 6.42 (dd, J=1.8, 6.0 Hz, 1H), 6.38 (dt, J=1.5, 5.7 Hz), 5.66–5.82 (m, 1H), 5.00–5.16 (m, 3H), 4.56 (dt, J=6.6, 8.4 Hz, 1H), 3.80 (s, 3H), 2.60 (dd, J=1.8, 8.7 Hz, 1H), 2.24–2.38 (m, 3H), 1.62 (dd, J=8.7, 11.7 Hz, 1H); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 173.8, 158.1, 135.6, 134.2, 132.9, 129.6, 127.2.1, 118.3, 114.3, 90.6, 78.5, 60.4, 55.4, 47.6, 32.9, 28.6; IR (cm^{-1}, film) 3077, 3002, 2953, 2837, 2243, 1697, 1642, 1513, 1364, 1247, 1036, 918, 835, 732; MS (*m*/*z*, %): 297 (M^+, 44.30), 256 (24.16), 202 (100), 77 (14.87). Anal. Calcd for $C_{18}H_{19}NO_3$: C 72.73, H 6.40, N 4.71; found C 73.03, H 6.58, N 4.56.

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Polystyrene-supported triphenylarsines: useful ligands in palladium-catalyzed aryl halide homocoupling reactions and a catalyst for alkene epoxidation using hydrogen peroxide

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Abstract—The utility of both soluble (non-cross-linked) and insoluble (cross-linked) polystyrene-supported triphenylarsine reagents were examined. These reagents were prepared by standard radical polymerization methodology and used in palladium-catalyzed homocoupling reactions of aryl halides. The insoluble reagent was also used as a catalyst precursor in heterogeneous alkene epoxidation reactions in which aqueous hydrogen peroxide was the stoichiometric oxidant. For the aryl halide homocoupling reactions, both reagents worked well and afforded similar results. Unhindered aryl iodides afforded the best yields in the shortest reaction times compared to aryl bromides. The epoxidation reactions of unfunctionalized alkenes were not very efficient. This was probably due to the hydrophobicity of the polystyrene matrix, which did not swell in the reaction medium. Thus, since a microporous, gel-type polystyrene matrix was used, the majority of the arsine groups were inaccessible to the reaction components and therefore incapable of participating in catalysis.

1. Introduction

The use of polymer-supported reagents and catalysts in polymer-assisted solution-phase organic synthesis has become commonplace since they can reduce product purification to simple filtration and concentration operations and are potentially easily recycled.[1] A large variety of such reagents and catalysts have been reported that utilize both insoluble[2] and soluble[3] polymers as their carriers and new ones are continually being developed in order to broaden their utility and increase their efficiency. We have a long-standing interest in the development of both soluble and insoluble polymer-supported amine,[4] fluorinated ketone,[5] nitroxyl radical,[6] phosphine,[7] sulfide,[8] sulfoxide,[9] and triflimide[10] reagents for use in solution-phase organic synthesis, especially in systems that simultaneously use multiple polymers.[4,6,7c] Herein, we report an update on the further utilization of our previously reported polystyrene-supported triphenylarsine reagents that were previously found to be useful as ligands for palladium in a variety of Suzuki–Miyaura coupling reactions.[11]

Triphenylarsine is an important reagent in organic synthesis that is complimentary to much more widely used triphenylphosphine.[12] It has been found to be useful as a ligand for palladium in a variety of palladium catalyzed cross-coupling reactions,[13] including the Suzuki–Miyaura coupling[14] of boronic acids with aryl and vinyl halides.[15] Furthermore, triphenylarsine is useful for the generation of arsonium ylides, which are more nucleophilic than the corresponding phosphonium ylides.[16] Due to the toxicity of organoarsenic compounds in general, they are prime candidates for immobilization onto a polymer support so that they can be easily recovered and reused. Indeed, early reports demonstrated that an arsenic acid functionalized polystyrene resin was useful in Baeyer–Villiger oxidation[17] and alkene epoxidation[18] reactions using aqueous hydrogen peroxide under conditions such that the polymers could be recovered and reused. Subsequently, a polystyrene-supported triphenylarsine oxide[19] was found to be an effective reagent for the preparation of carbodiimides.[20] Finally, prior to our recent report, the only other description of a supported arsine showed that a silica-supported alkyldiarylarsine was a good ligand for palladium in Heck coupling reactions.[21] In this current report, we describe the application of our soluble and insoluble polystyrene-supported reagents in palladium-catalyzed homocoupling reactions of aryl halides and in organocatalytic alkene epoxidation reactions using aqueous H_2O_2.

Keywords: Triphenylarsine reagents; Homocoupling; Suzuki–Miyaura coupling; Hydrogen peroxide; Epoxidation.
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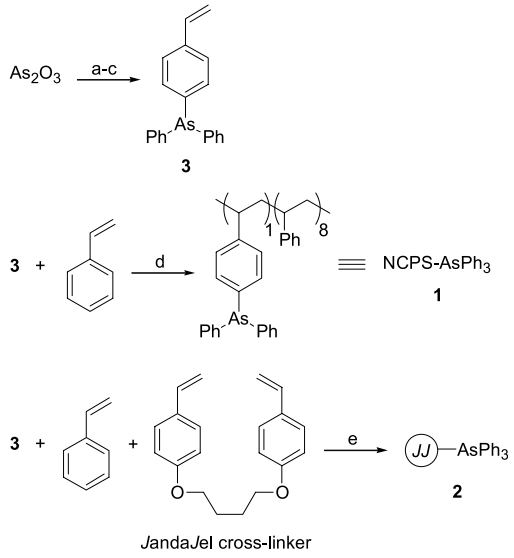
2. Results and discussion

The soluble, non-cross-linked polystyrene reagent, NCPS–$AsPh_3$ (**1**), and the insoluble, cross-linked polystyrene reagent, *J*anda*J*el-$AsPh_3$ (*JJ*-$AsPh_3$, **2**),[22,23] were prepared as previously reported using functional monomer **3** for incorporation of the arsine groups (Scheme 1).[11] The *J*anda*J*el platform was chosen over other cross-linked polymers because it has been shown by EPR,[24] fluorescence,[25] and NMR[26] spectroscopy to provide better performance in terms of reagent/substrate accessibility to interior sites of the resin in solvents that it swells well in. Furthermore, it has been used successfully as a synthesis platform in a variety of synthetic applications[27] and as a support for chiral catalysts.[28–31]

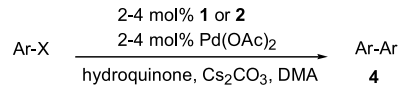


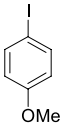
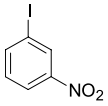
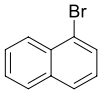
Scheme 1. Reaction conditions: (a) PhMgBr, THF, 0 °C to rt; (b) HCl; (c) *p*-BrMg–$C_6H_4CH{=}CH_2$, THF, 0 °C to rt; (d) AIBN, PhMe, 85 °C; (e) PhCl, H_2O, acacia gum, NaCl, AIBN, 85 °C.

Considering our previous success in using both **1** and **2** in Suzuki–Miyuara coupling reactions, we wanted to examine them in another palladium-catalyzed process. Since symmetrical biaryl compounds can be used to prepare useful chiral phosphine ligands,[32] and new methods for the homocoupling of aromatic compounds are continuously being developed,[33] we chose to study the reaction system reported by Rawal and co-workers in which they used a sterically crowded triarylarsine, tri-*o*-tolylarsine, as a ligand for palladium in the homocoupling of aryl bromides and iodides.[34] Thus, various aryl iodides and aryl bromides were examined in the homocoupling reactions using reagents **1** and **2** as ligands for palladium (Table 1).

The reactions were performed according to the published procedure,[34] using $Pd(OAc)_2$, ligand, hydroquinone, and Cs_2CO_3 in *N*,*N*-dimethylacetamide (DMA) at elevated temperature. In general aryl iodides reacted more readily than aryl bromides and aryl halides substituted at *meta*- or *para*-positions afforded good to excellent yields of the desired symmetrical biaryl compounds **4a–c** (Table 1, entries 1–4). When 1-bromonapthalene was the substrate,

Table 1. Homocoupling reactions of aryl halides



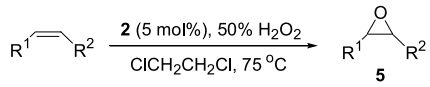
Entry	Ar-X	Product	Time (h)[a]	Yield (%)	
				1	**2**
1[b]		**4a**	16	90	88
2[c]		**4a**	40	92	95
3[b]		**4b**	16	80	92
4[b]		**4c**	16	60	74
5[c]		**4d**	60	65	40
6[c]		**4e**	60	21	11

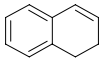
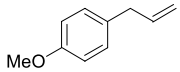
[a] Time for reactions using both **1** and **2**.
[b] Two mole percentage of $Pd(OAc)_2$, 2 mol% **1** or **2**, 0.5 equiv hydroquinone, 1.0 equiv Cs_2CO_3, 0.4 M, 75 °C.
[c] Four mole percentage of $Pd(OAc)_2$, 4 mol% **1** or **2**, 0.5 equiv hydroquinone, 1.0 equiv Cs_2CO_3, 1.0 M, 100 °C.

only moderate yields of **4d** were obtained after prolonged reaction times (Table 1, entry 5) and 2-bromotoluene afforded poor yield **4e** with both **1** and **2** (Table 1, entry 6). It was found that the product yields obtained from the reactions involving **2** were slightly higher than those with **1** (Table 1, entries 2–4). This was most likely due to the easier removal of **2** from the reaction mixture (filtration) compared to **1** (precipitation followed by filtration). On the other hand, in the cases where low yield was observed, **1** afforded higher yields than **2** (Table 1, entries 5–6), most likely due to its homogeneity.

To investigate other application of reagent **2**, a range of alkenes were studied in epoxidation reactions using H_2O_2 catalyzed by the oxide of **2** (Table 2). It has been previously shown that treatment of triphenylarsine with H_2O_2 affords triphenylarsine oxide, which is a good epoxidation reagent.[35] Thus, by using an excess of H_2O_2, triphenylarsine oxide can function as a catalyst. For the epoxidation reactions with **2**, 1,2-dichloroethane was chosen as solvent since appeared to swell **2** to a large degree and a control reaction in which **2** was omitted afforded only a small amount of the desired product **5a** (Table 2, entry 1). As seen from the Table 2, entry 2, addition of **2** greatly improved the conversion of cyclooctene to **5a**. While good yield can be

Table 2. Epoxide reactions of alkenes



Entry	Alkene	Time (h)	Product	Yield (%)[a]
1[b]		8	**5a**	12[c]
2		8	**5a**	85 (98[c])
3		12	**5b**	80 (92[c])
4		24	**5c**	38
5		28	**5d**	47
6		30	**5e**	28

[a] Isolated yield.
[b] No catalyst **2**.
[c] Determined by GC.

obtained using **2**, it is a sluggish catalyst precursor compared to other homogeneous, electron-rich arsines.[35] Regardless, good isolated yield of **5b** could also be obtained from the epoxidation of cycloheptene (Table 2, entry 3). Unfortunately the epoxidation of substituted styrenes and a primary alkene afforded poor isolated yields of the desired products (Table 2, entries 4–6). In these reactions, the conversion rate of the alkene was slower than before and the products seemed to be moderately unstable to the reaction conditions since several unidentified, more highly polar products were observed in addition to the desired product.

3. Conclusions

In summary, we extended the use of our previously reported soluble and insoluble polystyrene-supported triphenylarsine reagents, **1** and **2**, respectively, to the homocoupling of aryl halides to form symmetrical biaryl compounds and in epoxidation reactions using H_2O_2 as the stoichiometric oxidant. It was found that both reagents proved to be good ligands for Pd and the resulting complex showed good catalytic activity in the homocoupling reaction.

The performance of **2** as a catalyst precursor for epoxidation reactions was not very efficient. This could stem from the fact that polystyrene is hydrophobic and thus the H_2O_2 has a difficult time accessing the arsine groups attached to our gel-type, microporous polymer. Thus, only a small portion of the potential catalytic groups are actually active. Due to this limitation of **2**, we are currently examining the immobilization of electron-rich arsine groups to insoluble, hydrophilic and macroporous polymers with the aim of identifying better heterogeneous arsine catalysts for these expodiation reactions.

4. Experimental

4.1. General

All reagents were obtained from the Aldrich, Lancaster or Acros chemical companies and were used without further purification. All moisture sensitive reactions were carried out in dried glassware under a N_2 atmosphere. Merck silica gel 60 (230–400 mesh) was used for chromatography. Thin-layer chromatography analysis was performed using glass plates coated with silica gel 60 F_{254}. Gas chromatographic analyses were performed using a Thermo Finnigan Focus chromatograph equipped with an RTX-5 column. NMR spectra were recorded using either a Bruker DRX 300 or an AV400 spectrometer. Chemical shift data is expressed in ppm with reference to TMS. MS data was recorded on a Finnigan MAT 96 mass spectrometer.

4.2. General procedure for biaryl synthesis using 1

To a mixture of aryl halide (1.5 mmol), hydroquinone (0.083 g, 0.75 mmol), and Cs_2CO_3 (0.49 g, 1.5 mmol) was added a pre-stirred DMA solution (3.8 or 1.5 mL) of $Pd(OAc)_2$ (0.007 g, 0.03 mmol or 0.013 g, 0.06 mmol) and **1** (0.038 g, 0.03 mmol or 0.076 g, 0.06 mmol, loading = 0.8 $AsPh_3$ mmol/g) in a 8 mL vial. The reaction mixture darkened immediately upon addition of the catalyst solution to the solid reagents. The vial was placed in a shaking reaction block and heated at 75 or 100 °C for the indicated time. The reaction mixture was cooled to room temperature, quenched with 1 N HCl (20 mL), diluted with water (20 mL), and extracted with EtOAc (2×40 mL). The organic layers were combined and washed sequentially with 10% NaOH (3×30 mL), and brine (2×30 mL), dried over $MgSO_4$, concentrated under reduced pressure, and purified by flash column chromatography on silica gel (100% hexane) to afford the desired product.

4.3. General procedure for biaryl synthesis using 2

To a mixture of aryl halide (1.5 mmol), hydroquinone (0.083 g, 0.8 mmol), and Cs_2CO_3 (0.49 g, 1.5 mmol) was added a pre-stirred DMA solution (3.8 or 1.5 mL) of $Pd(OAc)_2$ (0.007 g, 0.03 mmol or 0.013 g, 0.06 mmol) and **2** (0.021 g, 0.03 mmol or 0.042 g, 0.06 mmol, loading = 1.44 $AsPh_3$ mmol/g) in a 8 mL vial. The reaction mixture darkened immediately upon addition of the catalyst solution to the solid reagents. The vial was placed in a shaking reaction block and heated at 75 or 100 °C for the indicated time. The reaction mixture was cooled to room temperature and the polymer was filtrated off and washed with water and EtOAc. The filtrate was extracted with EtOAc (2×40 mL). The organic layers were combined and washed sequentially with 1 N HCl (3×30 mL), 10% NaOH (3×30 mL), and brine (2×30 mL), dried over $MgSO_4$, concentrated under reduced pressure, and purified by flash column chromatography on silica gel (100% hexane) to afford the desired product.

4.3.1. Characterization data for biphenyl (4a). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (m, 2H), 7.44 (d, J = 6.3 Hz, 4H), 7.58–7.61 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 127.2

(2C), 127.3 (2C), 128.8 (2C), 141.3 (2C). EI-MS: calcd for $C_{12}H_{10}$, 154.08; found, 154 (M+).

4.3.2. Characterization data for 4,4′-dimethoxybiphenyl (4b). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.83 (s, 6H), 6.94 (d, J=8.8 Hz, 4H), 7.46 (d, J=8.8 Hz, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.4 (2C), 114.2 (4C), 127.8 (4C), 133.5 (2C), 158.7 (2C). HR EI-MS: calcd for $C_{14}H_{14}O_2$, 214.0994; found, 214.0988.

4.3.3. Characterization data for 3,3′-dinitrobiphenyl (4c). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (t, J=8.0 Hz, 2H), 7.94–7.97 (m, 2H), 8.27 (d, J=1.2 Hz, 2H), 8.48 (t, J=2.0 Hz, 2H). ^{13}C NMR (75 MHz, DMSO) δ 122.3 (2C), 123.7 (2C), 131.2 (2C), 134.2 (2C), 139.9 (2C), 148.9 (2C). HR EI-MS: calcd for $C_{12}H_8N_2O_4$, 244.0484; found, 244.0489.

4.3.4. Characterization data for 1,1′-binaphthyl (4d). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (t, J=8.0 Hz, 2H), 7.37 (d, J=8.5 Hz, 2H), 7.47–7.50 (m, 4H), 7.55–7.59 (m, 2H), 7.95 (dd, J=8.1, 1.3 Hz, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 125.4 (2C), 125.8 (2C), 126.0 (2C), 126.6 (2C), 127.9 (2C), 128.0 (2C), 128.2 (2C), 132.9 (2C), 133.6 (2C), 138.5 (2C). HR EI-MS: calcd for $C_{20}H_{14}$, 254.1096; found, 254.1086.

4.3.5. Characterization data for 2,2′-dimethylbiphenyl (4e). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.05 (s, 6H), 7.09 (d, J=6.7 Hz, 2H), 7.20–7.26 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.8 (2C), 125.5 (2C), 127.1 (2C), 129.3 (2C), 129.8 (2C), 135.8 (2C), 141.6 (2C). HR EI-MS: calcd for $C_{14}H_{14}$, 182.1096; found, 182.1094.

4.4. General procedure for alkene epoxidation using 2

A solution of the alkene (1.0 mmol) was added to a mixture of **2** (0.035 g, 0.05 mmol) and 50% H_2O_2 (0.5 mL, 8.7 mmol) in 1,2-dichloroethane (2 mL). The reaction mixture was stirred at 75 °C and monitored by TLC and GC analysis. After the complete disappearance of the alkene, the suspension was filtered and the resin was washed by diethyl ether (2×10 mL). The combined organic layer was concentrated and the crude residue was filtered through a plug of silica gel with diethyl ether to provide the essentially pure epoxide product after solvent removal. Reactions were also performed where the yields were determined by GC analysis by comparison to an internal standard.

4.4.1. Characterization data for *cis*-cyclooctene epoxide (5a). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26–1.63 (m, 10H), 2.12–2.18 (m, 2H), 2.87–2.94 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.5, 26.2, 26.4, 55.5. This data matches that of a commercially available sample.

4.4.2. Characterization data for cycloheptene epoxide (5b). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20–1.59 (m, 6H), 1.89–1.94 (m, 4H), 3.08 (t, J=2.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.5, 29.0, 31.0, 56.1. EI-MS: calcd for $C_7H_{12}O$, 112.09; found, 112 (M+).

4.4.3. Characterization data for 1,2-dihydronaphthalene epoxide (5c). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.69–1.80 (m, 1H), 2.36–2.39 (m, 1H), 2.43–2.57 (m, 1H), 2.72–2.79 (m, 1H), 3.71 (t, J=3.1 Hz, 1H), 3.83 (d, J=4.2 Hz, 1H), 7.08 (d, J=7.1 Hz, 1H), 7.19–7.25 (m, 2H), 7.37 (d, J=1.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.8, 24.4, 52.8, 55.1, 126.1, 128.4, 129.5, 132.6, 136.7. HR EI-MS: calcd for $C_{10}H_{10}O$, 146.0732; found, 146.0736.

4.4.4. Characterization data for 1-phenylcyclohexene epoxide (5d). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26–1.59 (m, 4H), 1.95–2.00 (m, 2H), 2.12–2.13 (m, 1H), 2.23–2.27 (m, 1H), 3.06 (s, 1H), 7.08–7.38 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.8, 20.1, 28.9, 60.2, 61.9, 125.3, 127.2, 128.3, 142.5. EI-MS: calcd for $C_{12}H_{14}O$, 174.10; found, 174 (M+).

4.4.5. Characterization data for 2-(4-methoxybenzyl)-oxirane epoxide (5e). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.51 (dd, J=5.0, 2.6 Hz, 1H), 2.73–2.83 (m, 3H), 3.09–3.11 (m, 1H), 3.77 (s, 3H), 6.82–6.87 (m, 2H), 7.15 (dd, J=6.9, 2.0 Hz, 2H). HR EI-MS: calcd for $C_{10}H_{12}O_2$, 164.0837; found, 164.0839.

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Aerobic oxidation of alcohols to carbonyl compounds mediated by poly(ethylene glycol)-supported TEMPO radicals

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Abstract—Two poly(ethylene glycol)-supported TEMPO (PEG-TEMPO) has been successfully applied as soluble, recyclable catalysts in the chemoselective oxidation of primary and benzylic alcohols with molecular oxygen in the presence of $Co(NO_3)_2$ and $Mn(NO_3)_2$ as co-catalysts (Minisci's conditions). Under those conditions, secondary alcohols are also oxidized to ketones, although usually in lower yields. The insertion of a spacer between the PEG moiety and TEMPO has beneficial effects on both the activity and ease of recovery of the supported catalyst.

1. Introduction

Catalytic oxidation using the stable nitroxyl radical 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) in combination with safe and easy to handle primary oxidants has become one of the most promising procedures to convert primary and secondary alcohols into the corresponding carbonyl compounds.[1–4] Indeed, efficient traditional methods for this functional group transformation involve the use of stoichiometric amounts of either inorganic oxidants (e.g., chromium (VI) salts) or organic oxidants (e.g., activated DMSO).[5–7] These methods hardly satisfy the current demand for non-polluting chemical processes of high atom efficiency, thus rendering new selective procedures, which do not generate large amounts of by-products highly desirable.[8,9]

Several organic and inorganic oxidants react with TEMPO generating the corresponding oxoammonium salt. The latter is a much stronger oxidant than the nitroxyl radical and cleanly reacts with alcohols to give aldehydes or ketones.[10] Based on this, several catalytic systems in which the oxoammonium salt is (re)generated in situ from sub-stoichiometric amounts of TEMPO have been developed. Early examples of TEMPO-mediated reactions included the oxidation of secondary alcohols to ketones with *m*-chloroperbenzoic acid,[11] and the oxidation of primary, secondary and benzylic alcohols in an electrochemical process.[12] A more versatile and efficient catalytic procedure in which buffered bleach acts as the terminal oxidant was introduced in 1987 by Montanari and co-workers.[13] The oxidation reaction proceeds under mild conditions and both primary and secondary alcohols are converted to carbonyl compounds in high yields, even in large scale operations. In addition, the oxidation of primary alcohols can be driven to give carboxylic acids by adding a phase-transfer catalyst to the biphasic aqueous/organic system.[14] Many other organic and inorganic terminal oxidants (e.g., [bis(acetoxy)iodo]-benzene (BAIB),[15] trichloroisocyanuric acid (TCCA),[16] oxone,[17] or iodine[18]) have been subsequently introduced with the aim of further expanding the already wide applicability of Montanari's procedure.

A different approach, pioneered by Semmelhack and co-workers,[19] consists of the use of oxygen as the primary oxidant in conjunction with a TEMPO/metal catalyst combination. The use of oxygen would be preferred over that of the above-mentioned oxidants from both an economic and an environmental standpoint and Semmelhack actually demonstrated the aerobic oxidation of allylic and benzylic alcohols to aldehydes by TEMPO/CuCl in DMF. Unfortunately, this method is ineffective with aliphatic and alicyclic alcohols and its applicability is therefore, limited.[†] Better results were obtained by Sheldon

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[†] According to Semmelhack, an oxoammonium salt generated by oxidation of TEMPO by Cu(II) is the actual oxidant, but, as pointed out by Sheldon, the lack of reactivity of aliphatic alcohols is not consistent with this hypothesis. For an exhaustive discussion and more plausible reaction mechanisms see Ref. 4.

and co-workers who achieved the aerobic oxidation of a broad range of alcohols using a combination of $RuCl_2(PPh_3)_3$ and TEMPO in chlorobenzene, toluene or even in the absence of a solvent.[8,20,21] Besides requiring an expensive transition-metal complex, the method operates at a relatively high temperature (100 °C) and, in the case of secondary alcohols, high oxygen pressure (up to 10 bar). These drawbacks are partly avoided by using a combination of TEMPO and the polyoxometalate $H_5[PV_2Mo_{10}O_4]$.[22] More recently, the aerobic oxidation of alcohols under fluorous biphasic conditions and atmospheric pressure in the presence of TEMPO and synthetically demanding fluorous Cu(I) complexes has been independently described by two groups.[23,24] A mixture of $CuBr_2$, 2,2′-bipyridine and *t*-BuOK was shown to catalyze the aerobic oxidation of primary and benzylic alcohols in the presence of TEMPO in CH_3CN/H_2O 1:1 as a solvent under mild conditions.[25,26] Another uncomplicated and cheap catalytic system comprised of TEMPO in combination with tiny amounts of $Mn(NO_3)_2$ and $Co(NO_3)_2$ in CH_3COOH was reported by Minisci and co-workers.[27,28] This combination is particularly effective for the oxidation of primary and benzylic alcohols, but good results are also obtained with less reactive secondary alcohols. In order to avoid the use of metal salts, Hu and co-workers developed two aerobic processes in which TEMPO is used in combination with $Br_2/NaNO_2$ or 1,3-dibromo-5,5′-dimethylidantoin/$NaNO_2$ TEMPO, respectively.[29,30] Teflon-lined apparatus, operating pressures up to 9 bar and relatively high amounts of TEMPO and co-catalysts (up to 10 mol% in the case of the oxidation of secondary alcohols in the presence of 1,3-dibromo-5,5′-dimethylidantoin/$NaNO_2$) were required.

Recovery and recycling of TEMPO by immobilization on either inorganic or organic supports has been actively investigated. Indeed, whichever oxidant is used, separation of the products from TEMPO could require lengthy workup procedures, especially when reactions are run on large scale. Moreover, TEMPO is quite expensive, so it is desirable to be able to separate the catalyst after the oxidation reaction and to reuse it. Electrochemical processes were readily adapted to meet these goals and several examples of graphite felt electrodes and glassy carbon electrodes coated with TEMPO and related radicals have been used for the electrochemical oxidation of alcohols.[31,32] In 1985, Miyazawa and Endo reported the synthesis of soluble and insoluble polystyrene-type polymers featuring TEMPO residues, which were used as catalysts for the oxidation of benzyl alcohol to benzaldehyde with $K_3Fe(CN)_6$ or $CuCl_2/Cu(OH)_2$ as the terminal oxidants.[33,34] While no mention of recovery and recycling of these catalysts was provided, the same group later reported that 4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl (4-OH-TEMPO) immobilized onto silica or ferrite (previously functionalized by the reaction of their surface hydroxyl groups with 4-trimethoxysilyl-1,2,5,6-tetrahydrophthalic anhydride) could be recycled up to 45 times in the benzyl alcohol oxidation promoted by $CuCl_2/Cu(OH)_2$.[35] Silica-supported TEMPO radicals and their use in alcohol oxidations were subsequently reported by several groups. Both silica gel and ordered mesoporous silica (e.g., MCM-41) were used,[36–39] the best results being obtained by Bolm and co-workers who attached 4-oxo-2,2,6,6-tetramethylpiperidine-1-oxyl to a commercially available aminopropyl-functionalized silica and an aminopropyl-functionalized porous glass. These catalysts were employed in combination with bleach under Montanari's conditions affording high yields and selectivities. Ten subsequent reaction runs were demonstrated, although partial degradation of the supported TEMPO catalysts was observed.[38,40] Silica matrices doped with TEMPO prepared under mild conditions by the sol–gel approach were also found to be selective and recyclable heterogeneous catalysts for the oxidation of alcohols with bleach.[41,42] A polymer immobilized nitroxyl radical derived from a commercially available oligomeric 2,2,6,6-tetramethylpiperidine (Chimassorb 994) was developed by Sheldon and co-workers.[43] Analogously to TEMPO, this catalyst allowed the smooth conversion of benzylic, primary and secondary alcohols to carbonyl compounds with bleach as the terminal oxidant. In addition, when using methyl-*tert*-butylether or no solvent, the catalyst proved to be heterogeneous and could be recycled.[44] Very recently, Toy and co-workers have shown that TEMPO attached to a swellable resin and polystyrene-supported diacetoxyiodosobenzene can be used simultaneously for the selective oxidation of a variety of alcohols.[45] The polymeric oxidant in excess and the supported TEMPO catalyst can be recovered by simple filtration and reused.

As a result of the increasing interest in recoverable soluble reagents and catalysts,[46] in the last few years immobilization of TEMPO onto soluble polymers has started to emerge as an alternative to the above-mentioned heterogeneous supports. Soluble polymer-supported TEMPO radicals have been prepared by ring-opening methatesis of norbornene derivatives.[47] Preliminary tests revealed that the activity of these catalysts was consistently lower than that of TEMPO in the oxidation of alcohols under Montanari's conditions. Promising results have been obtained in the oxidation of alcohols with various primary oxidants (including bleach) catalyzed by a TEMPO derivative tethered onto a modified commercially available poly(ethylene glycol) (PEG) monomethyl ether of molecular weight of about 5000 Da.[48] The catalyst was easily recovered by selective precipitation from Et_2O and its recyclability was studied using the oxidation of 1-octanol with the mild oxidant BAIB as a model reaction. The results of independent studies on the catalytic performance and recyclability of a series of PEG-supported TEMPO derivatives in the oxidation of alcohols under Montanari's conditions has been also disclosed.[49,50] Even more recently, it has been shown that recoverable soluble TEMPO catalysts can be designed without recourse to polymeric supports. Fluorous TEMPO derivatives have been used as selective catalysts for the oxidation of alcohols under mild, homogeneous conditions.[51] The peculiar solubility properties ensured by the presence of highly fluorinated domains allowed the easy recovery of some of these catalysts by liquid–liquid or solid-phase extraction of the reaction mixture. Gao and co-workers reported the synthesis of a TEMPO radical attached to an imidazolium cation and investigated its catalytic activity for the oxidation of alcohols with bleach in a biphasic system ionic liquid/water. The catalytic activity of this system was similar to

that observed with TEMPO and the ionic liquid phase containing the catalyst was recycled up to three times.[52]

Despite the obvious advantages of using of oxygen as terminal oxidant, examples of aerobic oxidation of alcohols in the presence of recoverable and recyclable nitroxyl radicals are limited. A few solid polymer-supported TEMPO derivatives have been tested as catalysts for the aerobic oxidation of benzylic alcohols under Semmelhack's conditions (CuCl/DMF).[39,44] A tetranitroxyl radical poorly soluble in most organic solvents, developed by Ciba chemists, gave good results in the aerobic oxidation of a wider range of substrates under slightly modified Minisci's conditions and was recycled for four times.[53] Analogously, a new polymer-supported TEMPO prepared by reaction between 4-OH-TEMPO and a carboxylic acid functionalized fiber was used as an heterogeneous catalyst under Minisci's conditions showing high activity and selectivity for the oxidation of primary alcohols to aldehydes.[54]

We here show that PEG-supported TEMPO derivatives can be conveniently employed as homogeneous, recoverable and recyclable catalysts for the aerobic oxidation of alcohols under Minisci's conditions, combining the advantages typical of heterogenized TEMPO with those of the soluble parent compound.

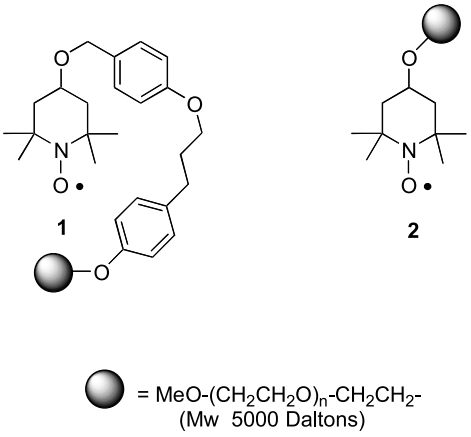


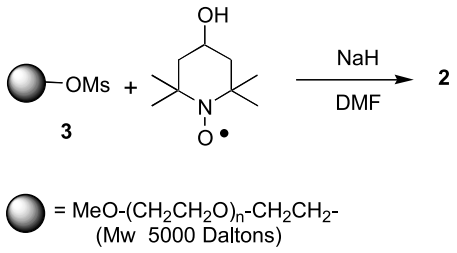
Figure 1. PEG-supported TEMPO radicals.

2. Results and discussion

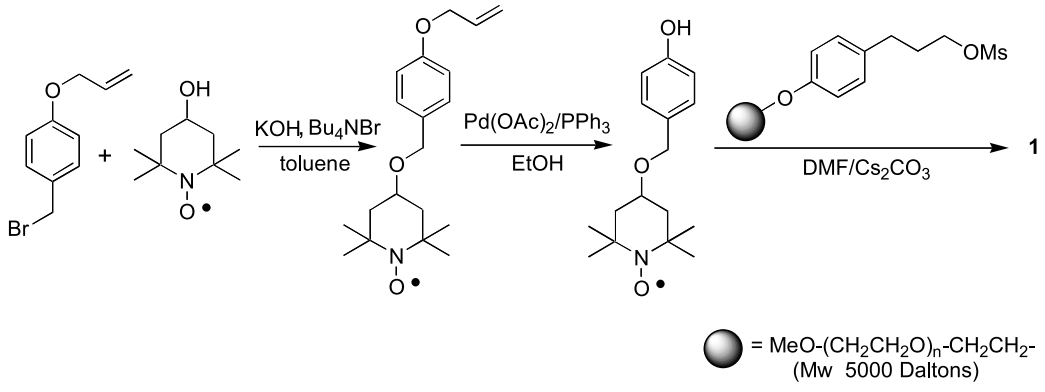
Poly(ethylene glycol)s (PEGs) of M_w greater than 2000 Da are readily functionalized, inexpensive polymers that exhibit excellent solubility in many organic solvents, including CH_2Cl_2 and CH_3COOH. PEG precipitation as a semicrystalline solid can be then induced by dilution of the solution with an incompatible solvent, such as Et_2O. This behavior and the ease of functionalization make PEG a popular soluble polymeric support for homogeneous catalysts.[55] Indeed, the choice of proper solvent combinations makes it possible to run a reaction under homogeneous catalysis conditions (where the PEG-supported catalyst is expected to perform at its best) and then to recover the catalyst by precipitation/filtration as if it were bound to an insoluble matrix.

In a recent communication, we described the synthesis of the PEG-supported nitroxyl radical **1** (PEG-TEMPO **1**, Fig. 1) in which a TEMPO moiety is connected to the polymeric backbone ($M_w=5000$)[‡] by a benzylic ether linker (Scheme 1).[48] As shown by Ferreira et al., the same TEMPO residue can be attached directly to the PEG chain terminus via an ether linkage.[49] A slight modification of their original method (Scheme 2) allowed us to prepare PEG-TEMPO **2** in 80% yield from 4-OH-TEMPO and the known PEG mesylate derivative **3**.[56]

Both PEG-supported TEMPO derivatives were found to be completely soluble in CH_3COOH, the solvent of choice for the oxidation of alcohols under the conditions developed by Minisci, which are the most convenient among those



Scheme 2. Synthesis of PEG-TEMPO **2**.

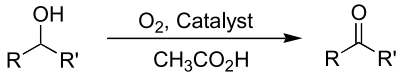


Scheme 1. Synthesis of PEG-TEMPO **1**.

[‡] Commercially available PEGs possess very narrow polydispersity indices. M_w of the PEG used actually ranges from 4500 to 5500 Da.

proposed for the aerobic oxidation of alcohols catalyzed by TEMPO.[27,28] Thus, the oxidation of the model compound 4-bromobenzyl alcohol was studied using a combination of $Mn(NO_3)_2 \cdot H_2O$ (2 mol%), $Co(NO_3)_2 \cdot H_2O$ (2 mol%) and PEG-TEMPO (**1** or **2**) in acetic acid (Scheme 3). We were pleased to observe that using 5 mol% of either **1** or **2**, 4-bromobenzaldehyde was formed quantitatively at room temperature under atmospheric pressure of oxygen in less than 3 h (Table 1, entries 1 and 2). It should be noted that under similar conditions, but in the presence of TEMPO, the aerobic oxidation of *para*-substituted benzyl alcohols proceeds much slower, requiring up to 6 h and 10 mol% of nitroxyl radical to go to completion.[27] When the amount of PEG-TEMPO was reduced to 2 mol%, the oxidation still went to completion smoothly in 4 h in the case of **1**, whereas only 92% conversion was attained using the linker-less radical **2** (entries 3 and 4). The higher activity of **1** was further evidenced by experiments carried out using 1 mol% of PEG-TEMPO (entries 5 and 6).

Attempts to recover and recycle the two PEG-TEMPO radicals also gave good results (Table 2). The post-reaction work-up was particularly straightforward in the case of **1**, which was precipitated out from the acetic acid solution by adding ice-cold Et_2O. The radical was recovered by filtration, dried under vacuum and re-used without any further treatment. Fresh $Mn(NO_3)_2 \cdot H_2O$ and $Co(NO_3)_2 \cdot H_2O$ were added to each successive run. No decrease in the rate and in the selectivity of oxidation was observed in the first three runs. However, the activity of the catalytic system progressively decreased in the fourth and fifth run and conversion of 4-bromobenzyl alcohol to 4-bromobenzaldehyde was as low as 74% after a reaction time of 3 h in the sixth run. These results compare well with those reported in the case of a soluble tetranitroxyl radical, which has been used as catalyst in the oxidation of benzyl alcohol with a ratio substrate/radical = 41 (corresponding to a concentration = 10 mol% of nitroxyl radical) and recycled for four times affording benzaldehyde in 95% yield in the fourth run.[53]



R = Alk, Ar, Bn, H; R' = Alk, H

Catalyst = **1** or **2** + $Mn(NO_3)_2$ + $Co(NO_3)_2$

Scheme 3. Aerobic oxidation of alcohols under Minisci's conditions catalyzed by PEG-TEMPO.

Table 2. Aerobic oxidation of 4-bromobenzyl alcohol

Run	PEG-TEMPO	Conversion (%)	Selectivity (%)
1	**1**	>99	>99
2		>99	>99
3		>99	>99
4		91	>99
5		83	>99
6		74	>99
1	**2**	>99	>99
2		98	>99
3		96	>99
4		92	>99
5		84	>99
6		80	>99

Recycling of PEG-TEMPO radicals. $T = 25$ °C; $O_2 = 1$ atm; PEG-TEMPO = 5 mol%; $Mn(NO_3)_2 = 2$ mol%; $Co(NO_3)_2 = 2$ mol%; reaction time = 3 h; conversion and selectivity determined by GC (see Section 4 for details).

Recovery and recycling of PEG-TEMPO **2** was also demonstrated, but in that case direct precipitation of the radical was not viable. Indeed, a slurry formed upon addition of ice-cold Et_2O to the reaction solution and a sensible loss of **2** was observed after filtration. A procedure similar to that employed for the recovery of the above-mentioned tetranitroxyl radical, proved to be more effective. Acetic acid was first evaporated, followed by addition of ice-cold Et_2O to dissolve the reaction product leaving the insoluble PEG-TEMPO **2** as a solid residue. Six subsequent runs using 4-bromobenzyl alcohol as a substrate were thus carried out, with results very close to those obtained in the case of PEG-TEMPO **1**.

The aerobic oxidation of a variety of alcohols catalyzed by PEG-TEMPO radicals under Minisci's conditions was next examined (Table 3). Benzylic alcohols were readily oxidized with high conversion and high selectivity to the corresponding aldehydes both in the presence of PEG-TEMPO **1** and PEG-TEMPO **2** (catalyst loading = 5 mol%, entries 1–3). Analogously to what was observed with TEMPO,[27] the oxidation of primary alcohol was best performed at 40 °C in the presence of either 5 or 10 mol% of PEG-TEMPO **1** depending on the substrate (entries 4, 7 and 9). Besides aldehydes, small amounts of carboxylic acids (<5% of the starting alcohol) were detected. The difficult conversion of unreactive aliphatic primary alcohols using oxygen as terminal oxidant proceeded more slowly in the presence of PEG-TEMPO **2**. For instance, with a catalyst loading of 5 mol% conversion of 1-octanol attained 65% in 4 h (entry 5) against 97% attained in the reaction catalyzed by PEG-TEMPO **1** (entry 4). The reaction did not go to completion even in the presence of 10 mol% of PEG-

Table 1. Aerobic oxidation of 4-bromobenzyl alcohol to aldehyde, catalyzed by PEG-TEMPO radicals in combination with Mn(II) and Co(II) nitrates[a]

Entry	Radical	Mol%	Time (h)	Conversion (%)	Selectivity (%)
1	**1**	5	3	>99	>99
2	**2**	5	3	>99	>99
3	**1**	2	4	>99	>99
4	**2**	2	4	92	>99
5	**1**	1	5	90	>99
6	**2**	1	5	72	>99
7[b]	TEMPO	10	6	>99	>99

[a] $T = 25$ °C; $O_2 = 1$ atm; $Mn(NO_3)_2 = 2$ mol%; $Co(NO_3)_2 = 2$ mol%; conversion and selectivity determined by GC (see Section 4 for details).
[b] Literature data (Ref. 27). Substrate = 4-methylbenzyl alcohol. $T = 20$ °C.

Table 3. Aerobic oxidation of alcohols to carbonyl compounds, catalyzed by PEG-TEMPO radicals in combination with Mn(II) and Co(II) nitrates[a]

Entry	PEG-TEMPO	Alcohol	T (°C)	Time (h)	Conversion (%)	Selectivity (%)
1	**1**	Benzyl alcohol	25	3	>99	>99
2	**2**	Benzyl alcohol	25	3	>99	>99
3	**1**	4-Nitrobenzyl alcohol	25	3	>99	>99
4	**1**	1-Octanol	40	4	97	95
5	**2**	1-Octanol	40	4	65	94
6	**2**[b]	1-Octanol	40	4	75	94
7	**1**	1-Undecanol	40	4	>99	96
8	**2**[b]	1-Undecanol	40	4	78	96
9	**1**[b]	Cinnamyl alcohol	40	6	>99	>99
10	**1**	1-Phenylethanol	25	5	96	>99
11	**1**[b]	Cyclooctanol	40	4	>99	>99
12	**2**[b]	Cyclooctanol	40	4	68	>99
13	**1**[b]	2-Octanol	40	24	51	>99
14	**2**[b]	2-Octanol	40	24	43	>99
15	**1**[b]	2-Undecanol	40	24	52	>99

[a] O_2=1 atm; PEG-TEMPO=5 mol%; $Mn(NO_3)_2$=2 mol%; $Co(NO_3)_2$=2 mol%; conversion and selectivity determined by GC (see Section 4 for details).
[b] PEG-TEMPO=10 mol%.

TEMPO **2** (entry 6). Secondary alcohols were also oxidized to ketones (entries 10–15) at 40 °C, reaction rates depending on the steric hindrance of the substrate as found in the case of other primary oxidants.[48] Thus, in the presence of PEG-TEMPO **1**, 1-phenylethanol and cyclooctanol were readily oxidized in high yield to acetophenone and cyclooctanone, respectively, (entries 10 and 11), whereas conversion of 2-octanol and 2-undecanol slightly exceeded 50% after 24 h (entries 13 and 15). The lower activity of PEG-TEMPO **2** with respect to PEG-TEMPO **1** was demonstrated again in the oxidation of 2-octanol and cyclooctanol (entries 12 and14). Seen as a whole, these results clearly show that the insertion of a spacer separating the PEG chain from the TEMPO moiety has a beneficial effect on the catalytic activity of these supported systems. The presence of a spacer possibly prevents that partial hindrance of the active site within the polymeric structure as a result of coiling of the PEG polymeric backbone, which was suggested to be the cause of the reduced catalytic activity of certain linkerless PEG-TEMPO.[49]

3. Conclusions

Two poly(ethylene glycol)-supported TEMPO (PEG-TEMPO) prepared from readily available precursors proved to be efficient catalysts in the chemoselective oxidation of alcohols with molecular oxygen under mild conditions. Catalytic activities and selectivities of these soluble TEMPO derivatives are similar to those exhibited by the parent compound, and even higher in the case of PEG-TEMPO **1**. In addition, both PEG-TEMPO offer the advantages of simplified workup procedure and easy recycling, which are usually associated with the use of heterogenized TEMPO.

4. Experimental

4.1. General

Solvents were purified by standard methods and dried if necessary. Commercially available reagents were used as received. PEG-TEMPO **1** and PEG mesylate **3** was prepared as previously described.[48,56] GC analyses were performed on an Agilent 6850 instrument (column: HP-1 100% dimethylpolysiloxane 30 m×320 μm×0.25 μm). Carrier=He (constant flow, 2.2 mL/min); mode=split (split ratio=80:1); injector T=250 °C; detector (FID) t=280 °C. The products of the oxidation reactions were determined by comparison with the commercially available carbonyl compounds and carboxylic acids.

4.2. PEG-TEMPO 2

To a suspension of 60% NaH in mineral oil (25 mg, 0.63 mmol) in dry DMF (4 mL) was added 4-hydroxy-TEMPO (108 mg, 0.63 mmol) and the resulting slurry was stirred at room temperature for 1 h under nitrogen. A solution of PEG-mesylate **3** (800 mg, 0.16 mmol), previously dried under vacuum at 100 °C for 1 h, in dry DMF (4 mL) was then added and the mixture was stirred for 70 h at 70 °C. After cooling to room temperature, the suspension was filtered and the filtrate evaporated to dryness under reduced pressure. The residue was taken up in CH_2Cl_2 (2 mL) and added to Et_2O (70 mL). The precipitate was collected by filtration, washed with Et_2O (3×30 mL) and dried under vacuum. PEG-TEMPO **1** (650 mg, 80%) was obtained as a pale orange solid (physical data in agreement with those reported in the literature).[50]

4.3. General procedure for the aerobic oxidation of alcohols

Reactions were carried out in a jacketed 20 mL Schlenk tube thermostated by circulating water (Haake F3 Cryostat) and fitted with a stirring bar. The reactor was charged with (a) a freshly prepared solution of alcohol (1 mmol) and *n*-decane (71.1 mg, 0.5 mmol, internal standard for GC) in acetic acid (1 mL); (b) a freshly prepared solution of $Mn(NO_3)_2 \cdot H_2O$ (5.0 mg, 0.02 mmol) and $Co(NO_3)_2 \cdot H_2O$ (5.8 mg, 0.02 mmol) in acetic acid (1 mL). The combined solutions were stirred 5 min, then PEG-TEMPO (0.05–0.1 mmol) was added. The Schlenk tube was attached to a gas burette filled with oxygen and the solution was stirred for the time indicated in Tables 1–3. A 20 μL sample of the solution was diluted with 0.2 mL ice-cold Et_2O.

The precipitated catalyst was eliminated by filtration on PTFE septum and the liquid layer was analyzed by GC.

4.4. Oxidation of 4-bromobenzyl alcohol: catalyst recycling

The jacketed reactor thermostated at 25 °C was charged with (a) a freshly prepared solution of 4-bromobenzyl alcohol (374.1 mg, 2 mmol) and *n*-decane (142.2 mg, 1 mmol, internal standard for GC) in acetic acid (2 mL); (b) a freshly prepared solution of $Mn(NO_3)_2 \cdot H_2O$ (10.0 mg, 0.04 mmol) and $Co(NO_3)_2 \cdot H_2O$ (11.6 mg, 0.04 mmol) in acetic acid (1 mL). The combined solutions were stirred 5 min, then PEG-TEMPO **1** (550 mg, 0.1 mmol) was added and the solution was stirred for 3 h under an atmosphere of molecular oxygen. Ice-cold Et_2O (10 mL) was added and the precipitated PEG-TEMPO **1** was filtered on a sintered glass funnel and washed with cold Et_2O (3×3 mL). The combined organic phase was analyzed by GC, whereas the recovered PEG-TEMPO **1** was dried under vacuum and used for the subsequent run. When PEG-TEMPO **2** (510 mg, 0.1 mmol) was used, acetic acid was evaporated under reduced pressure prior to the addition of Et_2O. Results are reported in Table 2.

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Polymer-supported palladium catalysed Suzuki–Miyaura reactions in batch and a mini-continuous flow reactor system

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Abstract—A polymer-supported palladium(II) salen-type complex exhibited catalytic activity in the cross-coupling reaction of various aryl bromides and heteroaryl bromides with phenylboronic acid in a mini-continuous flow reactor system at elevated temperatures in a phosphine-free system. The reaction was also performed in batch using a number of different solvent systems in order to optimise conditions. The catalytic mini-reactor can be used repeatedly over several cycles in the Suzuki–Miyaura cross-coupling reaction. While the diameter of the flow channel is 3 mm, the macroporous resin supported catalyst is solvent expanded to completely fill the channel. Consequently, the liquid path is through the micro channels of the macroporous resin structure. Intensification of the process over the stirred batch reaction is through increased reagent-catalyst contact and results in a 20-fold increase in the rate of reaction. The residence/space time on the reactor is 10.5 min, compared to 24 h in batch, which means that a diversity of starting materials can be screened over a short period of time. To demonstrate the utility of the system, a diversity of aryl and heteroaryl bromides have been studied.

1. Introduction

Metal-catalysed cross-coupling reactions have gained popularity over the past 30 years, in particular as convenient techniques for the formation of carbon–carbon bonds.[1] Numerous reactions have been developed to achieve cross-coupling, of which the Suzuki–Miyaura reaction is one of the most efficient methods for the synthesis of biaryl and heterobiaryl derivatives.[2,3] The tolerance of various functional groups in the coupling process, the diversity of organoboron compounds that are environmentally safer than other organometallic reagents, and the ease of handling and removal of boron-containing by-products offer the Suzuki–Miyaura reaction advantages over other related techniques.[4] Catalysts used in the standard processes are generally based on either homogeneous nickel or palladium phosphine complexes, which are rarely recoverable without elaborate and wasteful procedures, and, therefore, commercially undesirable.[2,5] Moreover, phosphine ligands are expensive, toxic, and in large-scale applications the phosphines may be a more serious economical burden than even the metal itself.[6] In recent years there has been an increasing interest in developing greener processes. In this context, heterogeneous catalysis is emerging as an alternative to homogeneous processes so that catalysts can be recovered and reused several times before they deactivate completely.[7] At the same time, the catalyst recovery also decreases contamination of the desired products with hazardous or harmful compounds, and also environmental pollution caused by residual of toxic metals and organic and inorganic waste can be reduced.[8] So far, palladium metal immobilised on cross-linked polystyrene resins and silica gels have been used in Suzuki–Miyaura reactions.[9,10] However, they normally suffer from limited mass transfer, low specificity and selectivity and leaching of the catalytic species from the surface of the support.[9] Recently new catalysts have been described that go some way to achieving greener heterogeneous processing, in particular the now commercially available EnCat™ polymer encapsulated palladium complexes[11] of Ley et al. and the Chitosan-supported materials[12] reported by Hardy et al. Kwong and co-workers have also described reactions using chloroaromatics at low catalyst loading that give excellent turnover numbers and yields[13] but which is at present confined to homogeneous catalysts with semi-labile phosphine ligands.

Reactor miniaturisation, for example micro reactors in which microlitre quantities of reagents are manipulated, has been shown to confer many advantages over conventional laboratory scale chemical apparatus.[14] Micro reactor technology clearly offers considerable advantages in performing safer and more efficient chemical reactions. In particular, the number of compounds that can be prepared and screened can be considerably increased thereby

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enhancing the discovery phase.[15,16] Furthermore, the capability of producing a parallel network of micro reactors, the so-called 'scaling out' of the process, offers a clear route to generating product volume on demand, at the point of use, so reducing the need to store and transport hazardous or highly reactive chemicals.[17,18] To date the scope of liquid phase synthesis in micro reactors has, in the majority, been limited to non metal-catalysed reactions, with the exception of a few examples of heterogeneous catalysis.[19,20] There are only a couple of reports of heterogeneously catalysed Suzuki–Miyaura reactions in miniaturised continuous-flow reactors. Greenway et al., have reported the Suzuki–Miyaura reaction within a micro reactor operating under electro osmotic flow, using palladium on silica as catalyst to produce 4-cyanobiphenyl in 67% yield at room temperature.[21] However, the electric field played a major role in this catalytic process as no reaction was observed in an identical reactor system where EOF was replaced by pressure driven flow. He et al., recently investigated the microwave-assisted heterogeneous Suzuki–Miyaura reaction in a micro reactor, with 99% yield of 4-cyanobiphenyl being achieved at 100 °C.[22]

Recently we reported the synthesis and characterisation of an unsymmetrical salen-type palladium(II) complex and its immobilisation onto a polystyrene–divinylbenezene cross-linked Merrifield resin.[23] The supported catalyst was air- and moisture-stable, and could be reused several times without a significant degradation in catalytic activity in the Suzuki–Miyaura reaction of 4-bromoanisole and phenylboronic acid at 90 °C. Importantly, the reaction was carried out successfully without the need for intrinsic or added phosphine ligands. Leaching of the palladium into solution from the supported catalyst proved almost negligible.[24] In this paper we report for the first time, to the best of our knowledge, the cross-coupling reactions of various aryl bromides and heteroaryl bromides with phenylboronic acid in a mini-continuous flow reactor system using the heterogeneously polymer-supported homogeneous palladium catalyst. The use of the polymer-supported catalyst in the continuous flow system enabled product streams to be palladium free as leaching was minimised, removing the requirement for downstream catalyst separation. Reasonable conversions could be achieved in a matter of minutes, compared to conversions obtained after 24 h in a batch reaction, albeit on a much smaller scale. This allows small quantities of products to be prepared and screened quickly, allowing diversity studies and high throughput synthesis to be carried out. The compact design of the reactors also offer the opportunity of scale-out through reactor parallelisation although this will not be discussed in this paper.

2. Results and discussion

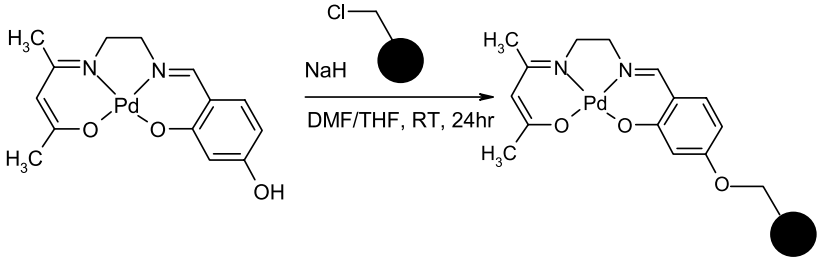
2.1. Catalyst preparation

The Merrifield resin-supported salen-type palladium(II) complex was prepared according to previously reported procedures (Scheme 1).[23]

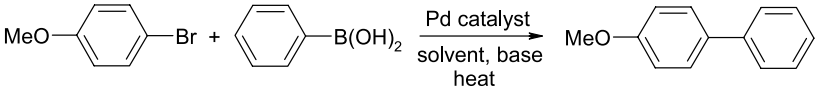
Inductively coupled plasma-atomic emission spectroscopy (ICP-AES) analysis indicated there to be ca. 2% (wt/wt) palladium on the Merrifield beads, corresponding to a catalyst loading of 0.2 mmol palladium/g of resin. Initial studies focused on the coupling reaction of 4-bromoanisole and phenylboronic acid (Scheme 2) in stirred batch reactors in order to obtain comparative data.

2.2. Solvent studies in batch

The combination of K_3PO_4 suspended in DMF and the palladium resin catalyst has been shown to produce the desired coupling product, that is, 4-methoxybiphenyl, in satisfactory yields.[24] However, in order to transfer the reaction to a continuous flow reactor, a totally homogeneous mixture was necessary as any solid in the flowing liquid would potentially cause blockages in the reactor. It was, therefore, decided to investigate a number of solvent-base combinations in order to optimise the process. Reactions were carried out in a Radley's Carousel Parallel Synthesiser fitted with a fuzzy logic temperature controller, using DME/water 1:1, ethanol/water 1:1 and PEG-300/water 1:1 and 4:1 with sodium carbonate as base and also DMF/H_2O 1:1 with *N*,*N*-diisopropyl ethyl amine as the base. In each case the reaction time was set to 24 h and the temperature thermostated at 100 °C. Yields were determined by GC against standard calibrations for each of the expected products. These data were used to determine the turnover frequencies (TOFs) before transferring the optimised



Scheme 1. The immobilisation of the salen-type palladium(II) complex.



Scheme 2. The Suzuki–Miyaura reaction of 4-bromoanisole and phenylboronic acid.

conditions to the continuous flow system. All reactions were carried out under a nitrogen atmosphere to prevent oxidation of the boronic acid to the phenol, which leads to the formation of the homocoupled product, unsubstituted biphenyl.

Reactions in PEG-300/water 1:1 and ethanol/water 1:1 failed to yield any product while DME/water 1:1 gave only 5% yield, although the homocoupled product was detected. It was, therefore, decided to use a procedure modified from a method that originally involved microwave heating of the reaction solution.[25] The original procedure used palladium(II) chloride in a mixture of PEG-400/water. Reactions were attempted using PEG-300/water in the ratio 4:1 using the palladium resin catalyst as well as homogeneous $PdCl_2$. The reactions were studied over a 24 h period and the kinetics studied as well as determining the TOFs. For the homogeneous catalyst a pseudo-first order overall rate constant of $1.4\times10^{-5}\ s^{-1}$ was determined at 100 °C using sodium carbonate as the base. The heterogeneous resin supported catalyst showed an enhanced rate with a pseudo-first order overall rate constant of $3\times10^{-5}\ s^{-1}$ under the same conditions. TOF studies also revealed some interesting characteristics of the heterogeneous catalyst relative to $PdCl_2$. All reactions were performed using 1.0 mmol of 4-bromoanisole and 1.1 mmol benzene boronic acid with an accurately weighed quantity of catalyst. A higher mole fraction of the homogeneous salt was required (28 mol%) giving a typical TOF of $0.18\ h^{-1}$. For the resin-supported palladium catalyst TOFs of 0.40 and $0.38\ h^{-1}$ were determined at 5 and 18 mol%, respectively. Further reactions were studied using 18 mol% of the resin-supported catalyst with increasing amounts of starting materials, maintaining a 10% excess of the boronic acid. At 2.0 and 5.0 mmol 4-bromoanisole respective TOFs of 0.74 and 1.84 were determined. However, after due consideration it was decided to use DMF/H_2O 1:1 and *N*,*N*-diisopropyl ethyl amine as the solvent/base system in the flow reactor. Although this organic amine has been shown to be less effective than Na_3CO_3 or K_3PO_4[21] in the Suzuki–Miyaura reaction in batch, it is totally soluble under the reaction conditions used in the continuous flow reactor and showed satisfactory results in our batch studies. Using a mole fraction of only 0.5 mol%, a TOF of 6.4 was determined.[24] The results from the TOF studies are summarised in Table 1.

2.3. Mini flow reactor studies

The continuous Suzuki–Miyaura reaction was carried out in a pressure driven mini flow reactor (bed size = 25 mm × 3 mm) constructed from Omnifit glassware with back-pressure being supplied by a syringe pump (RAZAL A-99).

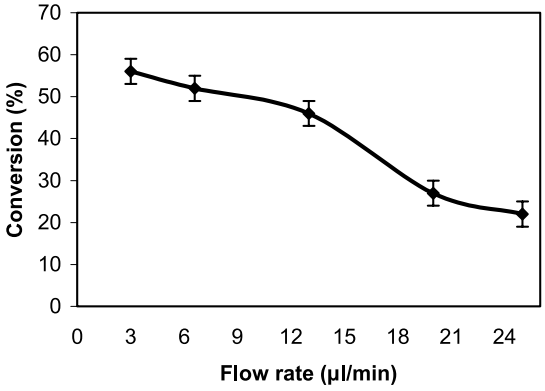


Figure 1. Study of the conversion dependence on flow rates in the continuous Suzuki–Miyaura reaction between 4-bromoanisole and phenylboronic acid at 100 °C.

The Omnifit reactor is a low pressure liquid chromatography column, which is packed with the catalyst particles; these are held in place by 25 µm pore size stainless steel frits integrated in to the screw caps that connect the column to the fluidic system, at the reactor entrance and exit. The catalyst particles swell in the solvent to tightly pack into the reactor body. Solvent removal allows the particles to de-swell. The design of the reactor system makes catalyst filling and removal an extremely easy and quick process. The reactor was heated by immersing it in a water bath at 100 °C. Reactants from a syringe at room temperature were then pumped through 0.8 mm internal diameter PTFE tubing at 100 °C and then through the palladium resin catalyst in the flow reactor at known flow rates for 5 h.

The reaction was carried out in the continuous flow reactor at different flow rates to investigate the effect of the residence time of the reagents within the catalyst bed on the coupling process. The results of conversion dependence on flow rates are shown in Figure 1. It was found that 4-methoxybiphenyl was formed in a yield of only 46% at a flow rate of 13 µl/min. This indicates that the residence time at this flow rate was too fast for the continuous Suzuki–Miyaura reaction, reducing reagent contact with the catalyst bed. Increasing the flow rate to more than 13 µl/min resulted in a significant drop in reaction conversion, with only 27 and 22% of 4-methoxybiphenyl being produced at flow rates of 20 and 25 µl/min, respectively. As expected, decreasing the flow rate to less than 13 µl/min increased the conversion to 52% at a 6 µl/min flow rate and up to 56% conversion for 3 µl/min. Since the reaction conditions such as concentration, ratio of phenylboronic acid to 4-bromoanisole, base, solvent and temperature remained unchanged in all cases, the observed increase in conversion with decreasing flow rate was obviously due to an effective increase in residence

Table 1. Turnover frequencies (TOF) in the Suzuki–Miyaura reaction of 4-bromoanisole with 1.1 equiv $PhB(OH)_2$ at 100 °C with different palladium catalysts, base and solvent under stirred batch conditions (based on GC–S data)

Substrate concn (mol)	Catalyst (mol%)	Solvent system	Base	TOF (h^{-1})
1.0	$PdCl_2$ (28)	PEG300/H_2O (4:1)	Na_2CO_3	0.18
1.0	Pd resin (5)	PEG300/H_2O (4:1)	Na_2CO_3	0.40
1.0	Pd resin (18)	PEG300/H_2O (4:1)	Na_2CO_3	0.38
2.0	Pd resin (18)	PEG300/H_2O (4:1)	Na_2CO_3	0.74
5.0	Pd resin (18)	PEG300/H_2O (4:1)	Na_2CO_3	1.84
1.0	Pd resin (0.5)	DMF/H_2O (1:1)	$^iPr_2NEt$	6.40

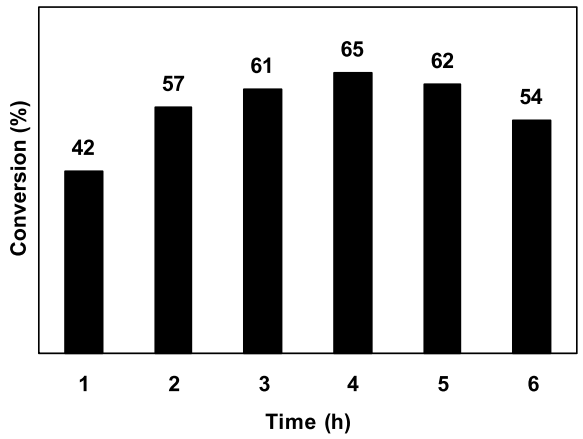


Figure 2. Study of the conversion against reactor run time in the continuous Suzuki–Miyaura reaction at the flow rate of 3 μl/min over 6 h. The actual residence time was 21 min.

time within the continuous reactor and hence an increase in the reaction time. It should be noted that because of the solvent induced swelling of the catalyst particles, the catalyst tightly packs the body of the reactor causing fluid and reagent flow through the internal macroporous structure of the resin as well as, to some extent, around the particles.

The conversion data presented in Figure 1 were achieved using a total 5 h reaction time (i.e., the average conversion over this period). However, it became clear that the reaction conversion changed during the period. The continuous reactor using the supported palladium catalyst was run continuously for 6 h at the flow rate of 3 μl/min with product samples being collected every hour. The results of this study are shown in Figure 2. It was found that 4-methoxybiphenyl was produced in a yield of approximately 40% over the first hour while an average conversion of approximately 60% was achieved over the subsequent 4 h. The lower conversion achieved in the first hour is most likely due to an induction period that corresponds to the delay required for the reduction of the catalyst precursor Pd(II) to the catalytically active Pd(0) oxidation state, although a complete reaction pathway for the Suzuki–Miyaura reaction using the polymer-supported salen-type palladium(II) catalyst is on-going and still remains to be elucidated. As the palladium catalyst could be reused in the batch reaction without a significant degradation in activity, we decided to test the activity of the recycled catalyst after this 6 h period of reaction in the continuous flow reactor. The palladium catalyst was washed several times with DMF, water and THF to remove any excess or surface deposited reagents, and dried under vacuum prior to re-use. A similar trend in activity was observed for the recycled catalyst.

2.4. Kinetics studies

Many chemical reactions have been demonstrated to show improved reactivity, product yield and selectivity when performed in micro reactors, compared with those generated using conventional laboratory practices.[14–17] We, therefore, decided to investigate if there was an enhancement of the observed rate constant for the continuous flow reaction of 4-bromoanisole and phenylboronic acid, when compared with that of the batch reaction under the same reaction conditions. For the batch reaction, aliquots were withdrawn at different time intervals to measure the corresponding conversion. The data were then analysed using the first order reaction design equation (Eq. 1), where x is the mole fraction of 4-methoxybiphenyl produced and t is the corresponding reaction time (Fig. 3). The reaction was shown to be pseudo first order overall with respect to the bromide, giving an observed overall rate constant of $5\times10^{-5}\ s^{-1}$ ($0.18\ h^{-1}$). It should be noted that in a continuous flow reactor, the mean residence time is also the reaction time and that the residence time in the mini flow reactor is much shorter than in the batch process. The continuous reaction was also assumed to be pseudo first order because the mechanism in batch and flow modes should be the same, so comparisons were made using this assumption. The residence time of the solution within the catalyst bed was measured according to a standard literature procedure[26], giving a value of 10.5 min at the flow rate of 6 μl/min. This means that the observed rate constant of the coupling reaction was considerably faster, with $k_{obs}=1\times10^{-3}\ s^{-1}$ ($3.6\ h^{-1}$) using the continuous mini flow reactor. This represents an enhancement of the reaction rate of 20 times as compared to the batch reaction. This enhancement of the rate can be reconciled with the fact that the actual relative catalyst concentration within the element of the continuous flow reactor, relative to the reactants, is much higher than in the stirred batch reactor system. This means that there is much more efficient contacting of the reactants with the catalyst surface, and interior, as the reaction solution if

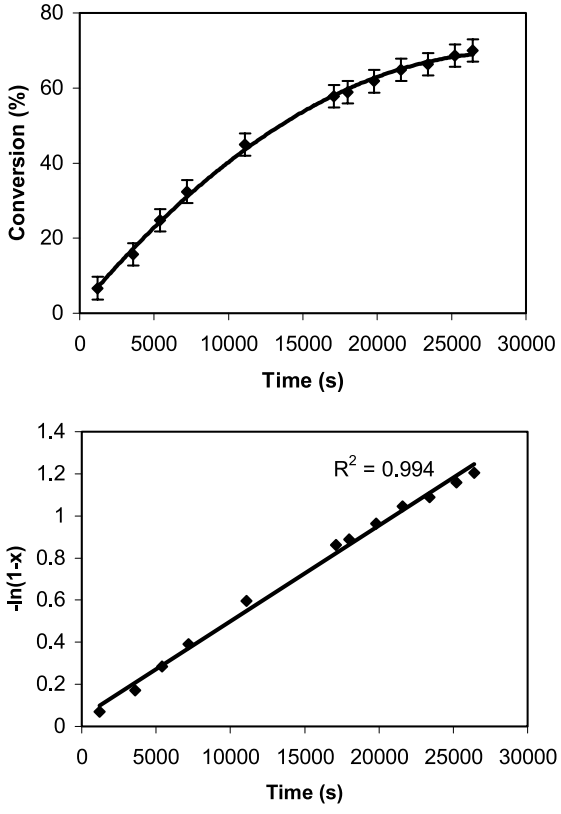


Figure 3. Kinetic data of the Suzuki–Miyaura reaction in a stirred batch reactor using the palladium resin catalyst over 7 h at 100 °C, showing an observed pseudo first order rate constant of $5\times10^{-5}\ s^{-1}$.

pumped through the fixed bed when compared to the batch system, which is dependent on mass transport phenomena between the liquid and solid phases.

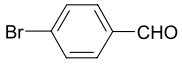
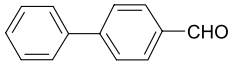
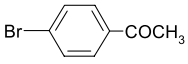
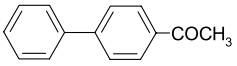
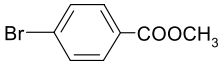
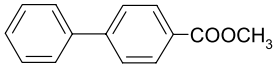
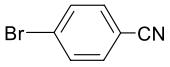
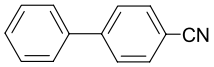
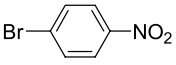
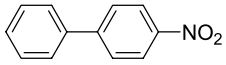
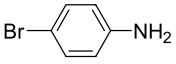
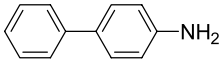
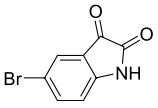
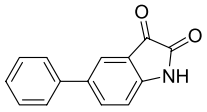
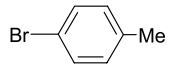
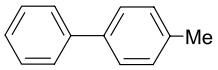
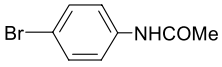
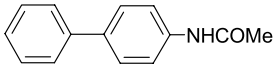
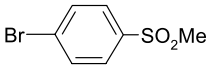
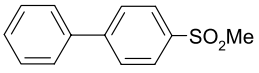
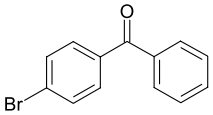
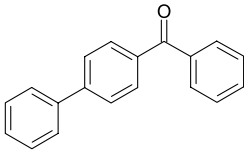
$$k_{obs} = -[\ln(1-x)] \times \frac{1}{t} \quad (1)$$

2.5. Substrate diversity studies

The study was then extended to several substituted bromobenzenes containing both electron-withdrawing and electron-donating groups using the palladium resin catalyst, in order to test the tolerance of functional groups as well as their effects on the conversion. The reactions in the continuous flow reactor were run for 5 h at the flow rate of 6 μl/min at 100 °C. The results are shown in Table 2. As with the batch reactions,[24] it was found that electron-deficient substrates such as 4-bromobenzaldehyde (entry 1), 4-bromoacetophenone (entry 2) and 4-bromobenzonitrile (entry 4) were more reactive than 4-bromoanisole, giving higher yields of 74, 67 and 77%, respectively. The ester function (entry 3) survived the reaction, giving the ester-substituted coupled product in a yield of 65% with no detectable traces of the corresponding carboxylic acid. A favourable effect of electron-withdrawing substituents is normally observed in palladium-catalysed coupling reactions.[27] However, the continuous Suzuki–Miyaura reaction of 4-bromonitrobenzene failed with the coupling product being detected only in trace amount (entry 5), despite the fact that the nitro group is strongly electron-withdrawing. All attempts to carry out the reaction of 4-bromoaniline (entry 6) were also unsuccessful. Similarly, 5-bromoisatin, which possesses a secondary amine function and two carbonyl groups (entry 7), was also completely unreactive. This unexpected behaviour with this catalytic system still remains to be clarified but further studies are ongoing. 4-Bromotoluene, which is electron-rich, still afforded the coupling product in a good conversion of 68% (entry 8). This is in accordance with the results of Ikegami et al., where 4-bromotoluene was found to be more reactive than 4-bromoanisole in the Suzuki–Miyaura reaction.[28] However, conversely Leadbeater et al. have also reported that the reaction of 4-bromoanisole and phenylboronic acid gave a better yield.[29,30]

Because of the synthetic importance of heterobiaryl derivatives, we also wished to carry out the Suzuki–Miyaura reactions of bromopyridines, bromothiophenes

Table 2. The Suzuki–Miyaura reaction of aryl bromides in the continuous flow reactor using the palladium resin catalyst, 1.5 equiv $PhB(OH)_2$, 3 equiv *N*,*N*-diisopropyl ethyl amine in DMF/water 1:1 at 100 °C, at the flow rate of 6 μl/min

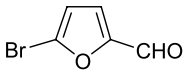
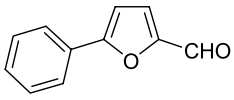
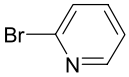
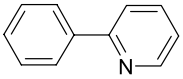
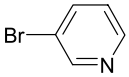
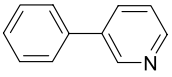
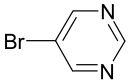
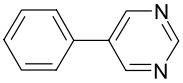
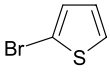
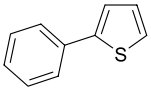
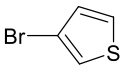
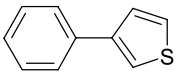
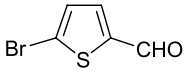
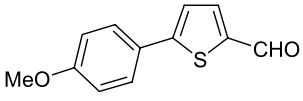
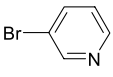
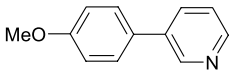
Entry	Substrate	Product	Conversion (%)
1			74
2			65
3			65
4			77
5			Trace
6			0
7			0
8			68
10			37
11			71
12			76[a]

The data represent conversions of the bromides to cross-coupling products (based on GC–S data).
[a] DMF/water 3:1 was used instead of DMF/water 1:1.

and bromofurans with phenylboronic acid in the continuous flow reactor using the palladium resin catalyst (Table 3). Palladium was previously found to possess strong thiophilicity, which was reflected in the poisoning effect of the sulphur atom on some palladium-catalysed reactions. This poisoning effect was also observed in the presence of nitrogen atoms.[31] For this reason, the position of the bromide on a heteroaromatic ring should have an important effect on the coupling reaction. Due to the electronegativity of the nitrogen atom, it was reasoned that 2-bromopyridine should be more reactive towards the oxidative addition, which is normally the rate-limiting step of the reaction, than 3-bromopyridine.[32] In fact, a conversion of 70% was achieved for the reaction of 3-bromopyridine with phenylboronic acid (entry 15), while 2-bromopyridine remained almost unreacted under the same reaction conditions (entry 14). The same trend in the reactivity between substitution in the 2- and 3-postitions has also been observed by others, although the difference in reactivity between the two isomers of bromopyridines was much less significant.[31–34] It was previously presumed that the capacity for 2-bromopyridine to complex to the palladium catalyst prevented the coupling reaction.[34] The reaction of 5-bromopyrimidine, although it is an electron-poor heteroaryl bromide, proceeded with low yield (entry 16). The Suzuki–Miyaura reaction of 5-bromo-2-furaldehyde proceeded with very good conversion being achieved (entry 13), in accordance with results of Feuerstein et al.[31,32] It was found that the reaction of 2-bromothiophene led to a high yield of over 80% (entry 17), while a conversion of only 39% was afforded in the reaction of 3-bromothiphene (entry 18). This is in accordance with results previously reported by Molander and Biolatto.[34] However, over 10% of both 2- and 3-bromothiophene ended up in the corresponding homo-coupling product, which was not observed in the Suzuki–Miyaura reaction of any other organobromide used in this study. It is possible there is a substrate–metal interaction in one of the possible catalytic transition states that is affecting the outcome. However, a complete reaction pathway still remains to be elucidated. It is interesting that in general no homocoupled product was observed, even though the continuous flow reactions were not carried out in a nitrogen atmosphere. Therefore, the reaction in the mini-reactor is more selective than the reaction in batch.

Wiles et al. have recently reported a Michael addition reaction in a micro reactor under EOF conditions, in which enhancements in conversions through the application of the stopped flow technique were achieved.[35] This procedure involved the mobilisation of reagents through the glass micro reactor device for a designated period of time using an applied electric field, and the flow was subsequently paused by the removal of the applied field, prior to re-applying the field. The authors proposed that the observed increase in conversion, when using the technique of stopped flow, was due to an effective increase in residence time within the reactor. We, therefore, decided to apply the stopped-flow technique to the Suzuki–Miyaura reaction of 4-bromobenzaldehyde with phenylboronic acid using the palladium resin catalyst in the continuous flow reactor. In fact, this technique is an alternative route to decreasing the flow rate to increase the space time of reagents within the catalyst bed. The results are shown in Figure 4. As the residence time was found to be 10.5 min at a flow rate of

Table 3. The Suzuki–Miyaura reaction of heteroaryl bromides in the continuous flow reactor using the palladium resin catalyst, 1.5 equiv $PhB(OH)_2$, 3 equiv *N*,*N*-diisopropyl ethyl amine in DMF/water 1:1 at 100 °C, at the flow rate of 6 μl/min

Entry	Substrate	Product	Conversion (%)
13			91
14			1
15			70
16			42
17			82
18			39
19			88[a]
20			55[a]

The data represent conversions of the bromides to cross-coupling products (based on GC–S data).
[a] 4-Methoxybenzeneboronic acid was used instead of benzeneboronic acid.

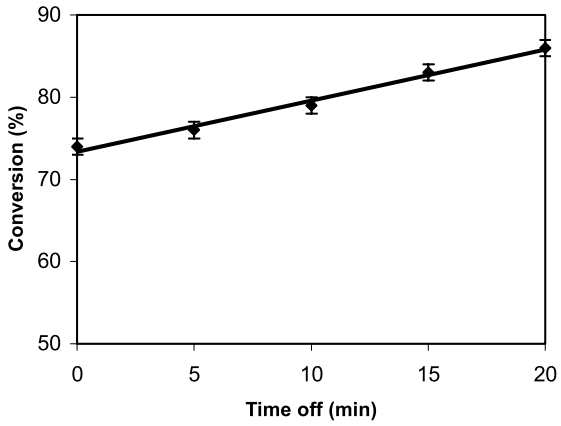


Figure 4. Study of stopped flow technique in the Suzuki–Miyaura reaction of 4-bromobenzaldehyde using the continuous flow reactor at the low rate of 6 μl/min, with the regime of 10 min on and between 0 and 20 min off.

6 μl/min, reactants were pumped through the reactor for 10 min and the flow was subsequently paused for a designated period of time, prior to re-injecting the solution. The syringe pump was controlled using an automated cyclic timer unit, which was designed and constructed in-house. Using the regime of 10 min on and 5 min off, the conversions were slightly improved to 76%. Lengthening the stopped flow period to 10 min resulted in a further increase to around 80% conversion. The conversion could be improved to 83 and 86% by stopping the flow for 15 and 20 min, respectively. No by-products were observed, the mass balance being completed by unreacted starting material.

3. Conclusions

The polymer-supported palladium(II) complex exhibited catalytic activity in the cross-coupling reactions of various aryl bromides and heteroaryl bromides with phenylboronic acid in a mini-continuous flow reactor system without the need for phosphine ligands. Using the mini-flow reactor system, reasonable conversions can be achieved in a matter of minutes. Although simple in design and concept, with easily replaceable catalyst beds and interchangeable reagents premixes, as there is no reaction in the absence of the catalyst, the mini-flow reactor system provides a powerful tool in catalyst screening and a route to high throughput synthesis. Therefore, the mini flow system is ideal for the rapid production of small inventories of reagents. Products can be generated on demand, at the point of use, so reducing the need to store and transport hazardous chemicals. Furthermore, we have demonstrated that the use of stopped-flow techniques are applicable to the Suzuki–Miyaura reaction, leading to increased residence time in the reactor and an increase in product yield.

4. Experimental

4.1. General

Chemicals were obtained from Aldrich and Fisher and were used as received. The unsymmetrical salen-type palladium(II) complex was synthesised according to previously published methods.[20] Mass Spectra were recorded by Jane Stanbra and Simon Thorpe, ICP-ES analyses were performed on a Spectro Ciros^{CDD} instrument (Spectro Analytical, UK) by Ian Staton from the Department of Chemistry, The University of Sheffield. GC–MS analyses were performed using a Perkin Elmer GC–MS with a 30 m×0.25 mm×0.25 μm Phenomenex-2B5 column. The temperature program was 60–260 °C at 10 °C min^{-1} with a final temperature isothermal hold for 10 min. The MS mass limit was set between 50 and 450 Da.

4.2. Catalyst preparation

A yellow solution of palladium complex (0.20 g, 0.54 mmol) in dry DMF (40 ml) and THF (20 ml) was added dropwise at room temperature to a dispersion of excess 60% sodium hydride in mineral oil (0.06 g, 1.5 mmol) and the resulting mixture stirred for 10 min. A suspension of Merrifield resin (2 g, 200–400 mesh, 1.7 mmol-Cl/g, 3.4 mmol) that had been pre-swelled in DMF (40 ml) for 30 min was then added and the mixture stirred gently at room temperature for 24 h. The initially white Merrifield resin beads became yellow and the solution turned pale yellow. The beads were filtered off, washed several times with water (3×50 ml), triturated several times for a total of 24 h with DMF (5×50 ml), THF (3×50 ml), diethyl ether (3×50 ml) to remove physically adsorbed palladium complex and air-dried to yield yellow beads (2.0 g). Inductively coupled plasma-atomic emission spectroscopy (ICP-AES) measurements showed there to be ca. 2% (wt/wt) palladium on the Merrifield beads, corresponding to a catalyst loading of 0.2 mmol palladium/g of resin.

4.3. ICP analysis of the supported catalysts

Calibration against palladium standards and a blank was linear, using 2% nitric acid solutions containing 0, 1, 5 and 10 ppm palladium made from a 1000 ppm stock solution (Aristar). Weighed samples (20.0 mg) of immobilised palladium catalysts were placed in glass tubes and digested at 180 °C in a mixture of concentrated nitric acid (5 cm^3, Aristar) and concentrated perchloric acid (0.5 cm^3, Aristar). Three parallel samples were digested in 2, 4 and 6 h, respectively. The yellow palladium catalyst became a white residue after digestion. The digest was then diluted to 50 cm^3 with water. Analysis showed that all the palladium was removed from the support within 2 h as increasing the digestion time to 4 and 6 h achieved no increase in the amount of the palladium in the digest.

4.4. Catalysis studies

4.4.1. Batch reactions. Unless otherwise stated, a solution of 4-bromoanisole (0.0561 g, 0.3 mmol) in DMF (0.75 ml) was added to a Radley's Carousel reaction tube constaining the palladium resin catalyst (7.5 mg, 0.0015 mmol). A solution of *N*,*N*-diisopropyl ethyl amine (0.116 g, 0.9 mmol) in water (1.5 ml) and a solution of phenylboronic acid (0.054 g, 0.45 mmol) in DMF (0.75 ml) were then added and the tube was heated at 100 °C for 24 h with magnetic stirring under a nitrogen atmosphere. To work-up,

the mixture was allowed to cool to room temperature and saturated aqueous NaCl solution (3 ml) was added. The organic components were extracted into diethyl ether (3× 3 ml), which was dried over anhydrous $MgSO_4$ and the resulting solution analysed by GC and GC–MS with reference to standard solutions of 4-methoxybiphenyl.

4.4.2. Micro flow reactions. Unless otherwise stated, the Suzuki–Miyaura coupling reaction of 4-bromoanisole with phenylboronic acid was carried out in a pressure driven micro flow reactor (length = 25 mm; I.D. = 3 mm) build up from Omnifit glassware containing the Merrifield resin-supported palladium catalyst (110 mg). Standard HPLC connectors allowed one end of the reactor to be connected to a disposable solvent-resistant syringe, while the other end was attached to a syringe needle leading to a quenching vessel containing diethyl ether and saturated aqueous Na_2CO_3. The reactor was heated by immersing it in a water bath at 100 °C. Reactant mixtures consisting of 4-bromoanisole (0.1 M), phenylboronic acid (0.15 M) and *N*,*N*-diisopropyl ethyl amine (0.3 M) in DMF/water 1:1 at room temperature were then pumped continuously through the palladium resin catalyst bed at known flow rates for 5 h, using a syringe pump (RAZAL, A-99). The organic components were extracted into diethyl ether and analysed by GC and GC–S as described above.

4.5. Residence time distribution measurement

The mean residence/space time of the reaction solution within the catalyst bed was measured using a standard experimental method, the step experiment.[22] A solution of $CoCl_2$ in DMF/water 1:1 was pumped through the Omnifit flow reactor containing the palladium resin catalyst (110 mg) at the flow rate of 6 μl/min. The outlet absorbance distribution, and hence the outlet concentration distribution, versus time was measured online using a fibre optic spectrometer (USB 2000-UV–vis, Ocean Optics Inc.) at different wavelength ranging from 450 to 560 nm. The absorbance distribution at the wavelengths of 520 nm versus time is shown in Figure 5. Taking into account the residence time of the solution in the HPLC standard connectors based on their volumes and the known flow rate, the mean space time within the catalyst bed was found to be 10.5 min at the flow rate of 6 μl/min.

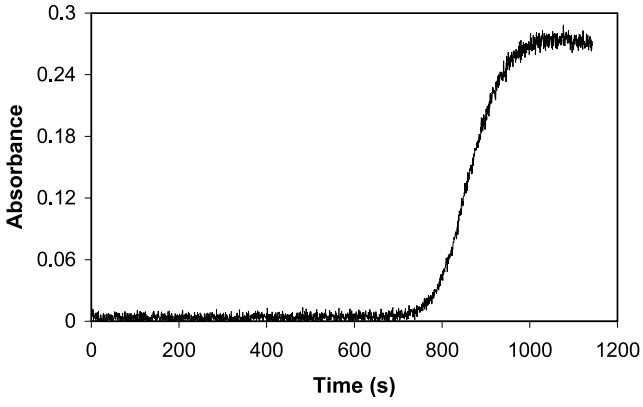


Figure 5. The outlet absorbance distribution versus time at the wavelength of 520 nm and the flow rate of 6 μl/min using $CoCl_2$ in DMF/H_2O.

Acknowledgements

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Asymmetric Mukaiyama aldol reaction of silyl enol ethers with aldehydes using a polymer-supported chiral Lewis acid catalyst

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Abstract—Chiral *N*-sulfonylated α-amino acid monomer (**5**) derived from (*S*)-tryptophan was copolymerized with styrene and divinylbenzene under radical polymerization conditions to give a polymer-supported *N*-sulfonyl-(*S*)-tryptophan (**6**). Treatment of the polymer-supported chiral ligand with 3,5-bis(trifluoromethyl)phenyl boron dichloride afforded a polymeric Lewis acid catalyst (**16**) effective for asymmetric Mukaiyama aldol reaction of silyl enol ethers and aldehydes. Various aldehydes were allowed to react with silyl enol ethers in the presence of the polymeric chiral Lewis acid to give the corresponding aldol adducts in high yield with high levels of enantioselectivity.

1. Introduction

Catalytic asymmetric Mukaiyama aldol reactions have emerged as one of the most important carbon–carbon bond forming reactions affording synthetically useful optically active β-hydroxycarbonyl compounds.[1–3] Various methodologies of the asymmetric Mukaiyama aldol reaction have been studied, which include chiral Lewis acid promoted reaction,[4] Lewis base mediated reaction,[5] and the reaction via transition metal enolate intermediates.[6] These chiral Lewis acid catalysts include a number of chirally modified boron complexes that have been prepared and studied as Lewis acid catalysts for the asymmetric reactions including Mukaiyama aldol reaction. Chiral *N*-sulfonyl oxazaborolidinones are examples that are readily prepared from α-amino acid and boron compounds. The chiral *N*-sulfonyl oxazaborolidinones were originally developed for the catalyst of asymmetric Diels–Alder reaction by Yamamoto[7] and Helmchen.[8] Kiyooka indicated the efficiency of the methodology using oxazaborolidinones as chiral catalyst for the Mukaiyama aldol reaction.[9,10] Corey chose (*S*)-tryptophan as a chiral α-amino acid and revealed its effectiveness mainly due to its possibility of π–π stacking effect based on the indole ring.[11] Yamamoto and Ishihara further improved the efficiency of the (*S*)-tryptophan derived *N*-sulfonyl oxazaborolidinone system by introducing a new boron substituent of 3,5-bis(trifluoromethyl)phenyl group.[12,13] By using this catalyst asymmetric aldol reaction between benzaldehyde and silyl enol ether smoothly occurred to give the corresponding aldol adduct in quantitative conversion with high enantioselectivity. For example, the reaction of benzaldehyde with 1-phenyl-1-(trimethylsilyloxy)ethylene afforded the chiral aldol adduct in 99% yield with 94% ee.[12] We have applied the same chiral oxazaborolidinone catalyst for the preparation of optically active polymers by means of asymmetric aldol polymerization method developed by us.[14–16] Optically active poly(β-hydroxycarbonyl)s having high optical purity were first obtained by this method. On the other hand we have also developed polymer-supported *N*-sulfonyl α-amino acids as chiral ligand of the asymmetric Diels–Alder reaction.[17] For example, polymer-supported oxazaborolidinone prepared from *N*-sulfonyl-(*S*)-valine and borane-dimethyl sulfide showed excellent activity in Diels–Alder reaction between cyclopentadiene and methacrolein to give the corresponding chiral adduct in quantitative yield with up to 95% ee, which was higher than that obtained from the low-molecular-weight catalyst in solution system.[18] We have now developed polymer-supported *N*-sulfonyl-(*S*)-tryptophan to prepare a polymeric version of the Yamamoto's oxazaborolidinone catalyst. In this paper we discuss the synthesis of a chiral monomer derived from (*S*)-tryptophan and its polymerization. Optimized reaction conditions for asymmetric aldol reaction between aldehyde and silyl enol ether using this polymeric catalyst was also discussed.

2. Results and discussion

2.1. Chiral monomer synthesis

Yamamoto and Ishihara introduced a new chiral Lewis acid *N*-sulfonyloxazaborolidinone **1** using arylboron dichloride bearing electron-withdrawing substituents as Lewis acid

Keywords: Mukaiyama aldol reaction; *N*-sulfonyl-(*S*)-tryptophan; Oxazaborolidinone; Chiral Lewis acid; Silyl enol ether.
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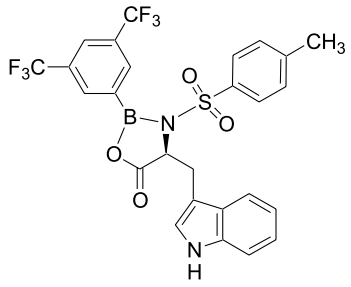

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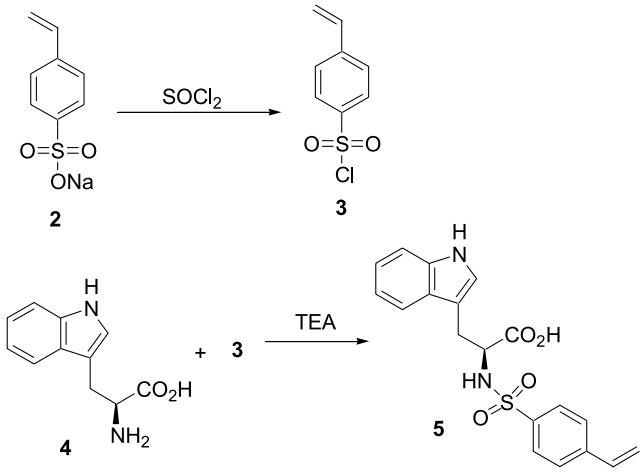
Scheme 1. Oxazaborolidinone catalyst derived from *N*-sulfonyl-(*S*)-tryptophan.

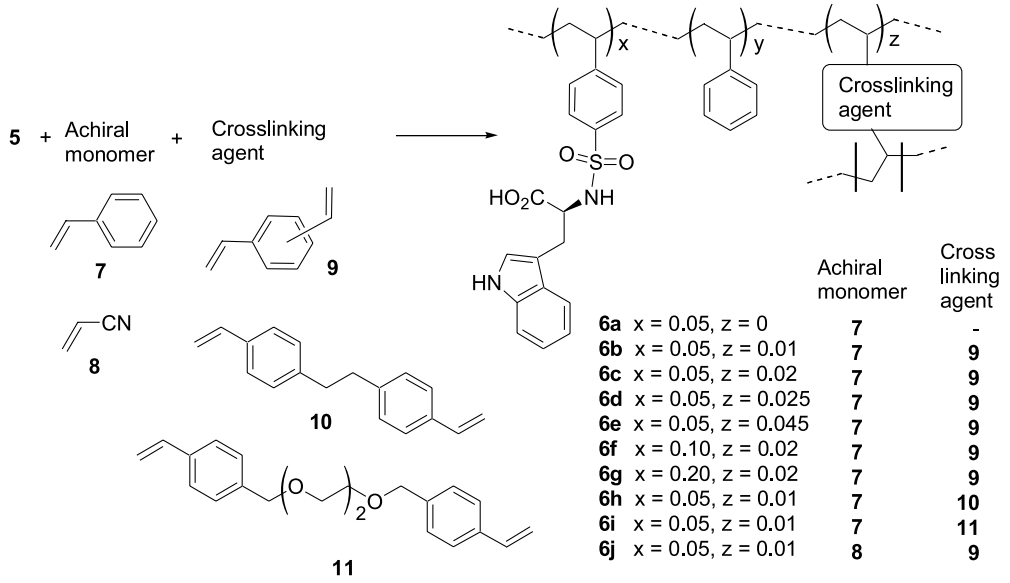


Scheme 2. Preparation of chiral *N*-sulfonyl-(*S*)-tryptophan monormer.

components.[12] The chiral Lewis acid **1** showed excellent catalytic activity in an enantioselective Mukaiyama aldol reaction.[12] The chirality of the catalyst is originated from (*S*)-tryptophan. The structure of *B*-substituent in the catalyst is important to obtain a high enantioselectivity. Introduction of 3,5-bistrifluoromethylphenyl group generated a highly enantioselective catalyst **1** (Scheme 1). Since we have synthesized various types of polymer-supported *N*-sulfonyl-amino acids and used them as polymeric chiral Lewis acid catalysts of asymmetric reactions including Diels–Alder reaction,[18] we could apply the method to the preparation of the polymer-supported version of *N*-sulfonyl-(*S*)-tryptophan. Sodium *p*-vinylbenzenesulfonate **2** was readily converted to *p*-vinylbenzenesulfonylchloride **3**, which was allowed to react with (*S*)-tryptophan **4** to prepare *N*-(*p*-styrenesulfonyl)-(*S*)-tryptophan **5** as shown in Scheme 2.[19] Because of the instability of the indole ring of (*S*)-tryptophan, purification of the chiral monomer required special care. As soon as the chiral monomer was purified the monomer should be subjected to the polymerization, otherwise the monomer was susceptible to decomposition under air. However, purified chiral monomer **5** could be stored for long period of time under argon at −20 °C.

2.2. Polymerization

In our previous paper, we have prepared chiral polymer beads containing *N*-sulfonylamino acid pendant groups by means of suspension polymerization method.[18] First we tried the suspension polymerization of *N*-sulfonyl-(*S*)-tryptophan monomer **5** with styrene in the presence of divinylbenzene as crosslinking agent. However, mainly due to the low solubility of the chiral monomer in organic solvent the diluted monomer solution did not form stable particles in water. Several attempts of suspension polymerization failed to obtain the corresponding polymer beads in satisfactory yield. Although the monomer showed higher solubility in THF and DMF, the use of such water miscible solvents would cause the difficulty in the suspension polymerization in water. Thus, we changed the polymerization method to solution polymerization. In this case we could even use the solvents miscible with water. THF was chosen as the polymerization solvent, because all the monomers including *p*-vinylbenzenesulfonyl-(*S*)-tryptophan, styrene and divinylbenzene dissolved well in it. As soon as the polymerization of the monomers was initiated in THF the viscosity of the solution increased and finally gel was formed. As shown in Scheme 3, polymerization



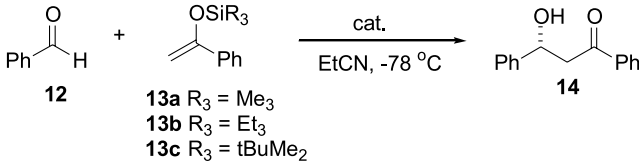
		Achiral monomer	Cross linking agent
6a	x = 0.05, z = 0	**7**	-
6b	x = 0.05, z = 0.01	**7**	**9**
6c	x = 0.05, z = 0.02	**7**	**9**
6d	x = 0.05, z = 0.025	**7**	**9**
6e	x = 0.05, z = 0.045	**7**	**9**
6f	x = 0.10, z = 0.02	**7**	**9**
6g	x = 0.20, z = 0.02	**7**	**9**
6h	x = 0.05, z = 0.01	**7**	**10**
6i	x = 0.05, z = 0.01	**7**	**11**
6j	x = 0.05, z = 0.01	**8**	**9**

Scheme 3. Preparation of polymer-supported chiral *N*-sulfonyl-(*S*)-tryptophan.

Table 1. Asymmetric aldol reaction of benzaldehyde with silyl enol ether derived from acetophenone catalyzed by oxazaborolidinone catalyst

Entry	Lewis acid catalyst	Silyl enol ether	–OSiR$_3$		–OH	
			Yield (%)[a]	ee (%)[b]	Yield (%)[a]	ee (%)[b]
1	**15**	**13b**	18	—	76	—
2[c]	**1**	**13a**	91	93	4	68
3	**1**	**13b**	95	92	4	87
4[d]	**1**	**13b**	69	65	30	42
5	**1**	**13c**	69	16	29	88

[a] Isolated yield.
[b] Determined chiral HPLC.
[c] Data from Ref. 12.
[d] Reaction was performed at room temperature.



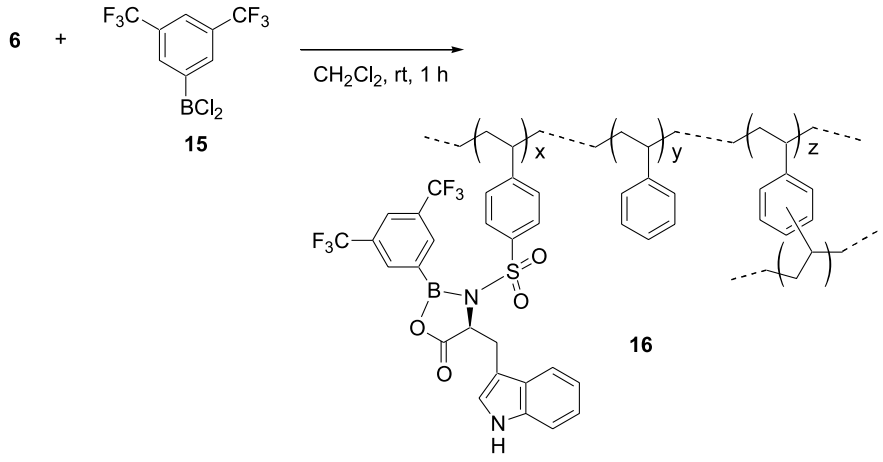
Scheme 4. Asymmetric aldol reaction using polymer-supported chiral oxazaborolidinone.

occurred to give the corresponding crosslinked polymer **6**. The obtained gel was crushed in methanol and washed on a glass filter to give the powdered polymer-supported *N*-sulfonyl-(*S*)-tryptophan. The degree of crosslinking and the chiral ligand loading were controlled by the change of the monomers composition. Crosslinking agents (**10**, **11**) other than divinylbenzene could be used in this polymerization. Acrylonitrile **8** instead of styrene as achiral monomer was also used to give the crosslinked chiral polymer **6j**. All these polymers were gel-like materials, which were insoluble in organic solvents but swellable in THF, DMF, and propionitrile. Polymerization without crosslinking agent afforded the linear chiral polymer that was soluble in THF.

2.3. Asymmetric aldol reaction

Mukaiyama aldol reaction between benzaldehyde and silyl enol ether proceeded smoothly in the presence of boron dichloride **15** to give the corresponding aldol adduct in high yield as shown in Table 1, run 1. The chloride was easily substituted with *N*-(*p*-toluenesulfonyl)-(*S*)-tryptophan chiral ligand to form oxazaborolidinone **1**, which was an efficient chiral Lewis acid catalyst of the aldol reaction to afford optically active β-hydroxyketone in quantitative conversion at −78 °C.[12,13] We surveyed the effect of several silyl substituents on the silyl enol ether. From the results obtained in Table 1, we chose triethylsilyl enol ether as a substrate of the asymmetric aldol reaction. In order to keep high enantioselectivity the reaction should be performed at lower temperature (−78 °C). The absolute configuration of the aldol adducts indicated in Table 1 was uniformly *R* (Scheme 4).

2.3.1. Asymmetric aldol reaction using polymeric oxazaborolidinone. Since the *B*-aryloxazaborolidine could not be prepared from arylboronic acid,[20,21] the oxazaborolidinones were prepared from arylboron dichlorides. We have prepared the polymeric oxazaborolidinone **16** from the chiral polymer **6** possessing *N*-sulfonyl-(*S*)-tryptophan moiety and arylboron dichloride **15** in dichloromethane according to the method reported by Ishihara.[12] (Scheme 5) Our initial studies using the polymeric oxazaborolidinone were conducted with benzaldehyde and enol silane **13b** derived from acetophenone at −78 °C in propionitrile as a solvent in the presence of **16** as a catalyst. The asymmetric aldol reaction smoothly occurred in the presence of the polymeric catalyst **16** to give the corresponding (*R*)-β-hydroxyketone in high yield with a high level of enantioselectivity. Table 2 shows the effect of catalyst loading and crosslinking degree on the asymmetric aldol reaction. Lightly crosslinked polymer **6b** having 5% catalyst loading showed the best result. The enantioselectivity obtained was almost same as that from



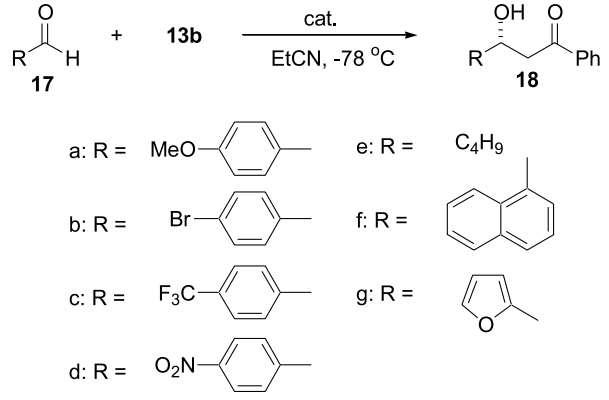
Scheme 5. Preparation of polymer-supported chiral oxazaborolidinone catalyst.

Table 2. Asymmetric aldol reaction of **12** and **13b** using polymer-supported oxazaborolidinone catalyst in propionitrile at −78 °C for 24 h

Entry	Polymer	Catalyst loading (%)	Crosslinking agent	Degree of cross-linking (%)	**14**	
					Yield (%)[a]	ee (%)[b]
1	**6a**	5	—	0	99	89
2[c]	**6b**	5	**9**	1	90	91
3	**6b**	5	**9**	1	99	91
4[d]	**6b**	5	**9**	1	99	90
5	**6c**	5	**9**	2	99	90
6	**6d**	5	**9**	2.5	99	88
7	**6e**	5	**9**	4.5	89	83
8	**6f**	10	**9**	2	83	80
9	**6g**	20	**9**	2	73	75
10	**6h**	5	**10**	1	98	76
11	**6i**	5	**11**	1	98	83
12	**6j**	5	**9**	1	99	71

[a] Isolated yield.
[b] Determined by chiral HPLC.
[c] After 3 h.
[d] Recycled polymer-supported *N*-sulfonyl-(*S*)-tryptophan was used.

the low-molecular-weight catalyst **1** in homogeneous solution system. Higher crosslinking and catalyst loading decreased both reactivity and enantioselectivity to some extent. After the reaction completed the polymeric catalyst could be readily removed by simple filtration. The polymeric catalyst prepared from the recycled polymer was shown to keep its activity (entry 4) in a second cycle. Polymers crosslinked with **10** and **11** were also effective for the same reaction (entries 10 and 11). Somewhat lower enantioselectivities were obtained with these polymeric catalysts compared to the corresponding divinylbenzene crosslinked polymers.



Scheme 6. Asymmetric aldol reaction of various aldehyde with silyl enol ether.

Table 3. Asymmetric aldol reaction of aldehyde and silyl enol ether **13b** with oxazaborolidinone catalyst **1**

Entry	Aldehyde	Aldol product		
			Yield (%)[a]	ee (%)[b]
1	**12**	**14**	99	92
2	**17a**	**18a**	97	82
3	**17b**	**18b**	93	82
4	**17c**	**18c**	99	93
5	**17d**	**18d**	99	81
6	**17e**	**18e**	98	95
7	**17f**	**18f**	98	80
8	**17g**	**18g**	99	80

[a] Isolated yield.
[b] Determined by chiral HPLC.

Not only benzaldehyde, also other several aldehydes reacted with the silyl enol ether in the presence of chiral oxazaborolidinone **1** to give the corresponding aldol products in high enantioselectivity (Scheme 6). Table 3 shows the results of the asymmetric aldol reactions with **8**. As shown in Table 4 the polymeric oxazaborolidinone **16** was also effective in forming the same product in the same level of the enantioselectivity. The amount of the polymeric catalyst used had no effect on the enantioselectivity of the aldol product (entry 2). Aliphatic aldehydes showed high enantioselectivity (95% ee) using both **1** and **16**.

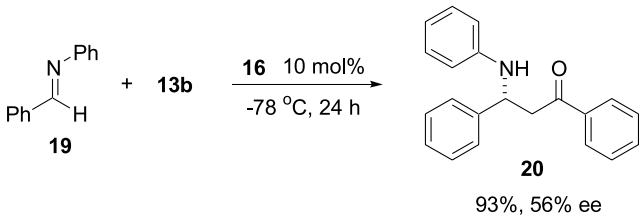
Table 4. Asymmetric aldol reaction of aldehyde and silyl enol ether **13b** with polymer-supported oxazaborolidinone catalyst **16** derived from **6b**

Entry	Aldehyde	Aldol product		
			Yield (%)[a]	ee (%)[b]
1	**12**	**14**	99	91
2[c]	**12**	**14**	99	91
3	**17a**	**18a**	81	71
4	**17b**	**18b**	74	83
5	**17c**	**18c**	71	91
6	**17d**	**18d**	69	75
7	**17e**	**18e**	72	95
8	**17f**	**18f**	47	72
9	**17g**	**18g**	72	70

[a] Isolated yield.
[b] Determined by chiral HPLC.
[c] Compound **16** (20 mol%) was used.

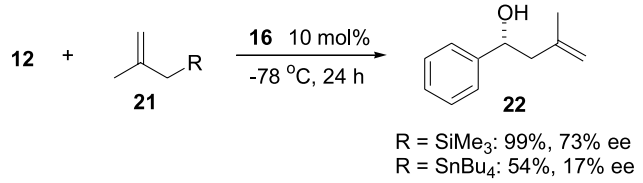
2.4. Some other asymmetric reactions using the polymeric oxazaborolidinone catalyst

Chiral oxazaborolidinones are known to be an efficient Lewis acid catalyst for various kinds of carbon–carbon bond forming reactions. Since we succeeded in maintaining the catalytic activities of chiral oxazaborolidinone on the crosslinked polymer, the polymer-supported oxazaborolidinone would be applicable to these reactions. The polymeric catalyst **16** was used for reactions including Mannich type reaction of imine with silyl enol ether and allylation of aldehyde. Scheme 7 revealed that the silyl enol ether **13b** reacted with aldimine **19** to yield the β-aminoketone **20** in high yield with enantioselectivity of 56%. The same catalyst



Scheme 7. Asymmetric Mannich reaction.

was also active in the asymmetric allylation reactions. Especially methallyltrimethylsilane **21** (R=$SiMe_3$) reacted with benzaldehyde to give the optically active homoallyl alcohol **22** in quantitative yield with 73% ee (Scheme 8).



Scheme 8. Asymmetric allylation of benzaldehyde.

3. Conclusion

The chiral monomer of *N*-sulfonylated (*S*)-tryptophan was prepared and polymerized with styrene and crosslinking agent such as divinylbenzene to give polymeric chiral ligand **6**. The reaction of the obtained polymer **6** and 3,5-bis(trifluoromethyl)phenylboron dichloride **15** gave polymeric chiral oxazaborolidionone **16**. We have found that **16** worked well as a catalyst in the asymmetric Mukaiyama aldol reaction of aldehyde and silyl enol ether. High level of enantioselectivity was obtained using the polymeric chiral catalyst. Other than the Mukaiyama aldol reaction Mannich type reaction and allylation reaction were asymmetrically catalyzed by the same polymeric catalyst.

4. Experimental

4.1. General

Unless otherwise noted, all reactions were performed in oven-dried glassware, under an atmosphere of argon. ^{1}H NMR (300 MHz) spectra were recorded on Varian Mercury 300 spectrometer using tetramethylsilane as an internal standard, and *J* values are recorded in Hz. IR spectra were recorded with a JEOL JIR-7000 FT-IR spectrometer and are reported in reciprocal centimeter (cm^{-1}). Elemental analyses were performed at the Microanalytical Center of Kyoto University. HPLC analyses were performed with a JASCO HPLC system composed of 3-line degasser DG-980-50, HPLC pump PV 980, column oven CO-965, equipped with a chiral column (Chiralcel OD-H, Daicel) using hexane/2-propanol as an eluent. A UV detector (JASCO UV-975) was used for the peak detection. GC analyses of reaction conversion were performed with a Shimadzu Capillary Gas Chromatograph 14A equipped with a capillary column (Astec Chiraldex G-TA, 30 m× 0.25 mm). Precoated silica gel plates (Merck 5554, 60 F254) were used for thin layer chromatography. Silica gel (Wakogel C-200) was used for column chromatography. Optical rotations were taken on a JASCO DIP-140 digital polarimeter using a 10 cm thermostated microcell.

4.1.1. Preparation of silyl enol ethers 13. Silyl enol ethers **13** were prepared by quenching the corresponding lithium enolates, derived from ketones, with lithium *N*,*N*-diisopropylamine (LDA) in THF, with chlorosilane.[14,22]

4.1.2. Preparation of *N*-(*p*-vinylbenzenesulfonyl)-(*S*)-tryptophan 5. *p*-Vinylbenzenesulfonyl chloride was prepared by the reported procedure.[23] To a suspension of (*S*)-tryptophan (1.52 g, 8.0 mmol) in water (30 mL) and THF (5 mL) was added triethylamine (1.9 mL, 19.2 mmol). The resulting clear solution was stirred at 0 °C and a THF (3 mL) solution of *p*-vinylbenzenesulfonyl chloride (1.94 g, 9.6 mmol) was added to the mixture. The resulting mixture was then stirred at room temperature for 3 h. The solution was cooled to 0 °C and acidified with 2 M HCl to pH 2. The aqueous layer was extracted with ethyl acetate (20 mL×3). The combined organic layer was dried over $MgSO_4$ and evaporated to give the crude product, which was purified by silica gel column chromatography (hexane/ethyl acetate, 1:1). Yield 87% (2.58 g). Mp 67–68 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.05–3.28 (m, 2H), 4.23 (m, 1H), 5.37 (d, J=11 Hz, 1H), 5.50 (d, J=8 Hz, 1H), 5.77 (d, J=17 Hz, 1H), 6.60 (dd, J=11, 17 Hz, 1H), 6.90–7.55 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.9, 141.9, 137.9, 136.3, 135.6, 127.2, 126.6, 124.3, 122.2, 119.8, 117.6, 111.7, 108.6, 56.2, 28.9. IR (KBr) 3400, 1730, 1430, 1330, 1150, 1090 cm^{-1}. $[\alpha]_D^{23}$ +38 (*c* 1.0, ethanol). Anal. Calcd for $C_{19}H_{18}N_2O_4S$: C, 61.61; H, 4.90; N, 7.56. Found: C, 61.58; H, 4.92; N, 7.55%.

4.1.3. Preparation of polymer-immobilized *N*-(*p*-vinylbenzenesulfonyl)-(*S*)-tryptophan 6. A 20 mL glass ampoule equipped with a magnetic stirring bar was charged with THF (5 mL), **5** (0.749 g, 2.02 mmol), styrene (3.98 g, 38.2 mmol), 2,2′-azobis(isobutyronitrile) (AIBN) (60 mg). The ampoule was sealed after three freeze-thaw cycles under liquid nitrogen. Copolymerization was carried out at 70 °C for 24 h. The ampoule was opened and the resulting mixture was poured into methanol and the formed precipitate was filtered, washed with methanol and dried to give the corresponding polymer **6a** as a white powder (4.17 g, 88%). M_n=28,000, M_w/M_n=2.27. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.2–2.2 (polymer main chain CH, CH_2), 3.2 (br s, tryptophan CH_2), 4.2 (br s, tryptophan CH), 6.3–7.6 (aromatic protons). IR (KBr) 3627, 3427, 3025, 2920, 1731, 1600, 1490, 1450, 1330, 1156, 1090. Anal. Calcd for $(C_8H_8)_{0.95}(C_{19}H_{18}N_2O_4S)_{0.05}$: C, 87.43; H, 7.29; N, 1.19. Found: C, 87.50; H, 7.25; N, 1.22%.

Crosslinked polymers **6b**–**6j** were prepared from **5**, achiral monomer, and crosslinking agent by the same procedure described for the solution polymerization. After the polymerization was completed gel was treated with methanol. The methanol suspension of the gel was then washed with methanol on a glass filter. The obtained polymer was dried in vacuo.

4.2. General procedure for the Mukaiyama aldol reaction catalyzed by 16

A suspension of 3,5-bis(trifluoromethyl)boronic acid (5.8 g, 22.4 mmol) in benzene was heated for 12 h at reflux with removal of water using CaH_2 in a Soxhlet thimble. The resulting solution was cooled to room temperature and concentrated in vacuo to give trimeric anhydride as a white solid. A solution of boron trichloride (45 mL, 45 mmol) in heptane was added to the above solid and heated at reflux for 6 h. After the solvent was removed the product **15** was isolated as a colorless oil by distillation under reduced pressure.[12]

Compound **15** (32 mg, 0.11 mmol) prepared above was treated with polymer-supported *N*-sulfonyl-(*S*)-tryptophan **6b** (0.24 g, 0.1 mmol) suspended in dichloromethane (4 mL) at room temperature. After being stirred for 1 h, the reaction mixture was concentrated in vacuo to give the polymer-supported oxazaborolidinone **16**. A suspension of **16** in propionitrile (4 mL) was cooled to −78 °C. After benzaldehyde (106 mg, 1 mmol) was added to the mixture, 1-phenyl-1-(triethylsilyloxy)ethylene (281 mg, 1.2 mmol) in propionitrile (1 mL) was subsequently added dropwise. The reaction mixture was stirred at −78 °C for 24 h and then quenched by addition of saturated aqueous $NaHCO_3$. The polymeric catalyst was removed by filtration and the filtrate was extracted with ether. The combined organic phases were dried over $MgSO_4$ and evaporated. The residue was dissolved in THF (2 mL) and 1 M aqueous HCl (2 mL), and the resulting solution was allowed stand for 30 min. Saturated $NaHCO_3$ was added and the mixture was extracted with ether. The combined organic phases were dried over $MgSO_4$ and evaporated to an oily residue. Silica gel chromatography (hexanes/ethyl acetate, 4:1) afforded 224 mg (99% yield) of the aldol product **14**. ^{1}H NMR and IR spectroscopic data are in agreement with those reported in the literature.[24] The enantioselectivity was determined by chiral HPLC analysis using Chiralcel OD column (hexane/2-propanol, 20:1), flow rate = 0.4 mL/min, column temperature; 30 °C, t_S = 42.3 min (*S*), t_R = 47.0 min (*R*).

4.2.1. 3-Hydroxy-1-phenyl-3-(4-methoxyphenyl)-propan-1-one 18a. The enantiomeric excess was determined by chiral HPLC analysis using Chiralcel OD column (hexane/2-propanol, 20:1), flow rate = 0.4 mL/min, column temperature; 30 °C, t_S = 42.3 min (*S*), t_R = 47.0 min (*R*).

4.2.2. 3-Hydroxy-1-phenyl-3-(4-bromophenyl)-propan-1-one 18b. The enantiomeric excess was determined by chiral HPLC analysis using Chiralcel OD column (hexane/2-propanol, 20:1), flow rate = 0.4 mL/min, column temperature; 30 °C, t_S = 49.4 min (*S*), t_R = 56.2 min (*R*).

4.2.3. 3-Hydroxy-1-phenyl-3-(4-trifluoromethylphenyl)-propan-1-one 18c. The enantiomeric excess was determined by chiral HPLC analysis using Chiralcel OD column (hexane/2-propanol, 20:1), flow rate = 0.4 mL/min, column temperature; 30 °C, t_S = 49.4 min (*S*), t_R = 56.2 min (*R*).

4.2.4. 3-Hydroxy-1-phenyl-3-(4-nitrophenyl)-propan-1-one 18d. The enantiomeric excess was determined by chiral HPLC analysis using Chiralcel OD column (hexane/2-propanol, 20:1), flow rate = 0.4 mL/min, column temperature; 30 °C, t_S = 47.8 min (*S*), t_R = 56.5 min (*R*).

4.2.5. 3-Hydroxy-1-phenylheptan-1-one 18e. The enantiomeric excess was determined by chiral HPLC analysis using Chiralcel OD column (hexane/2-propanol, 20:1), flow rate = 0.2 mL/min, column temperature; 30 °C, t_S = 32.7 min (*S*), t_R = 36.8 min (*R*).

4.2.6. 3-Hydroxy-3-naphthalen-1-yl-1-phenylpropan-1-one 18f. The enantiomeric excess was determined by chiral HPLC analysis using Chiralcel OD column (hexane/2-propanol, 20:1), flow rate = 0.4 mL/min, column temperature; 30 °C, t_S = 52.2 min (*S*), t_R = 71.8 min (*R*).

4.2.7. 3-Furan-2-yl-3-hydroxy-1-phenylpropan-1-one 18g. The enantiomeric excess was determined by chiral HPLC analysis using Chiralcel OD column (hexane/2-propanol, 20:1), flow rate = 0.4 mL/min, column temperature; 30 °C, t_S = 48.4 min (*S*), t_R = 54.3 min (*R*).

4.3. Asymmetric Mannich reaction using polymer-supported oxazaborolidinone

Suspension of **16** (0.1 mmol, 10 mol%) prepared from **6b** (5% loading, 1% crosslinking) in THF (4 mL) was cooled to −78 °C. After *N*-benzilidenebenzenamine (181 mg, 1 mmol) was added to the mixture, 1-phenyl-1-(triethylsilyloxy)ethylene (281 mg, 1.2 mmol) in propionitrile (1 mL) was subsequently added dropwise. The reaction mixture was stirred at −78 °C for 24 h and then quenched by addition of saturated aqueous $NaHCO_3$. The polymeric catalyst was removed by filtration and the filtrate was extracted with ether. The combined organic phases were dried over $MgSO_4$ and evaporated. The combined organic phases were dried over $MgSO_4$ and evaporated to an oily residue. Silica gel chromatography (hexanes/ethyl acetate, 1:1) afforded 280 mg (93% yield) of β-amino ketone **20**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.47 (m, 2H), 5.02 (m, 1H), 6.50–7.90 (m, 15H). The enantiomeric excess (56% ee) was determined by chiral HPLC analysis using Chiralcel OD column (hexane/2-propanol, 3:1), flow rate = 0.2 mL/min, column temperature; 30 °C, t_S = 23.8 min (*S*), t_R = 29.1 min (*R*).

4.4. Asymmetric allylation of benzaldehyde using polymer-supported oxazaborolidinone

Suspension of **16** (0.1 mmol, 10 mol%) prepared from **6b** (5% loading, 1% crosslinking) in propionitrile (4 mL) was cooled to −78 °C. After benzaldehyde (106 mg, 1 mmol) in propionitrile (1 mL) was added to the mixture, trimethyl-2-methallylsilane (153 mg, 1.2 mmol) was subsequently added dropwise. The reaction mixture was stirred at −78 °C for 24 h and then quenched by addition of saturated aqueous $NaHCO_3$. The polymeric catalyst was removed by filtration and the filtrate was extracted with ether. The combined organic phases were dried over $MgSO_4$ and evaporated. The combined organic phases were dried over $MgSO_4$ and evaporated to an oily residue. Silica gel chromatography (hexanes/ethyl acetate, 1:1) afforded 161 mg (99% yield) of homoallylalcohol **22**. ^{1}H NMR

(300 MHz, $CDCl_3$): δ 1.78 (s, 3H), 2.28–2.48 (m, 2H), 4.80 (m, 1H), 4.83 (br, 1H), 4.91 (br, 1H), 7.20–7.40 (m, 5H). The enantiomeric excess (73% ee) was determined by chiral HPLC analysis using Chiralcel OD column (hexane/2-propanol, 20:1), flow rate = 0.4 mL/min, column temperature; 30 °C, t_S = 19.9 min (*S*), t_R = 21.9 min (*R*).

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Polyisobutylene supports—a non-polar hydrocarbon analog of PEG supports

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Abstract—Synthetic routes to terminally functionalized polyisobutylene oligomers useful as supports in synthesis and catalysis are discussed and described. Such hydrocarbon polymers serve as highly soluble non-polar analogs of well known poly(ethylene glycol) supports for synthesis and catalysis with the difference that they are separated after a reaction by an extraction with alkane solvent.

1. Introduction

The most common organic polymer support is polystyrene. In its cross-linked form with various pendant groups, this insoluble material is the organic polymer support most commonly used in biotechnology, in combinatorial chemistry, in organic synthesis, and in environmental chemistry. Many versions of this polymer with various crosslinkers or pendant groups exist and are commercially available.[1] Beginning in the 1960s, soluble polymers were examined as alternatives to insoluble polymer supports for organic chemistry.[2] Linear soluble polymers then and now are as widely available as their insoluble analogs. However, soluble polymers to this point are still used less in synthesis and catalysis. This partly reflects a perception that soluble polymer supports are harder to use or harder to separate from reaction mixtures. Recently alternative approaches using membranes or biphasic separations have developed that are leading to increasing attention being paid to such supports. Such soluble polymer supports have advantages because of the facility with which species on such supports can be characterized and modified and because groups on such supports can more faithfully mimic the chemistry of low molecular weight species.[3,4]

If one considers copolymers as well as homopolymers, there are a countless number of soluble supports that one might study. However, this paper and most work to date has focused on homopolymers lightly modified with pendant or terminal groups. The most common soluble polymer used in synthesis has been poly(ethylene glycol) (PEG), a terminally functionalized polyether.[2,5] This reflects the commercial availability of this polymer and its utility as a modifying group for drug delivery and for facilitation of drug bioavailability.[6] While PEG has historically been the most used soluble polymer, there remain many alternatives. The most contrasting alternative is polyethylene (PE)—poly(ethylene glycol) that has been stripped of its oxygens.[7] This polyolefin is perhaps the most common polymer. However, polyethylene as a support has limitations that limits its use in synthesis. First, the most useful forms of polyethylene for synthesis would be low molecular weight oligomers, which are not commercially available though they can be synthesized by several routes.[8,9] Second, there is the practical problem of polyethylene's solubility. Polyethylene oligomers that would likely be useful in synthesis are generally insoluble in any solvent below 60–70 °C. Nonetheless, PE has the virtues of the inertness of alkanes, a relatively transparent ^{1}H NMR spectrum, and synthetic versatility in end group modification.[8] This suggests that while PE might not be generally useful as a support, that other terminally functionalized polyolefins might merit more attention.

An alternative polyolefin support that we have recently begun to study is polyisobutylene (PIB).[10] PIB has the chemical inertness of polyethylene. As an oil or fuel additive, it is commercially available.[11] More usefully, unlike polyethylene, PIB and its derivatives are very soluble. As shown in this paper, vinyl terminated oligomers of polyisobutylene that are commercially available are easily modified by conventional chemistry and are viable precursors to many sorts of soluble polymeric reagents and supported ligands.

Keywords: Poly(ethylene glycol); PEG; Polyisobutylene; Polymer supported synthesis; Polymeric ligands.
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2. Results and discussion

Polyisobutylene (PIB) with vinyl groups is commercially available and is typically synthesized by cationic polymerization (Eq. 1).[12,13] It is a material that is prepared on a large scale because of its utility in adhesives and in fuel additives.[11] Our work has focused on modification of vinyl-terminated polyisobutylene. The polymer we have used here is available as a trade named product called Glissopal (M_w=1000, Dp=18 or M_w=2300, Dp=41) in tank car quantities and is predominantly vinyl terminated. A ^{1}H NMR spectrum of the starting polymeric material used here shows that the oligomer we used is predominantly terminated with a=CH_2 group (Fig. 1). While there are some internal trisubstituted alkene termini in these oligomers, the proportion of these groups is <10% and this impurity has little effect in the subsequent chemistry.

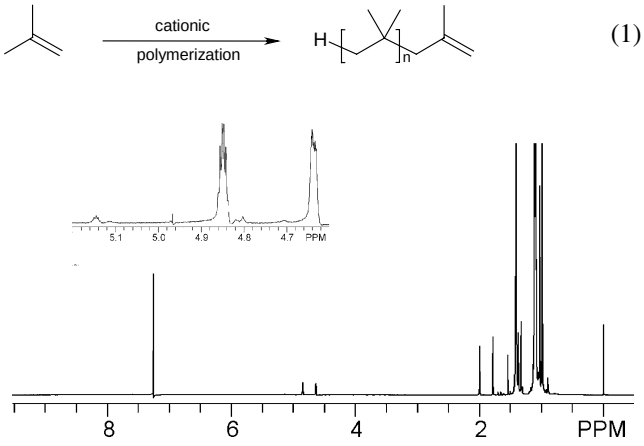


Figure 1. ^{1}H NMR spectrum of the starting vinyl-terminated polyisobutylene (**1**). The diastereomeric vinyl protons for the terminal =CH_2 group appear at δ 4.64 and δ 4.85. Some minor impurities are also present, principally an internal alkenyl group at δ 5.25.

Several strategies were used to convert the terminal double bond of **1** into functional groups useful in synthesis. Many of these strategies have precedence in earlier studies of others with PIB, PE, or PEG,[13–15] but are reiterated here to show the versatility of **1** for synthesis of useful organic functional groups. These strategies can be divided into three broad approaches—the design of functionality or the preparation of reactive intermediates at PIB termini that serve as nucleophilic sites for elaboration of the PIB, the design of functional groups or intermediates that serve as electrophilic entities for modification of PIB termini, and the incorporation of new functionality at PIB termini by concerted or catalytic reactions.

In the studies described below, the first chemical steps for synthesis for functional PIB oligomers for synthesis and catalysis involve oxidation of the terminal double bond of PIB. The simplest example of this approach involves conversion of the alkene into alcohols by hydroboration/oxidation. The resulting –CH_2OH groups can then be converted into a variety of other species as shown in Figure 2. An important feature of the chemistry in Figure 2 and of the chemistry described throughout this paper is that the terminally functionalized polyisobutylene oligomers being prepared are easily analyzed by ^{1}H NMR spectroscopy. ^{13}C NMR spectroscopy can be used as well. As is true in PEG derivatization chemistry, the ^{1}H NMR spectra of PIB derivatives is simplified by the fact that the protons of the PIB oligomers largely do not interfere with analysis of the functionality being introduced on PIB termini. In PEG chemistry, the –CH_2O– groups of the PEG backbone appear as a singlet at ca. 3.6 δ. While this peak overlaps regions of interest for some functional groups, with high field spectroscopy the PEG background signal only obscures a small portion of the useful region of the ^{1}H NMR spectrum. In PIB, the situation is even more favorable since the –CH_2–

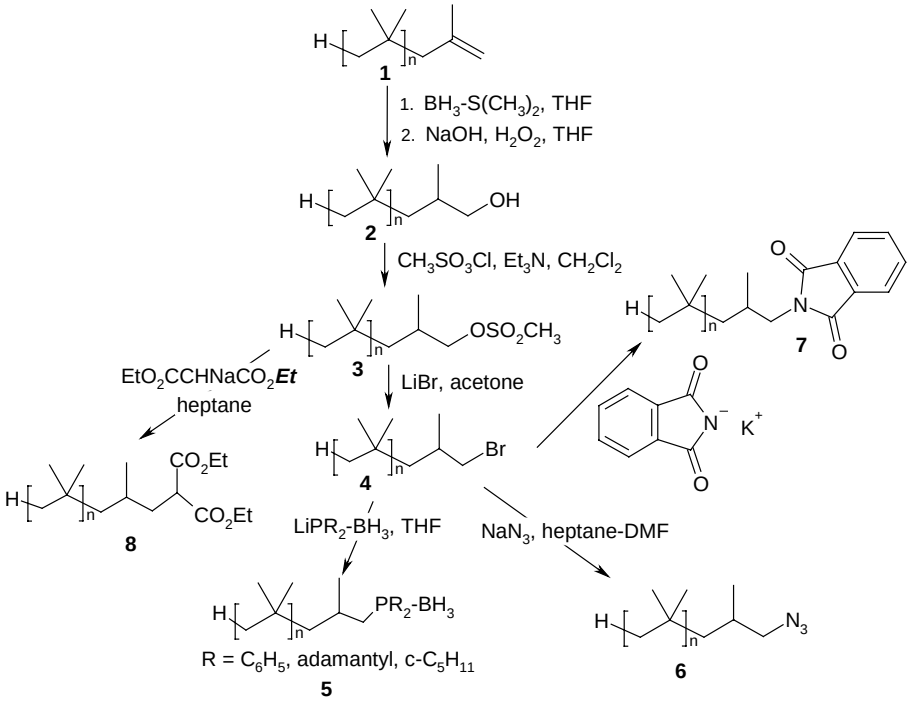


Figure 2. Examples of simple reactions that successfully introduce useful organic functional groups onto terminally functionalized polyisobutylene.

and $-CH_3$ groups of PIB appear at δ 1.40 and δ 1.08—regions that are largely unimportant in analysis of most organic functional groups. A second common feature of ^{1}H NMR analysis of PEG and PIB derivatives is the high quality of spectra for terminal functional groups. As shown in Figure 3, the diastereotopic $-CH_2-$ protons of a $-CH_2OH$, $-CH_2OSO_2CH_3$, $-CH_2Br$, $-CH_2-$ phthalimide, $-CH_2NH_2$, $-CH_2N_3$, $-CH_2$-2-hydroxymethyltriazole, and $-CH_2$-2-bromomethyltriazole lead to a well resolved set of doublets of doublets. A notable feature of these spectra is that even very subtle differences can be seen. A particularly good example of this is seen in the spectra the triazole derivatives in Figure 3g and h where the identity of a $-CH_2X$ substituent on the triazole rings leads to measurable differences ($\Delta\delta$ is <0.05 δ) in the ^{1}H NMR spectra.

The reactions in Figure 2 produce a mixture of functionality useful in further elaboration of PIB. Both the primary mesylates and halides are useful electrophilic derivatives of PIB and react readily with carbon and other heteroatom nucleophiles. The principle caveat in such chemistry is that some care has to be taken in the choice of solvent for such reactions. Unlike PEG, PIB is not soluble in polar solvents like *N*,*N*-dimethylformamide (DMF), methanol, and water. PIB and its derivatives are, however, soluble in solvents like THF, toluene, diethyl ether and in a homogeneous mixtures of heptane with DMF at 70 °C, EtOH, and acetone at room temperature. Generally, we have been able to take existing chemistry in polar solvents and adapt it for PIB modifications like those in Figure 2, in some cases using octadecyl groups as models of PIB.

Purification and isolation of PIB products of reactions like those in Figure 2 and in the chemistry below generally has involved simple heptane extraction. We had earlier shown that PIB derivatives like **9** and **10** could be prepared such that the terminal functionality consists of a polar azo dye or a dansyl fluorophore. Studies using these labeled PIB derivatives showed that PIB oligomers with such polar groups are selectively soluble in heptane rich phases of biphasic mixtures of a 1:1 (vol:vol) heptane and ethanol–water or heptane and DMF at room temperature or below. Thus, a PIB derivative prepared by a reaction in THF can be separated from other polar organic reagents or starting

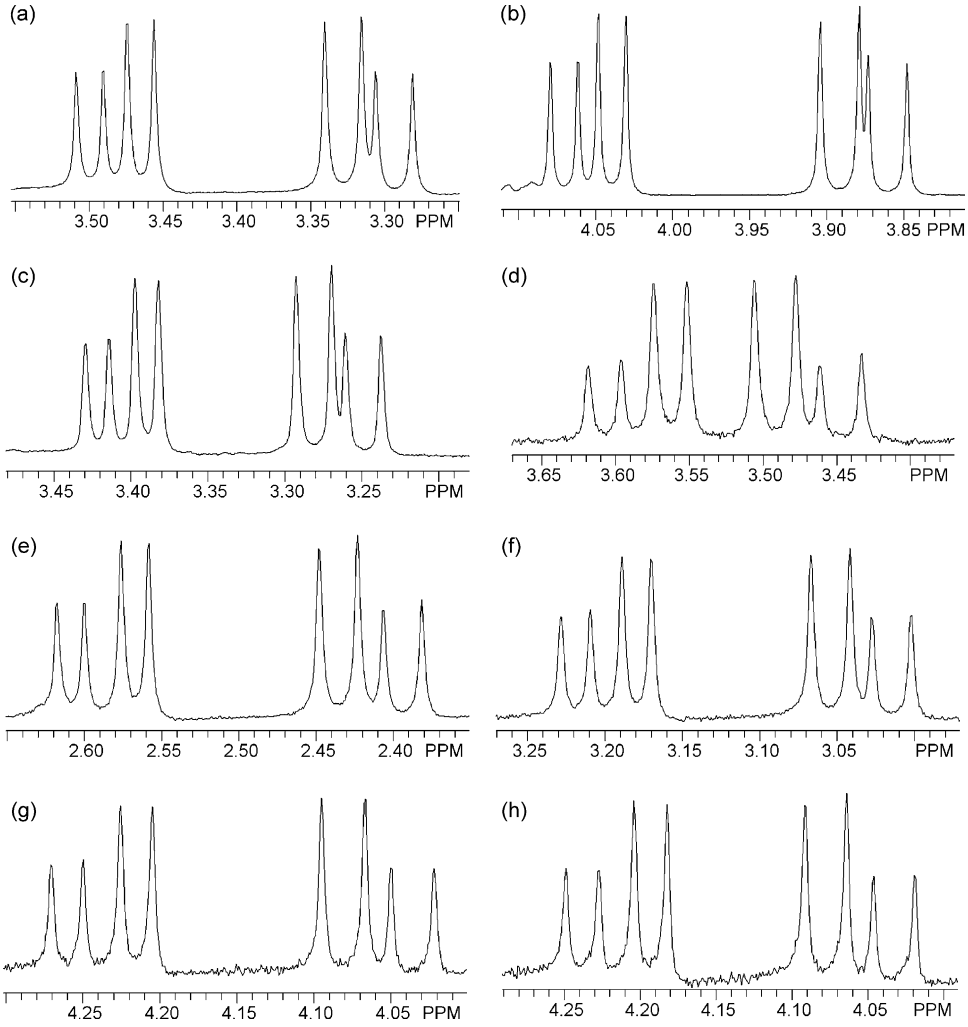
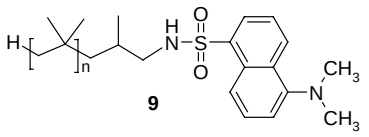
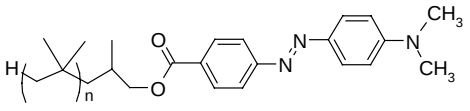


Figure 3. ^{1}H NMR spectra over various 0.3 δ regions for PIB derivatives showing the well resolved diastereopic doublet of doublets for the $-CH_2-$ terminal protons for (a) PIB–CH_2OH; (b) PIB–$CH_2OSO_2CH_3$; (c) PIB–CH_2Br, (d) PIB–CH_2–phthalimide; (e) PIB–CH_2NH_2; (f) PIB–CH_2N_3; (g) PIB–CH_2-2-hydroxymethyltriazole; and (h) PIB–CH_2-2-bromomethyltriazole. All the PIB derivatives shown had $n=17$. We have also prepared PIB derivatives with $n=40$. They have similarly well-resolved ^{1}H NMR spectra.

materials by addition of heptane along with some water or some other polar solvent to produce a biphasic mixture.[16] Typically, PIB derivatives can be designed to have a >99% phase selective solubility in the heptane-rich phase.



9

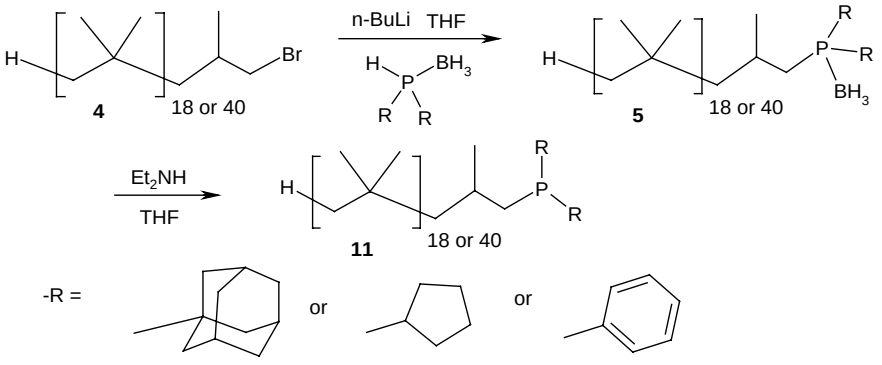


10

The conversions in Figure 2 were quantitative based on ^{1}H NMR spectroscopic analysis of the terminal functional groups of the starting PIB oligomers. In many cases, the mass balance yields are correspondingly high (see Section 4). An important feature of these conversions is the facility with which we can determine the presence of as little as 5 mol% of byproducts based on high resolution ^{1}H NMR spectroscopy. Other syntheses of polymeric reagents, especially syntheses on insoluble supports, are less easily assayed. In those cases, simple isolation of a predictable mass of a polymeric derivative and an IR or other spectroscopic analysis can fail to indicate the presence of impurities in the product because a polymeric byproduct has essentially the same solubility as the expected product and because pendant groups on a soluble or insoluble polymer chain generally have broadened ^{1}H HMR spectroscopic signals—signals that preclude a very quantitative assay of purity.

Another feature of PIB chemistry is that it is possible to separate these materials from byproducts by column chromatography. Column chromatography represents a very important tool in conventional synthesis that is obviously not useful in synthesis of cross-linked polymeric reagents for synthesis. In the case of PIB derivatives, we have, for example, successfully used column chromatography to separate PIB derivatives from reagents, byproduct, or even from other PIB derivatives. An example of this is the synthesis of triazole-terminated PIB derivatives that uses first a nucleophilic substitution of PIB–CH_2Br by NaN_3 followed by a Cu-catalyzed 'Click' reaction.[17,18] In this example, the nucleophilic substitution to form the azide produces a small amount of alkene terminated PIB (PIB–CHC(CH_3)=CH_2), which is separable from the triazole terminated PIB derivative using a silica gel column. Another example would be the synthesis of PIB–CH_2NH_2 from the PIB–CH_2N_3 using triphenylphosphine. In this case, the PIB–CH_2NH_2 could be separated from triphenylphosphine and other byproducts by column chromatography.

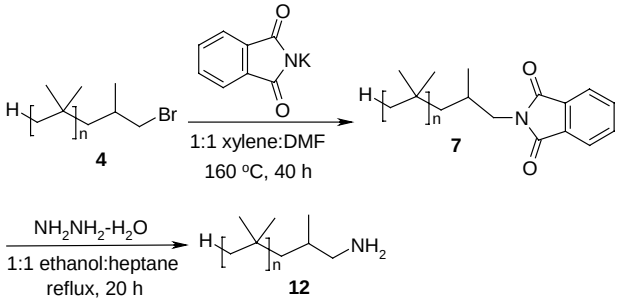
PIB terminated with a –CH_2Br or –$CH_2OSO_2CH_3$ (–CH_2OMs) is a good substrate for nucleophilic substitution reactions that lead to phosphine groups known to be useful as ligands or reagents in synthesis. Several examples of this chemistry are shown in Figure 2 above. The borane–phosphines that are the original products of this chemistry can be subsequently converted into free phosphines using diethylamine in THF as shown in Eq. 2 below.



4 **5** **11**

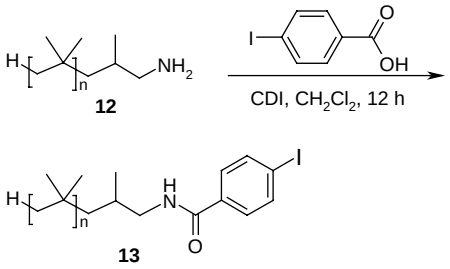
(2)

Other nucleophilic substitution reactions of PIB–CH_2Br successfully lead to amines and amino derivatives. As shown in Eq. 3 below, a primary amine-terminated polyisobutylene can be prepared by a Gabriel synthesis. This primary amine product in turn can be further elaborated by using the primary amine nucleophilicity to prepare amides, sulfonamides, maleimides as shown in Eqs. 4–6.



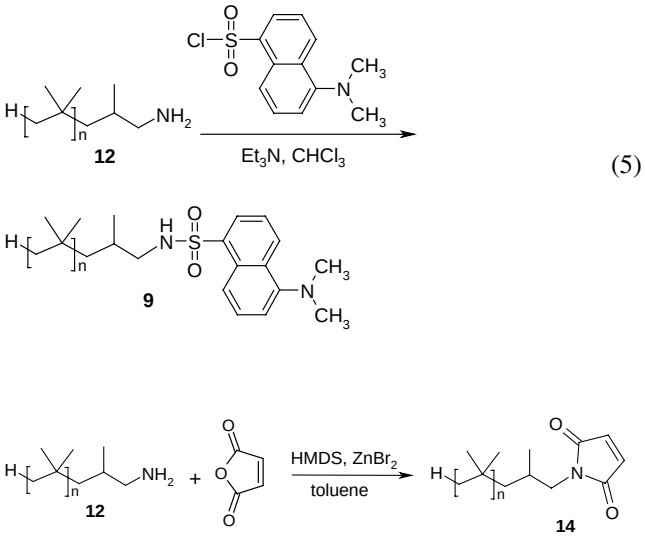
4 **7** **12**

(3)



12 **13**

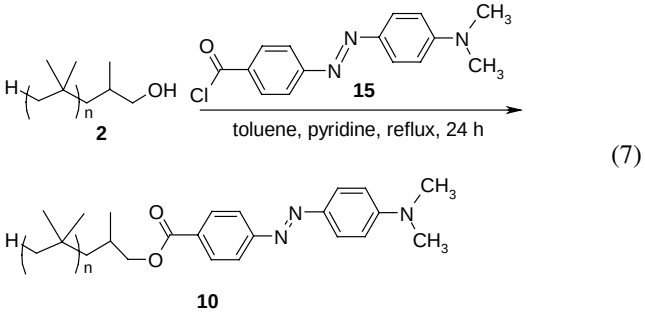
(4)



(5)

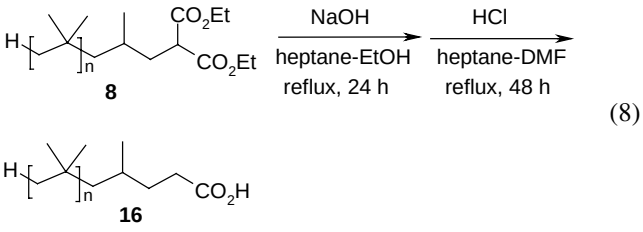
(6)

Ester-terminated polyisobutylenes can be prepared from PIB–CH_2OH using reactions like those in Eq. 7. The example shown below introduces a spectroscopic label that we used along with the dansyl groups in Eq. 5 to demonstrate the phase selective solubility of PIB-derivatives (vide supra).[16]



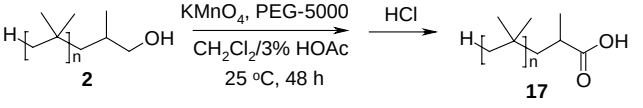
(7)

Substitution at the sp_2-hybridized carbon of carbonyl groups represents a very useful method for synthesis of polymer supported reagents and ligands. We have used several routes to prepare carboxylic acid derivatives of PIB as shown below. The first of these routes (Eq. 8) relied on a classical malonic ester synthesis. Starting with the diethyl malonate derivative **8**, base hydrolysis followed by acidification and heating produced a PIB–$CH_2CH_2CO_2H$ derivative. This proved to be the most useful route for large scale synthesis of a PIB carboxylic acid derivative.

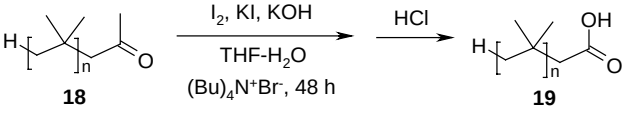


(8)

Alternative routes to form PIB–carboxylic acids are shown in Eqs. 9 and 10 below. The first of these routes used $KMnO_4$ promoted oxidation of a PIB–CH_2OH derivative. This reaction, however, only proceeded to the extent of 68%—the product was contaminated by the starting PIB–CH_2OH. A phase transfer agent (MeO-PEG5000-OH) had to be added in this case because of the insolubility of $KMnO_4$ and we believe that the insolubility of the oxidant is the source of the problem in this case. A second route to a carboxylic acid derivative used a haloform reaction. This reaction produced a product carboxylic acid that looked homogeneous by ^{1}H NMR spectroscopy (a single peak at δ 2.33 for the –CH_2– group next to the –CO_2H group). However, on esterification of this product (EtOH, p-$CH_3C_6H_4SO_3H$), an ester product was produced that had more than one type of –$CO_2CH_2CH_3$ group suggesting that some other unidentified acids were also present (this was not a problem with PIB–$CH_2CH_2CO_2H$ prepared by the malonic ester route above).

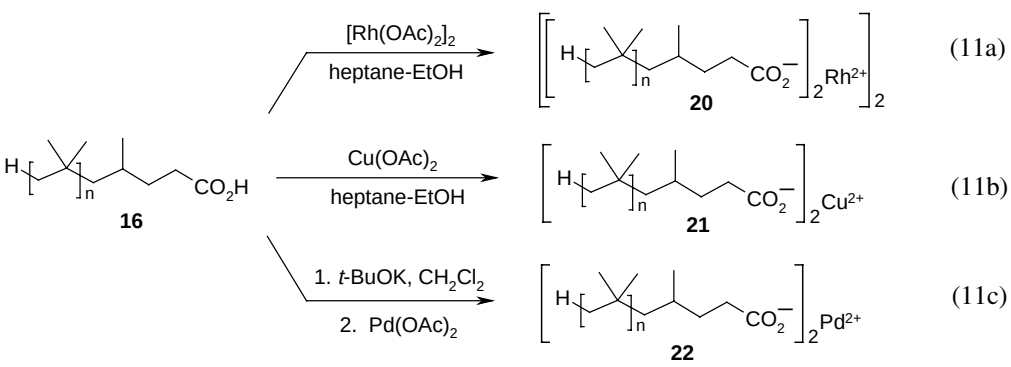


(9)



(10)

Our ultimate interests are organo- and transition metal catalysis. The –CO_2H-terminated PIB oligomers could be converted into metal salts. This is a very simple route into transition metal derivatives of PIB that we are now studying in catalysis. Three examples of metal salt formation shown in Eq. 11a–c. In the rhodium and palladium cases, the product metal salt is diamagnetic and can be analyzed by ^{1}H NMR spectroscopy, which shows a characteristic shift in the PIB–$CH_2CH_2CO_2H$ methylene signal from δ 2.33 to δ 2.21 or d 2.15 for formation of the $[(PIB–CH_2CH_2CO_2)_2Rh]_2$ or $(PIB–CH_2CH_2CO_2)_2Pd$ salt, respectively.

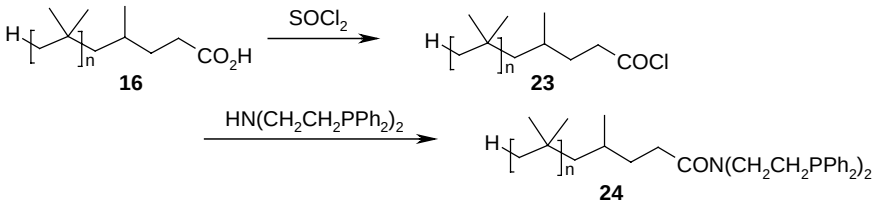


(11a)

(11b)

(11c)

The carboxylic acid groups of PIB–$CH_2CH_2CO_2H$ can also be made into an acid chloride group, PIB–CH_2CH_2COCl. This activated carboxylic derivative in turn can be used to prepare amides and esters. An example of the former reaction is the incorporation of a bis(aminopropyldiphenylphosphinyl) group that serves as a ligand for transition metal catalysts (Eq. 12).

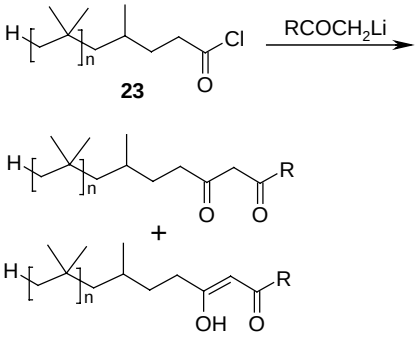


(12)

An alternative route to PIB derivatives involves ozonolysis of the terminal alkene group. This produces an ozonide intermediate that could be isolated and characterized by NMR spectroscopy (CAUTION—ozonides are often thermally unstable and, in many cases, can decompose violently). However, we have generally chosen to avoid isolation of this presumably unstable intermediate and have instead converted the oxonide directly to a methyl ketone by reduction with triphenylphosphine. A small amount of aldehyde is also formed in this reaction presumably by oxidation of the internal double bond of the starting PIB oligomer. As noted above, this methyl ketone can be used to prepare a carboxylic acid derivative.

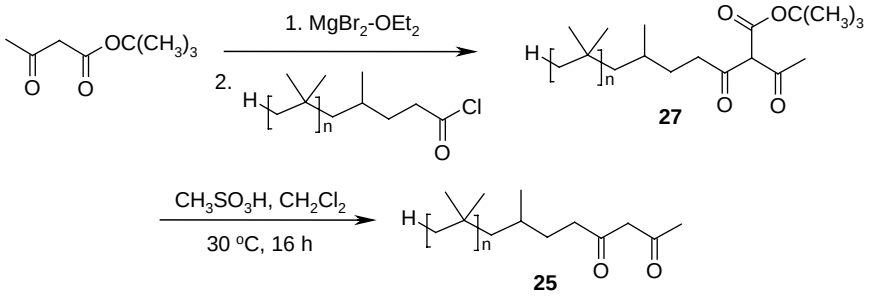
β-Diketones are a common anionic ligand used to form transition metal complexes. Such complexes can catalyze a variety of reactions. Such ligands are less commonly used though with most polymer supports because metals typically have two or more diketonate ligands. If these diketonate ligands are attached to a crosslinked polymer or are present as pendant groups on a soluble polymer, this polyvalency produces crosslinks that can alter the solubility or swellability of the support. However, in the case of PIB, introduction of β-diketonate groups on the terminus will not lead to crosslinking but rather will form star-like polymer-metal complexes.

Our group has successfully synthesized several types of PIB-supported β-diketones. First, starting with the PIB-acid chloride, PIB–CH_2CH_2COCl, as an electrophile, we formed β-diketones using as nucleophiles the lithium enolates of acetone and of pinacolone. After warming the enolate solution or suspension to room temperature, a solution of the acid chloride **23** was added dropwise (Eq. 13). After the reaction mixture was worked up with acid, the product PIB-bound β-diketones were isolated and characterized by ^{1}H NMR spectroscopy. The products as expected existed as a mixture of keto and enol tautomers with an enol H at 14–17 δ and an alkene C–H in the 4–6 δ range. Importantly, the spectra of the PIB–$CH_2CH_2COCH_2COCH_3$ and PIB–$CH_2CH_2COCH_2COC(CH_3)_3$ matched the spectra of lower molecular weight analogs, $CH_3COCH_2COCH_3$ and $CH_3COCH_2COC(CH_3)_3$.



(13)

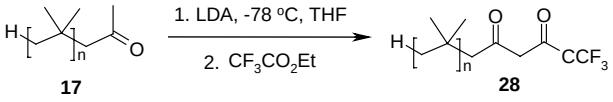
Several other routes leading to β-diketone terminated PIB oligomers were also explored. A second route shown below started with *t*-butylacetylacetonate (Eq. 14). Enolization of this acetoacetic acid ester followed by treatment with the electrophilic PIB–CH_2CH_2COCl led to a tricarbonyl product that could be decarboxylated after acidolysis of the *tert*-butyl ester. The product PIB–$CH_2CH_2COCH_2COCH_3$ was identical to the β-diketone prepared as described above.



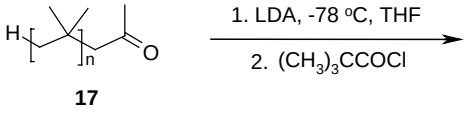
(14)

Although the above routes to β-diketone ligands were successful, the overall route is experimentally tedious. To simplify the route we redesigned our synthesis using the enolate of PIB–CH_2COCH_3 as a nucleophile. This route

used the solubility of PIB–CH_2COCH_3 to advantage in that we could deprotonate this oligomeric methyl ketone with LDA in THF at −78 °C. Our most successful work with this route is the chemistry shown in Eq. 15 where ethyl trifluoroacetate was used as the electrophile. An analogous reaction using pivalolyl chloride as the electrophile and PIB–CH_2COCH_2Li as the nucleophile (Eq. 16) was less successful. While the expected β-diketone product formed, there was another unknown species present as evidenced by a singlet in the ^1H NMR spectrum of the product at δ 3.7.

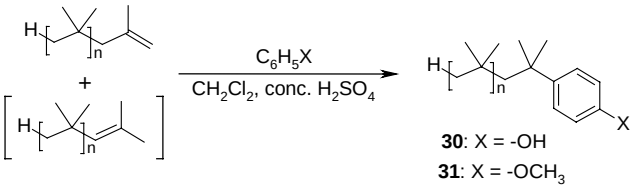


17 **28** (15)



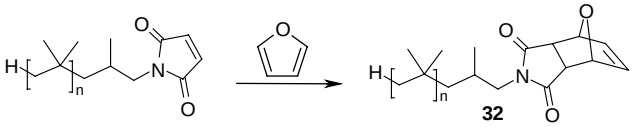
17 **29** (16)

Friedel Crafts chemistry also works as a method for modifying the starting vinyl-terminated PIB oligomer **1** (Eq. 17). This chemistry has the virtue that it avoids any problems that might arise from the modest amount of internal alkene in the starting material since the same arene product is expected in Friedel Crafts arylation regardless of whether the internal and terminal alkene starting material is used. Only the *para* alkylated product was seen. A disadvantage is that this chemistry in our hands required a strongly activated arene (e.g., a phenol derivative). In our hands, Friedel Crafts chemistry failed with an alkylbenzene arene nucleophile.

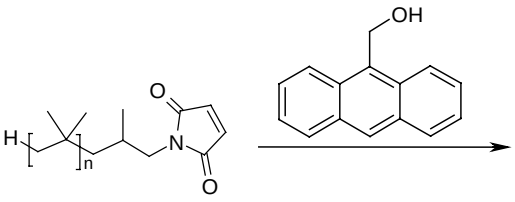


30: X = -OH
31: X = -OCH_3 (17)

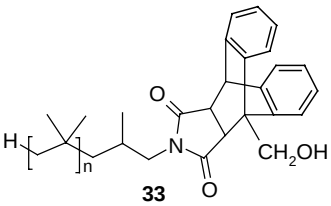
Finally, concerted reactions can be used to decorate the terminus of PIB with functionality that we expect to use in catalysis and synthesis. Two sorts of reactions have been studied. The first used a PIB-bound maleimide as a dienophile in reaction with both furan and with hydroxymethylanthracene (Eqs. 18 and 19). Both reactions work well. The latter product, **33**, has precedence as a supported species in polymer-supported chemistry.[19,20]



32 (18)

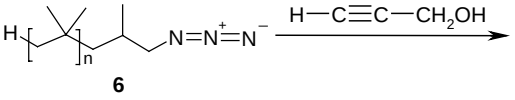


(19)

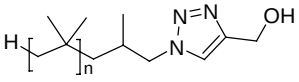


33

The second procedure used the relative new 'click' chemistry recently developed by the Sharpless group.[17] As noted above, we could easily prepare PIB–CH_2N_3 by nucleophilic substitution of PIB–CH_2Br. This azide in turn could be converted with high regioselectivity into a triazole by reaction with alkynes just as is seen in low molecular weight examples of triazole formation from azides and terminal alkynes (Eq. 20). Further modification of these products could be carried out using conventional chemistry. For example, as noted above, even subtle changes in terminal groups (i.e., conversion of the –CH_2OH group of the triazole **34** to a –CH_2Br group) could be detected by ^1H NMR analysis (cf. Fig. 2g and h above).



6



(20)

34: R = -CH_2OH
35: R = -$CH_2CH_2CH_2CH_2CO_2H$

3. Conclusions

Polyisobutylene is a suitable synthetic platform for a variety of organic transformations, transformations that make this readily available polymer into a hydrocarbon soluble analog of poly(ethylene glycol) as a support for use in synthesis and catalysis. Like poly(ethylene glycol), this support can be readily characterized by solution-state ^1H and ^{13}C NMR spectroscopy. Unlike poly(ethylene glycol), this support cannot be separated by precipitation. However, as shown by the synthetic work described here, this support and its end-functionalized derivatives can be separated by extraction or by virtue of its preferential phase selective solubility in non-polar phases of biphasic mixtures.

4. Experimental

4.1. General procedures

Polyisobutylene was obtained from BASF while all other reagents and solvents were obtained from commercial

sources (Aldrich). Two types of polyisobutylene were used—Glissopal 1000 and Glissopal 2300 ($n=17$ and 40 in Eq. 1). Reagents were used without further purification unless otherwise noted. ^{1}H NMR spectra were obtained on Varian Inova, 300, Mercury 300, or Inova 500 spectrometers at 300 or 500 MHz and reported in ppm referenced to TMS or $CDCl_3$. ^{13}C NMR spectra were obtained on Varian Inova 300, Mercury 300, or Inova 500 spectrometers at 75 or 125 MHz and reported in ppm referenced to the chloroform contaminant in $CDCl_3$ unless otherwise stated. The PIB derivatives generally contained peaks in the δ 0.8–1.6 range that were assigned to the ca. 180 protons of the oligomer chain. Crude products also often contained alkane solvent that appeared in this region, but even crude products' purities were readily assessed by examining the end groups whose functional groups' protons inevitably appeared downfield of the alkane region. IR spectroccopy data was obtained on a Mattson Instruments 4021 Galaxy Series FT-IR. Microwave reactions were completed in a Personal Chemistry Emrys Creator model microwave reactor.

4.1.1. PIB–CH_2OH (2). The starting vinyl-terminated PIB (50 g, 50 mmol) was dissolved in 100 mL of hexane and then was allowed to react with neat BH_3–SMe_2 (8.5 mL, 17 mmol). After 24 h, the reaction mixture was cooled to 0 °C and 40 mL of ethanol and 12 mL of 4 N NaOH were added, oxidation to form the alcohol was accomplished by dropwise addition of 8 mL of 30% H_2O_2. The oxidation was allowed to proceed for 2 h at which point 300 mL of H_2O was added. The solution was extracted with hexane (5× 100 mL), and then washed with H_2O (3×50 mL), brine (1×50 mL). The organic phase was dried over $MgSO_4$, filtered and solvents were removed under pressure. After drying under vacuum for 24 h, a total yield of 52 g (102% yield possibly containing trace hexanes) of product (PIB–CH_2OH) (**2**) was obtained: ^{1}H NMR 0.75–1.46 (m, 180H), 3.31 (dd, $J=7.5$, 10.2 Hz, 1H), 3.48 (dd, $J=5.4$, 10.2 Hz, 1H).

4.1.2. PIB–$CH_2OSO_2CH_3$ (3). PIB–CH_2OH (10 g, 9.8 mmol) was dissolved in 100 mL of CH_2Cl_2 and cooled to 0 °C. Then methanesulfonyl chloride (2.3 mL, 29 mmol) and triethylamine (4.3 mL, 31 mmol) were added dropwise. The reaction mixture was allowed to stir for 6 h after warming to room temperature. The solvent was removed under reduced pressure and the resulting mixture was taken up with 300 mL of hexane, washed with H_2O (3×30 mL) and 90% EtOH (4×50 mL). The organic phase was dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. A total yield of 10.5 g (97.8%) of product was obtained after drying under vacuum for 24 h: ^{1}H NMR 0.88–1.39 (m, 180H), 1.95 (m, 2H), 2.96 (s, 3H), 3.88 (dd, $J=7.5$, 9.3 Hz, 1H), 4.06 (dd, $J=5.4$, 9.3 Hz, 1H).

4.1.3. PIB–CH_2Br (4). A sample of PIB–CH_2OH (10 g, 9.8 mmol) was dissolved in 100 mL of dichloromethane and cooled to 0 °C and, methanesulfonyl chloride (2.3 mL, 29 mmol) and triethylamine (4.3 mL, 31 mmol) were added dropwise. The reaction mixture was allowed to stir for 6 h after warming to room temperature. The solvent was removed under reduced pressure and then the resulting mixture was dissolved in a mixture of 100 mL of heptane and 100 mL of acetone. LiBr (9 g, 103 mmol) was added and this reaction mixture was heated to 80 °C for 24 h. After cooling to room temperature, an additional 200 mL of hexane was added. The resulting alkane phase was separated and was washed with H_2O (1×50 mL) DMF (5×10 mL), H_2O (2×20 mL), and dried over Na_2SO_4. The solvent was removed and residue was dried under vacuum to give 9.4 g (88.6%) of product **4**: ^{1}H NMR 0.76–1.49 (m, 180H), 3.27 (dd, $J=6.9$, 9.6 Hz, 1H), 3.41 (dd, $J=4.8$, 9.6 Hz, 1H).

4.1.4. PIB–$CH_2P(C_5H_9)_2$–BH_3 (5). In a procedure representative of that used for other phosphines, dicyclopentylphosphine–borane (1 g, 5.4 mmol) was dissolved in 10 mL of freshly distilled THF. This solution was cooled to −78 °C and 3.8 mL of 1.6 M *n*-BuLi (6.1 mmol) in hexane was added by syringe. Stirring this solution first at this temperature for 2 h and at room temperature for 6 h produced a lithiated phosphine. This reaction mixture was then cooled to −78 °C and a solution of PIB–CH_2Br (2 g, 1.8 mmol) in 10 mL of freshly distilled THF was added by forced siphon using a cannula. This reaction mixture was stirred at this temperature for 2 h and at room temperature for 12 h. The solvent was removed under reduced pressure, the resulting mixture was taken up in 100 mL of diethyl ether, washed with H_2O (2×20 mL), and finally dried over $MgSO_4$. To isolate the product, this solvent was removed under reduced pressure and the residue was dissolved in 100 mL of hexane, washed by DMF (3×10 mL), 90% EtOH (5×10 mL), and the hexane phase was dried over Na_2SO_4. The product phosphine–borane complex was further purified by silica gel chromatography (hexane/EtOAc: 10:1). Final removal of solvent yielded 1.8 g (82.6%) of product **5**: ^{1}H NMR 0.81–1.39 (m, 180H), 1.52–1.68 (m, 16H), 1.82–1.87 (m, 2H), 1.94–2.05 (m); ^{31}P NMR 25.98.

4.1.5. PIB–$CH_2P(C_5H_9)_2$ (11). Removal of the borane group from the PIB phosphines followed this representative procedure. A solution of PIB–dicyclopentylphosphine–borane complex (0.8 g, 0.68 mmol) in 10 mL of freshly distilled THF and 10 mL of diethylamine was prepared. This solution was sealed and the air in the flask was removed by five freeze-pump-thaw cycles. Then the reaction mixture was heated to 55 °C for 24 h. After cooling to room temperature the solvent was remove under pressure. The resulting mixture was dissolved to 15 mL of hexane and washed with 90% EtOH (2×5 mL) and dried over Na_2SO_4. Removal of solvent and drying under vacuum for 24 h to yielded 0.6 g (75%) of product **11**, which was characterized by ^{31}P NMR spectroscopy: ^{31}P NMR −11.06.

4.1.6. PIB–CH_2N_3 (6). PIB–CH_2Br (16 g, 14.5 mmol) was dissolved in 250 mL of dry heptane. Then sodium azide (1.23 g, 18.8 mmol) and 250 mL dry of DMF were added to the solution. The resulting biphasic mixture was heated to 90 °C for 12 h. The monophasic reaction mixture that formed was allowed to cool to whereupon a biphasic mixture formed and the heptane and DMF layers were separated. The heptane phase was washed with three 30-mL portions of methanol followed by two 20-mL portions of brine. The resulting solution was dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to yield

14.6 g (94%) of the desired azide **6**: ^{1}H NMR 0.86–1.44 (m, 207H), 1.73–1.85 (br, 1H), 3.04 (dd, J=7.57, 11.72 Hz, 1H), 3.20 (dd, J=5.62, 11.72 Hz, 1H). IR (neat, cm^{-1}): 2097.

4.1.7. Phthalimide terminated poly(isobutylene) (PIB–phthalimide) (7). A mixture of potassium phthalimide (3.0 g, 16.2 mmol) and **4** (9.0 g, 8.3 mmol) in heptane/DMF (150 mL/150 mL) was stirred at 100 °C for 24 h. The reaction was cooled to room temperature and 300 mL of hexane was added. The non-polar hexane phase was isolated and washed with H_2O (3×40 mL), and 90% EtOH (4×25 mL). The organic phase was then dried over Na_2SO_4, and the solvent removed in vacuo to yield 8.5 g (89.3%) of **7**: ^{1}H NMR 0.76–1.49 (m, 180H), 3.47 (dd, J=8.1, 13.4 Hz, 1H), 3.59 (dd, J=6.6, 13.4 Hz, 1H), 7.68 (dd, J=3.0, 5.4 Hz, 2H), 7.82 (dd, J=3.0, 5.4 Hz, 2H).

4.1.8. Amine terminated polyisobutylene (PIB–NH_2) (12). A solution of hydrazine hydrate (18 mL, 314 mmol) and **7** (8.0 g, 7 mmol) in 400 mL of 1:1 ethanol/heptane was heated to reflux for 20 h. The reaction was allowed to cool to room temperature and 50 mL of H_2O was added. The organic phase was then washed with H_2O (3×40 mL), 90% EtOH (4×25 mL). The heptane phase was dried over Na_2SO_4 and the solvent removed under vacuum distillation to yield 7.5 g (106% presumably containing ca. 6% heptane solvent) of **12**: ^{1}H NMR 0.76–1.49 (m, 180H), 2.41 (dd, J=7.5, 12.4 Hz, 1H), 2.59 (dd, J=5.4, 12.4 Hz, 1H).

4.1.9. Dansyl-labeled poly(isobutylene) (PIB-dansyl) (9). A solution of dansyl chloride (0.34 g, 1.25 mmol), **12** (0.5 g, 0.5 mmol), and triethylamine (3.0 mL, 0.4 mmol) in 20 mL of chloroform was refluxed for 24 h. The solvent was removed under reduced pressure and the residue taken up 100 mL of hexane and washed by 90% EtOH (3×20 mL). The organic phase was dried over $MgSO_4$, the solvents removed under reduced pressure, and the product dried in vacuo for 24 h to give 0.40 g (64%) of **9** as a light yellow liquid: ^{1}H NMR 0.77–1.39 (m, 180H), 2.54–2.62 (m, 1H), 2.73–2.82 (m, 1H), 2.86 (s, 6H), 4.54 (t, J=6.3 Hz, 1H), 7.17 (d, J=7.5 Hz, 1H), 7.52 (m, 2H), 8.29 (m, 2H), 8.51 (d, J=8.4 Hz, 1H).

4.1.10. Methyl red-labeled polyisobutylene (PIB-MR) (10). A solution of **2** (1.8 g, 1.8 mmol) in 50 mL of toluene was allowed to react with the acid chloride derivative of *p*-methyl red **15** (0.5 g, 1.7 mmol)[16] in the presence of 1 mL of pyridine. The reaction was stirred at reflux for 24 h and the solvent removed under reduced pressure. The residue was taken up in 300 mL of hexane and washed with 90% EtOH (10×30 mL). The organic phase was dried over $MgSO_4$, the solvents were removed under reduced pressure and dried in vacuo for 24 h to give 1.7 g (74.5%) of **10** as a viscous red liquid: IR (neat, cm^{-1}) 2953, 2889, 2263, 1710, 1606, 1517, 1477, 1397, 1373, 1277, 1245, 1141, 916, 740; ^{1}H NMR 0.80–1.43 (m, 180H), 2.06 (m, 1H), 3.07 (s, 6H), 4.01–4.07 (dd, J=7.8, 10.5 Hz, 1H), 4.17–4.23 (dd, J=5.7, 10.5 Hz, 1H), 6.71 (d, J=9.3 Hz, 2H), 7.86 (t, J=9.3 Hz, 4H), 8.17 (d, J=8.7 Hz, 2H).

4.1.11. PIB–$CH_2NHCOC_6H_4I$ (13). A solution of *p*-iodobenzoic acid (0.92 g, 3.6 mmol) in 100 mL of dry CH_2Cl_2 was prepared and transferred to a flame-dried, two-necked flask fitted with a condenser, stir bar, and nitrogen inlet. Carbonyl diimidizole (0.51 g, 3.11 mmol) was added to the reaction and the mixture stirred at room temperature for 3 h. A dry solution of PIB–CH_2NH_2 (2.59 g, 2.55 mmol) in 100 mL of CH_2Cl_2 was transferred by forced siphon to the activated acid and the reaction heated at reflux for 24 h. The solvent was removed under reduced pressure and the product was dissolved in 300 mL of hexanes. The hexane solution was then washed with water (2×20 mL), Na_2CO_3 saturated methanol (3×60 mL), brine (3×30 mL), and finally dried over Na_2SO_4. The solvent was removed by reduced pressure to yield 2.93 g (92.2%) of the desired amide: ^{1}H NMR 0.90–1.41 (m, 165H), 1.78–1.90 (m, 1H), 3.35 (m,1H), 3.20 (m, 1H), 6.08 (br, 1H), 7.49 (d, J=8.55 Hz, 2H), 7.79 (d, J=8.55 Hz, 2H); ^{13}C NMR ($CDCl_3$, δ): 98.35, 128.58, 134.45, 137.94, 166.87; IR (neat, cm^{-1}) 3305, 1638.

4.1.12. PIB–$CH_2CH(COOEt)_2$ (8). A solution of Na (1.6 g, 68.9 mmol) in 100 mL of absolute ethanol was prepared. Then of diethyl malonate (11.4 mL, 74 mmol) was added and stirred at room temperature for 30 min. A solution of PIB–CH_2OMs (7 g, 6 mmol) in 50 mL of heptane was also prepared and the 35 mL of the ethanolic solution of the sodium diethyl malonate was added to this mesylate. After heating at 80 °C for 12 h, the reaction mixture was cooled to room temperature, 200 mL of hexane was added, and the hexane solution was washed with H_2O (2×30 mL) and dried over Na_2SO_4. The solvent was removed under pressure and the product was dried under vacuum for 24 h to yield 6.5 g (87.6%) of product: ^{1}H NMR 0.88–1.39 (m, 186H), 3.35–3.40 (dd, J=6.3, 8.7 Hz, 1H), 4.12–4.21 (m, 4H).

4.1.13. PIB–CH_2CH_2COOH (16). A mixture of PIB–CH_2-$CH(COOEt)_2$ (6.5 g, 5.6 mmol) and sodium hydroxide (2.6 g, 65 mmol) was dissolved in 50 mL of ethanol and 50 mL of heptane, and the solution was heated to 80 °C for 40 h. After cooling to room temperature, the solution was neutralized by concentrated HCl. Then 50 mL of H_2O was added, the organic phase was separated and the water phase was extracted by hexane (3×50 mL). The combined organic phases were washed by DMF (3×10 mL), 90% EtOH (3×10 mL), H_2O (2×20 mL), and finally dried over Na_2SO_4. After the solvents were removed under reduced pressure, the product was dried under vacuum for 24 h to give 5.4 g (87.3%) of PIB–$CH_2CH(CO_2H)_2$: ^{1}H NMR 0.76–1.48 (m, 180H), 1.98 (m, 2H), 3.49 (dd, J=6.3, 8.4 Hz, 1H); IR (neat, cm^{-1}): 1722. This diacid was then decarboxylated by adding this diacid product (5 g, 4.53 mmol) to a mixture of 5 mL of concentrated HCl, 5 mL of H_2O in 50 mL of DMF and 50 mL of heptane and heating this mixture at 120 °C for 40 h. After cooling to room temperature, the heptane rich phase was isolated. The DMF rich phase was extracted with hexane (3×30 mL). The combined heptane and hexane phases were washed by H_2O (2×20 mL), brine (20 mL) and dried over Na_2SO_4. The solvents were removed under reduced pressure and the product was dried under vacuum for 24 h to give 4 g (83.2%) of the desired product: ^{1}H NMR 0.84–1.76 (m), 2.30–2.36 (m).

4.1.14. PIB–CH_2CH_2COCl (23). A sample of PIB–CH_2-CH_2COOH (1.2 g, 1.1 mmol) and 20 mL of toluene (dry) was added to a 100 mL flask. Then thionyl chloride (2 mL, 27 mmol) was added to this solution dropwise at room temperature. The reaction mixture was heated to 115 °C for 4 h. After cooling, the solvent was removed under reduced pressure and the residue was examined by IR (1802 cm^{-1}) after drying under vacuo for 2 h. The PIB-acid chloride so obtained was typically used in further steps without further analysis.

4.1.15. PIB–$CH_2CH_2CON((CH_2)_2PPh_2)_2$ (24). A 2 g sample (2 equiv) of PIB–CH_2CH_2COOH (**16**) prepared as described above was dissolved in 20 mL of dichloromethane. Then the –CO_2H group was activated. This could involve formation of an acid chloride like **23**. It was equally effective to use ethylchloroformate and *N*-methylmorpholine to form a mixed anhydride. In either case, once the activated polyisobutylene carboxylic acid derivative was formed, the system was sealed and the air in the vial was removed by five freeze-pump-thaw cycles. Then bis(diphenylphosphinylethylamine) (DPPA) (0.21 g, 0.87 mmol) was added and the reaction mixture was stirred for 24 h at room temperature. The solvent was removed by vacuum at room temperature, 15 mL of deoxygenated hexane was added, and the hexane phase was washed by 90% EtOH (2×8 mL) and finally dried over Na_2SO_4. The alkane solvent was removed under reduced pressure and the residue dried under vacuum for 24 h to give 1.9 g (78%) of product **24**: ^{1}H NMR 0.81–1.65 (m, 180H), 2.00–2.12 (m, 2H), 3.28–3.35 (m, 6H), 7.29–7.40 (m, 10H); ^{31}P NMR −15.83.

4.2. Phase selectivity solubility tests of dye-labeled PIB derivatives

Phase selectivity solubility measurements of this dye-labeled PIB derivative were carried out as described previously.[16]

4.2.1. PIB–$COCH_3$ (18). Polyisobutylene (PIB) (18.3 g, 18.3 mmol) was dissolved in 150 mL of toluene in a 500 mL flask. This reaction mixture was then cooled to −78 °C and treated with ozone in an ozonolysis apparatus for 30 min. After the residual ozone was removed by degassing with N_2 for 20–30 min, triphenylphosphine (24 g, 91 mmol) was added. To insure complete reduction of the ozonide, this reaction mixture was allowed to stir at room temperature for 12 h. At this point, the absence of peroxides could be verified with a peroxide test. Then most of the toluene was removed under reduced pressure to form a slurry of the product and triphenylphosphine/triphenylphosphine oxide. Filtration was used to remove the solid and the filtrate was dissolved in a mixture of 150 mL of DMF and 150 mL of heptane. To facilitate removal of any residual triphenylphosphine, this solution was refluxed in air for 12 h (to oxidize the triphenylphosphine) and cooled to room temperature. The heptane phase of the biphasic mixture was separated. If any triphenylphosphine remained in this solution, more DMF was added and the reflux was continued. Otherwise, the heptane phase containing **18** was washed with DMF (20 mL×2), H_2O (20 mL×2), brine (20 mL), dried over Na_2SO_4. Finally the solvent was removed under reduced pressure to give 17 g (93%) of product **18**: ^{1}H NMR 0.84–1.48 (m, 180H), 2.10 (s, 3H), 2.42 (s, 2H); IR (neat, cm^{-1}) 1722.

4.2.2. PIB–C_6H_4OH (30). In a 500 mL of flask was added polyisobutylene (10 g, 10 mmol) and phenol (19 g, 200 mmol) in 100 mL of dichloromethane. The reaction mixture was cooled to 0 °C, 6 mL of concentrated H_2SO_4 was added slowly, and the resulting mixture was stirred first at 0 °C for 1 h and then at room temperature for 60 h. The solvent was removed under reduced pressure and the crude product was dissolved in 300 mL of hexane. This hexane-rich phase was washed with 90% EtOH (50 mL×2), DMF (50 mL×2), 90% EtOH (30 mL×2), and finally dried over Na_2SO_4. Then the hexane was removed under reduced pressure to yield 9 g (82%) of product **30** after drying for 24 h under vacuum: ^{1}H NMR 0.79–1.39 (m, 180H), 4.99 (s, br, 1H), 6.72 (d, J=8.7 Hz, 2H), 7.20 (d, J=8.7 Hz, 2H).

4.2.3. PIB–$C_6H_4OCH_3$ (31). A solution of polyisobutylene (10 g, 10 mmol) in 100 mL of anisole was carefully combined with 5 mL of concentrated H_2SO_4 at 0 °C and this reaction mixture was stirred first at 0 °C for 1 h and then at room temperature for 60 h. The solvent was removed under reduced pressure. The resulting organic product was dissolved in 400 mL of hexane and washed with 90% EtOH (50 mL×2), DMF (50 mL×2), 90% EtOH (30 mL×2), and finally dried over Na_2SO_4. After the solvent was removed and the product dried under vaccum for 12 h, 10 g (90%) of product **31** was obtained: ^{1}H NMR 0.82–1.43 (m, 180H), 3.79 (s, 3H), 6.84 (d, J=9.0 Hz, 2H), 7.29 (d, J=9.0 Hz, 2H).

4.2.4. PIB–$CH_2CH_2COCH_2COCH_3$ (25). This β-diketone derivative was prepared following a procedure analogous to that shown above for **26**. As was true for **26**, the ^{1}H NMR spectrum was mostly for the enol (ca. 90%) and consisted of the following peaks: 0.8–1.43 (m), 2.05 (s, enol CH_3), 2.15 (s, keto CH_3), 2.25 (m, PIB–CH_2–CO– of the enol tautomer), 2.46 (m, PIB–CH_2–CO– of the keto tautomer), 3.56 (s, –$COCH_2$CO– of the keto tautomer), 5.48 (s, =CH– of the enol tautomer), and 15.5 (–OH of the enol tautomer).

4.2.5. PIB–$CH_2CH_2COCH_2COC(CH_3)_3$ (26). To a solution of diisopropylamine (1.3 mL, 9 mmol, distilled from CaH_2 and stored over 4 Å molecular sieves) and 10 mL of dry THF was added dropwise 5.3 mL of a 1.6 M solution of *n*-BuLi (8.4 mmol) in hexane at −78 °C. After 30 min, pinacolone (1.1 mL, 9 mmol) was added dropwise to the solution of LDA in THF above made at −78 °C (a white solid was precipitated, which is the enolate of pinacolone). After another 30 min, when deprotonation of pinacolone was complete, the reaction mixture was warmed up to room temperature to dissolve the enolate. Then 15 mL of a THF solution of PIB-acid chloride (from PIB–acid, 3 g, 2.8 mmol) was added dropwise to this enolate solution using a syringe. The reaction mixture was then cooled to 0 °C with an ice-water bath and stirred overnight. The reaction mixture was quenched with 6 M HCl, and the solvent was removed under reduced pressure. The residue was dissolved in 60 mL of hexanes and washed with 90% EtOH (2× 15 mL), DMF (4×15 mL) and 90% EtOH (3×15 mL). The resulting solution was dried over sodium sulfate overnight.

The solvents were removed under reduced pressure and the residue was dried in vacuo for 24 h to give 2.8 g (88%) of product **26** as a viscous yellow liquid: ^{1}H NMR 0.8–1.43 (m), 2.07 (m, PIB–CH_2–CO– of the enol tautomer), 2.48 (m, PIB–CH_2–CO– of the keto tautomer), 3.62 (s, –$COCH_2CO$– of the keto tautomer), 5.6 (s, =CH– of the enol tautomer), 15.82 (s, –OH of the enol tautomer). The principle species present (ca. 85%) was the enol form of the β-diketone.

4.2.6. PIB–$COCH_2COCF_3$ (28). To a solution of diisopropylamine (4.6 mL, 32.6 mmol) and 35 mL of dry THF was added dropwise 19 mL of 1.6 M solution of *n*-BuLi (30.4 mmol) in hexane at −78 °C. After 30 min, 10.2 g (10.2 mmol) of **18** in 25 mL of THF was added dropwise at −78 °C to the solution of LDA in THF above made. After another 30 min, when deprotonation was completed, ethyl trifluoroacetate (2.4 mL, 20.4 mmol) was slowly added to the reaction mixture using a syringe. The reaction was kept at −78 °C for 2 h and then warmed up to room temperature overnight. The reaction mixture was quenched with 6 M HCl. After the reaction solvents were removed at reduced pressure, the residue was dissolved in 100 mL of hexanes and washed with 90% EtOH (2×20 mL), DMF (2×20 mL) and 90% EtOH (3×20 mL). The final hexane phase was dried over sodium sulfate and the hexane was removed under vacuum to yield 10.3 g (96.6%) of product **28**: ^{1}H NMR 0.8–1.43 (m), 2.35 (s, 2H), 5.82 (s, 1H); ^{13}C NMR 97.95 (s), 117.2 (q, J=284.12 Hz), 177.5 (q, J=36.21 Hz), 195.45 (s).

4.2.7. PIB–COOH from iodoform reaction (19). To a solution of **18** (1.35 g, 1.35 mmol) in 40 mL of THF in a 250-mL flask was added 30 mL of 5 M KOH and 0.3 g (1 mmol) of tetrabutylammonium bromide (TBAB). The resulting mixture was stirred for 1.5 h at room temperature. After that, 10 mL of 0.5 M I_2/KI (5 mmol) in water was added to the reaction mixture. After 48 h, the reaction mixture was separated and the organic solvent was removed under reduced pressure. The organic residue was dissolved in 40 mL of hexanes and then filtrated to remove TBAB. The organic phase was first washed with 6 M HCl (2× 10 mL), DMF (3×15 mL) and 90% EtOH (3×15 mL). The organic phase was finally dried over sodium sulfate and the solvent removed in vacuo to yield 1.28 g (94.1%) of product: ^{1}H NMR 0.8–1.9 (m), 2.33 (s, 2H).

4.2.8. PIB–$CH_2CH_2COCH(COCH_3)COOC(CH_3)_3$ (27). In a 100-mL, two-necked dry flask equipped with a magnetic stir bar, was placed $MgBr_2 \cdot OEt_2$ (1.55 g, 6 mmol) and 30 mL of dichloromethane under nitrogen. The resulting heterogeneous mixture was cooled down to 0 °C by ice bath, and then *tert*-butyl acetoacetate (0.7 mL, 4 mmol) was added to the reaction mixture by a syringe with vigorous stirring. Then pyridine (0.7 mL, 8 mmol) was slowly added to the heterogeneous mixture. After the mixture was stirred for 15 min at 0 °C, a solution of PIB-acid chloride (from PIB-acid, 2 g, 2 mmol) in 25 mL of dichloromethane was added dropwise to the flask by syringe. The resulting mixture was stirred for 15 min at 0 °C and 24 h at room temperature. The solvent was removed under reduced pressure and the residue was dissolved in 40 mL of hexanes. The hexane phase was washed with 6 M HCl (2×10 mL), DMF (4×10 mL) and 90% EtOH (3×10 mL) and water (2×10 mL). After drying over sodium sulfate, the solvent was removed under reduced pressure to give 2.0 g, (85.5%) of product **27**: ^{1}H NMR 0.8–1.43 (m), 2.26 (s, 3H), 2.6 (m, 2H), 17.43 (s, 1H).

4.2.9. PIB–CH_2COOH (17) by oxidation of PIB–CH_2OH. In a 100 mL flask equipped with a stir bar, PIB–CH_2OH (0.5 g, 0.49 mmol) was dissolved in 15 mL of dichloromethane, and then 15 mL of 3% acetic acid aqueous solution, $KMnO_4$ (0.3 g, 2 mmol) and PEG-5000 (0.05 g, 0.01 mmol) were added to the flask. The resulting two-phase reaction mixture was vigorously stirred for 24 h at room temperature. The byproduct MnO_2 was removed by filtration, and the organic phase was separated from aqueous phase. After evaporation of dichloromethane, the residue was dissolved in 30 mL of hexanes and washed with 3 M HCl (2×10 mL), with 90% EtOH (5×10 mL), and finally with water (2×10 mL). The hexane phase was then dried over sodium sulfate and the solvent was removed under reduced pressure to yield 0.5 g of PIB oligomer, which was a mixture of starting material and oxidized product (68.7% conversion) based on ^{1}H NMR spectroscopy.

4.2.10. PIB–CH_2–maleimide (14). PIB–CH_2NH_2 (4.60 g, 4.25 mmol) was dissolved in 60 mL of dry toluene and maleic anhydride (0.60 g, 6.16 mmol) was added to the solution. The suspension was allowed to stir at room temperature for 12 h under nitrogen. Dry $ZnBr_2$ (1.63 g, 7.22 mmol) was added to the solution and the reaction heated to 80 °C for 30 min. HMDS (1.6 mL, 7.7 mmol) was added to the mixture by syringe and the reaction heated for an additional 4 h. The reaction was cooled to room temperature and poured into 50 mL 1.0 M HCl. The aqueous layer was extracted with ethyl acetate (3×50 mL) and the combined organic extracts washed with saturated $NaHCO_3$ solution (2×50 mL) and saturated NH_4Cl solution (50 mL). The product was dried over $MgSO_4$, filtered, centrifuged, then concentrated under reduced pressure to give 4.6 g (93%) of the product **14**: ^{1}H NMR 0.88–1.41 (m, 228H), 3.26 (dd, J=8.3, 13.43 Hz, 1H), 3.38 (dd, J=6.84, 13.43 Hz, 1H), 6.68 (s, 2H); IR (neat, cm^{-1}) 1711.

4.2.11. Diels–Alder reactions of PIB–CH_2–maleimide. PIB–CH_2–maleimide (0.40 g, 0.34 mmol) was dissolved in toluene (24 mL) and the solution placed in a pressure tube. Distilled furan (1 mL) was added and the reaction was heated to 110 °C for 24 h. The reaction was allowed to cool and the solvent and excess furan were removed under reduced pressure. The crude product was passed through a silica gel plug with ether and the ether removed under reduced pressure to give 0.31 g (73%) of the Diels–Alder adduct: ^{1}H NMR 0.86–1.44 (m, 180H), 2.83 (dd, J=6.6, 8.30 Hz, 2H), 3.24 (dd, J=9.03, 12.94 Hz, 1H), 3.34 (dd, J=6.35, 13.18 Hz, 1H), 5.28 (d, J=7.57 Hz, 2H), 6.51 (s, 2H).

A similar procedure was used when hydroxymethylanthracene was used as the diene. PIB–CH_2–maleimide (0.24 g, 0.21 mmol) was dissolved in toluene (12 mL). Anthracene methanol (0.07 g, 0.22 mmol) was added to this maleimide solution and the reaction heated to reflux for 24 h. Maleic acid (0.01 g, 0.10 mmol) was added to the solution and the reaction heated to reflux for an additional 12 h. The crude product was passed through a basic alumina plug and flushed with ether to insure complete recovery of

the product. The solvent was removed under reduced pressure to yield 0.25 g (80%) of the Diels–Alder adduct: ^{1}H NMR 0.86–1.46 (m, 180H), 2.86–3.05 (m, 3H), 3.24.2.37 (m, 2H), 4.76 (t, J=3.18 Hz, 1H), 4.93–5.02 (m, 1H), 5.14 (dd, J=6.84, 11.71 Hz, 1H), 7.10–7.58 (m, 8H).

4.2.12. 'Click' chemistry with PIB–CH_2N_3 to form triazoles 34 and 35. Propargyl alcohol (155 mg, 2.8 mmol) and diisopropyl ethyl amine (119 mg, 0.9 mmol) were added to a solution of the azide (2.7 g, 2.5 mmol) in 12.5 mL of THF. The solution was separated into three equal portions and tris(triphenylphoshine)copper bromide (92 mg, 0.1 mmol) was added to each portion. The three portions were each heated in a microwave reactor for 5 min at 140 °C. The three fractions were combined, and the solvent removed under reduced pressure. The product was taken up in 30 mL of hexanes and washed with three 5-mL portions of DMF, three 5-mL portions of brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (ether) to give 1.0 g (37%) of the triazole: ^{1}H NMR 0.9–1.57 (m, 240H), 1.98 (t, J=6.11 Hz, 1H), 4.06 (dd, J=8.43, 13.43 Hz, 1H), 4.24 (dd, J=6.1, 13.43 Hz, 1H), 4.81 (d, J=6.11 Hz, 2H), 7.50 (s, 1H).

A similar reaction was also carried out with 5-hexyn-1-ol as the partner in the triazole synthesis. In this second example, 5-hexyn-1-ol (0.28 g, 2.8 mmol) and diisopropyl ethyl amine (0.12 g, 1.85 mmol) were added to a solution of the azide (2.66 g, 2.5 mmol) in 12.5 mL of THF. The solution was separated into three equal portions and tris(triphenylphosphine)copper bromide (92 mg, 0.1 mmol) was added to each portion. The three portions were each heated in a microwave reactor for 5 min at 140 °C. The three fractions were combined, and the solvent removed by reduced pressure. The product was taken up in 30 mL of hexanes and washed with three 5-mL portions of DMF, three 5-mL portions of brine, dried of Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (ether) to give 2.9 g (92%): ^{1}H NMR 0.86–1.91 (m, 250H), 2.05–2.17 (m, 1H), 2.76 (t, J=7.08 Hz, 2H), 3.68 (t, J=6.35 Hz, 2H), 4.02 (dd, J=6.59, 13.43 Hz, 1H), 4.29 (dd, J=8.3, 13.43 Hz, 1H), 7.25 (s, 1H); ^{13}C NMR ($CDCl_3$, δ): 62.71, 121.14, 147.92.

Further reaction of the hydroxyl groups of **34** to form –CH_2Br groups used standard PBr_3 chemistry. For example, **34** (0.82 mmol) was dissolved in 10 mL of dry toluene and the resulting solution cooled to 0 °C. Phosphorus tribromide (0.26 g, 0.95 mmol) was injected into the solution of polymer and stirred for 1 h at this temperature. The reaction was allowed to warm to room temperature and stirred for an additional 1.5 h. The solvent and unreacted phosphorus tribromide were then removed under reduced pressure and the resulting polymer taken up in 60 mL of hexanes. The hexane solution was washed with three 10-mL portions of Na_2CO_3 saturated methanol and three 10-mL portions of brine, dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to give 1.0 g (95%) of the bromide: ^{1}H NMR 0.86–1.46 (m, 180H), 2.08–2.20 (br, 1H), 4.06 (dd, J=8.3, 13.43 Hz, 1H), 4.22 (dd, J=6.59, 13.43 Hz, 1H), 4.59 (s, 2H), 7.55, (s, 1H).

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High-load, soluble oligomeric benzenesulfonyl azide: application to facile diazo-transfer reactions

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Abstract—The development of a high-load, soluble oligomeric sulfonyl azide using ROM polymerization is reported. The utility in diazo transfer reactions with active methylene compounds is demonstrated using an efficient protocol, with most reactions showing completion in 30 min. The sulfonamide byproduct, being insoluble in the reaction solvent, can be completely removed by simple filtration through a silica gel SPE cartridge.

1. Introduction

The growing demand for facilitated synthesis protocols to aid in drug discovery has directed efforts aimed at integrating the sciences of organic synthesis and purification. Towards this goal, the production of designer polymers with tunable properties has become a powerful technological advancement in the arena of facilitated synthesis. In this context, an array of polymer-bound reagents and scavengers[1] has appeared, effectively streamlining synthetic methods to simple mix, filter and evaporate protocols. The hallmark of these methods is that they avoid the use of insoluble polymers during the actual synthesis, yet retain the virtues of both solution-phase and solid-phase approaches. Despite advances in this area, limitations in reaction homogeneity (nonlinear reaction kinetics), low resin-load capacities, and means of distributing reagents, continue to warrant the development of new polymers for library production.

In order to address these limitations, novel soluble polymers have surfaced as a means of utilizing solution-phase reaction kinetics with all the advantages of their solid phase counterparts.[2] In the course of these developments, ring-opening metathesis (ROM) polymerization,[3,4] has emerged as a powerful means of generating high-load, immobilized reagents with tunable properties that circumvent many of the problems associated with conventional immobilized reagents. There are several salient features that make ROM polymers ideal supports for reagents. First, ROM polymerization is a very versatile technique in that the properties of the generated polymers can be readily modified by the addition of comonomers or cross-linking agents as well as by changing which catalyst is employed. Second, because noncrosslinked oligomers are often soluble in organic solvents, slow reaction kinetics can be avoided. Third, the ROM polymers are often insoluble in methanol and do not pass through silica gel columns, thereby minimizing purification. Lastly, because ROM polymerization is highly functional group tolerant, active polymeric reagents can often be formed directly from the corresponding monomer, minimizing the need for functionalizing the polymer itself. Furthermore because each polymerized monomer contains an active functional group, this technique has potential to generate very highly loaded polymers. In addition, ease of monomer production should not be overlooked, as most monomers are accessible through Diels–Alder or reductive Heck chemistry. To this end, we now report the development and utility of a high-load, soluble oligomeric sulfonyl azide using ROM polymerization.

Diazo compounds are important intermediates in organic synthesis.[5] Of particular interest is the rich chemistry associated with their transition metal-catalyzed reactions.[6]

Keywords: Sulfonyl azide; Ring-opening metathesis polymerization (ROMP); Diazo transfer; High-load polymer; Soluble polymer; Supported reagents.
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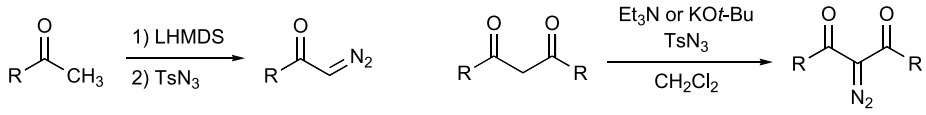


Scheme 1.

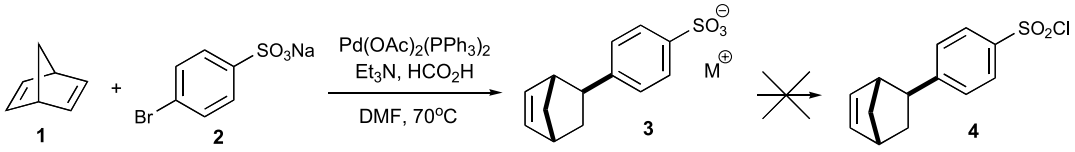
While many methods exist for synthesizing these compounds,[7] one of the most popular is through the reaction of an enolate or active methylene compound with a sulfonyl azide, typically tosyl azide (Scheme 1). While these methods have proven to be very reliable, at times they can be problematic due to stoichiometric amounts of *p*-toluenesulfonamide that are produced.

Several researchers have attempted to solve these problems by developing alternatives to *p*-toluenesulfonyl azide[8] or to generate the reagent in situ.[9] However, all of these approaches have been designed with an eye towards 'large scale' synthesis and still require purification of the diazo compound away from the sulfonamide byproduct. Surprisingly there have only been a few scattered reports on the use of polymeric sulfonyl azides,[10,11] a potentially useful strategy for parallel synthesis that would limit purification to a simple filtration step. These examples have focused on the use of insoluble polystyrene-based polymers. To the best of our knowledge, there are no examples of using soluble, high-load polymers to eliminate impurities from diazo transfer reactions. We felt that one way to facilitate the purification of these compounds would be through construction of a polymeric sulfonyl azide. Ideally, such a polymeric reagent would possess the following attributes: (1) high-load capacity, (2) broad solubility profile, allowing for delivery of the reagent via cannula, (3) facile removal from the reaction products, and (4) convenient availability via construction from cheap, readily available materials, thereby allowing for use in large-scale reactions. It was our belief that a ROM polymer-based sulfonyl azide would satisfy all of these requirements. We describe herein our development of such a reagent and its utility in diazo transfer reaction with active methylene compounds.

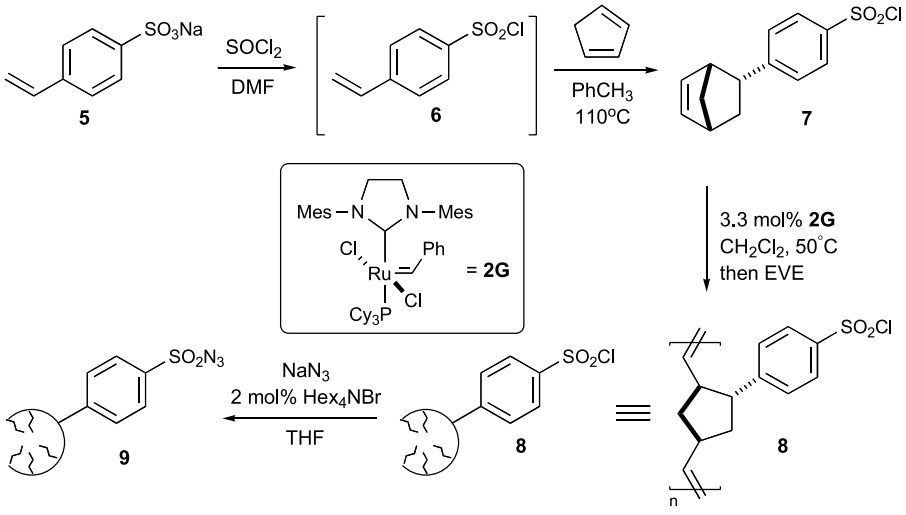
2. Results and discussion

Our initial approach to an oligomeric sulfonyl azide began with a reductive Heck reaction[12] between norbornadiene (**1**) and sodium *p*-bromobenzenesulfonate (**2**),[13] followed by chlorination of the resulting sulfonate **3** (Scheme 2). While the reductive Heck reaction proceeded smoothly, problems were encountered in attempting to convert sulfonate **3** into sulfonyl chloride **4**. Various standard reaction conditions were attempted, but all resulted in general decomposition of sulfonate **3**. We attribute this to adverse reactions occurring with the norbornene ring system.

In order to circumvent this problem, we decided to employ a Diels–Alder reaction to construct the requisite norbornenyl-tagged sulfonyl chloride. To this end, commercially available sodium 4-styrenesulfonate (**5**) was treated with $SOCl_2$ to form sulfonyl chloride **6** (Scheme 3).[14] Initial attempts at reacting purified sulfonyl chloride **6** with cyclopentadiene were unsuccessful as this compound



Scheme 2.



Scheme 3.

spontaneously polymerizes when concentrated and purified.[14] However, we found that when **6** was utilized directly after its formation, it smoothly reacted with cyclopentadiene to form Diels–Alder adduct **7**. By using this method, we could produce **7** on a multi-gram scale with an 8:1 *exo*/*endo* mixture as determined by ^{1}H NMR of the isolated material.

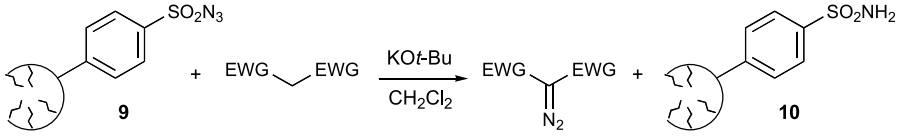
The diastereomeric mixture was not separated, and was found to polymerize readily with 1.6 (60-mer), 2.0 (50-mer), and 3.3 mol% (30-mer) using the second generation Grubbs catalyst [$(IMesH_2)(PCy_3)(Cl)_2Ru{=}CHPh$; cat-**2G**].[15] Subsequent quenching with ethyl vinyl ether (EVE), and precipitation from heptane, yielded the oligomeric sulfonyl chloride (OSC) **8**[16,17] as a free-flowing, light grey solid.[18] This oligomer was found to have a diverse solubility profile, as it was soluble in CH_2Cl_2, THF, and DMF while remaining insoluble in benzene, heptane, ether, acetone, and acetonitrile. Interestingly, the solubility in $CHCl_3$ could be altered simply by altering the length of the polymer formed (i.e., by changing the amount of catalyst). Oligomers produced with 3.3 mol% cat-**2G** were completely soluble in $CHCl_3$, while those produced with 1.6 and 2.0 mol% cat-**2G** were insoluble.

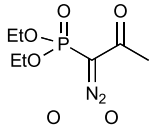
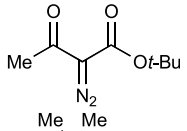
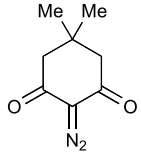
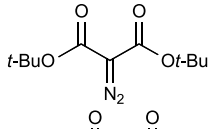
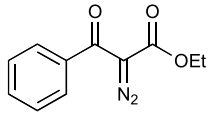
Initial attempts at forming sulfonyl azide **9** centered on reacting **8** with NaN_3 in DMF. While this method did form the desired sulfonyl azide, we observed inconsistent results when subsequent diazo transfer reactions were attempted. This may be due to reaction between DMF and polymer **8**; forming a Wilsmeyer–Haack-type product. However, it was subsequently found that reacting **8** with NaN_3 in THF, in the presence of 2 mol% Hex_4NCl,[19] cleanly produced the desired sulfonyl azide **9**. This oligomeric sulfonyl azide ($^{2G}OSA_{30}$)[20] has a theoretical yield of 3.6 mmol/g, and was found to be soluble in CH_2Cl_2, $CHCl_3$ (partially), THF, and DMF, but insoluble in heptane, methanol, acetonitrile, benzene, ethyl acetate, and Et_2O. We found that while OSA could be produced on >1 g scale, it underwent slow, nonviolent decomposition even if kept in the refrigerator. Best results were obtained if the polymer was used within 1–2 weeks of preparation. We believe this instability is due to the trace Ru impurities in oligomer **8**.[18] Several alternative purification methods were attempted to further purify oligomer **8** but were abandoned due to cost (large scale size exclusion chromatography) or decomposition during extended periods in solution (dialysis in THF or CH_2Cl_2 over several days).

Despite the absence of long-term stability, oligomer **9** was found to efficiently participate in diazo transfer reactions with various active methylene substrates (Table 1). Most reactions were found to be complete within 30 min as judged by TLC. We were pleased to find that product **11** (entry 1) could be produced in high yield and purity,[21] even on 200 mg scale. This diazo phosphonate has proven to be a useful alternative to the Seyferth–Gilbert reagent in the conversion of aldehydes to terminal alkynes.[22,23]

In practice, **9** was added as a solid to a CH_2Cl_2 solution of the substrate and KO^{t}Bu. Because the diazo transfer in this

Table 1.



Entry	Product	Time (min)	Yield[a] (%)	Purity[b] (%)
1		120	97[c]	>95[d]
2		30	88	>95
3		30	75	>95
4		30	74	>95[e]
5		30	90	>90

[a] All reactions performed on 0.2–0.26 mmol scale, with addition of 1.5 equiv **9** as a solid, unless otherwise noted.
[b] Purity by ^{1}H NMR of crude isolated products.
[c] Performed on 1 mmol scale.
[d] Contained 5% diethyl diazomethylphosphonate.
[e] Contained 7% starting material.

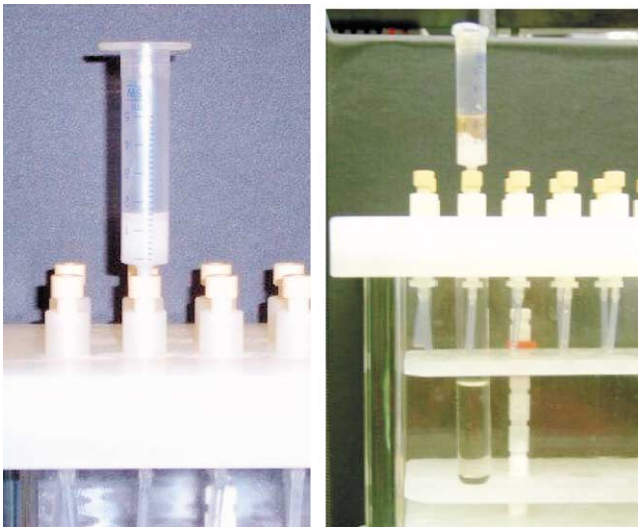
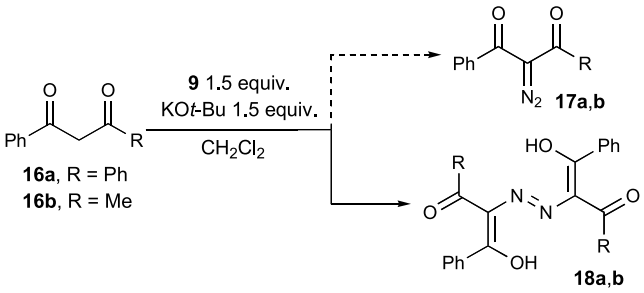


Figure 1. Silica gel SPE cartridge affixed to SPE manifold before filtering reaction (left), and after filtration (right).

system is so efficient, the polymeric sulfonyl azide is rapidly converted into polymeric primary sulfonamide **10**, which is not soluble in CH_2Cl_2. Due to this insolubility issue, the sulfonamide byproduct could be completely removed from the reaction products simply by filtering through a silica gel solid-phase extraction (SPE) cartridge and washing with EtOAc. As can be seen in Figure 1, the SPE cartridge retains all precipitated polymer, while the isolated filtrate is completely clear. Using this simple workup, all diazo products were isolated in high yield and excellent purity as judged by GC and ^{1}H NMR, which indicated an absence of any polymeric material (Fig. 2).

Interestingly, with dibenzoylmethane (**16a**) and 1-benzoylacetone (**16b**), the reaction took a different course (Scheme 4). In these cases, an 'azo coupling' reaction took place to generate azo compounds **18a**,**b**. This type of reaction has been reported by Regitz and Stadler by utilizing 0.5 equiv of TsN_3.[24] Various attempts were made to circumvent these spurious results (changing order of addition, changing base to Et_3N), but to no avail. It is interesting to note that this was not observed in the case of 5,5-dimethyl-1,3-cyclohexanedione (dimedone) (Table 1, entry 5). Perhaps there is a steric effect involved with the enolates derived from **16a**,**b** that is not felt with the flat enolate generated from dimedone.



Scheme 4.

3. Conclusion

In conclusion, we have constructed a high-load, oligomeric sulfonyl azide and demonstrated its utility in diazo transfer reactions with active methylene compounds. This system is extremely efficient with most reactions showing completion in 30 min. The sulfonamide byproduct, being insoluble in the reaction solvent, can be completely removed by a simple filtration through a silica gel SPE cartridge. Application of this reagent in the synthesis of synthetically relevant diazo compounds, as well as in other reaction types are being investigated and will be reported in due course.

4. Experimental

4.1. General methods

All air and moisture sensitive reactions were carried out in flame- or oven-dried glassware under argon using standard gas-tight syringes, cannulas, and septa. CH_2Cl_2,

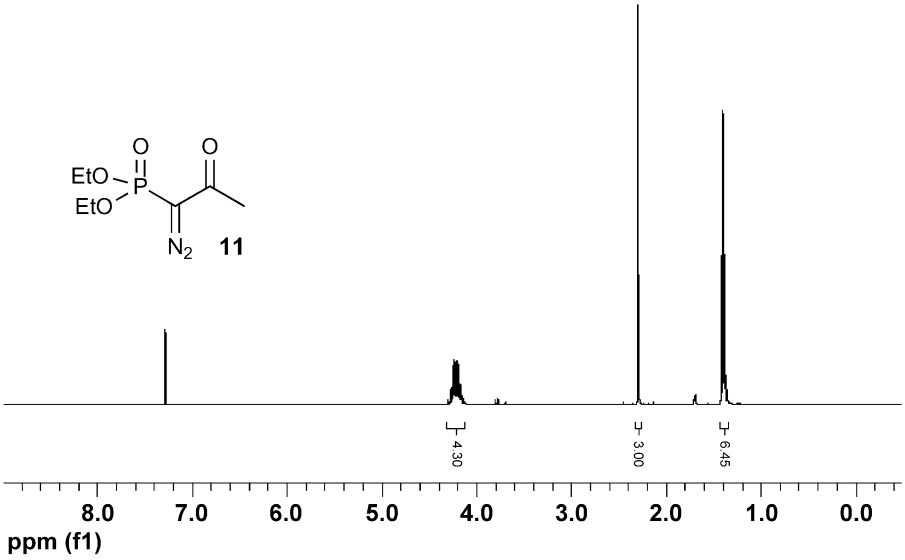


Figure 2. ^{1}H NMR spectrum of crude **11**.

THF, Et_2O, CH_3CN, and toluene were purified by passage through a Solv-Tek (www.solvtek.com) purification system employing activated Al_2O_3 (Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518). Benzene was purified by distillation over CaH_2. Et_3N was purified by passage through a column of basic alumina and stored over KOH. The second-generation Grubbs metathesis catalyst was obtained from Materia, Inc. and used without further purification. Thin layer chromatography was performed on silica gel $60F_{254}$ plates (EM-5717, Merck). Visualization of TLC spots was effected using $KMnO_4$ stain. Flash column chromatography was performed with Merck silica gel (EM-9385-9, 230–400 mesh). Deuterochloroform ($CDCl_3$) was purchased from Cambridge Isotope Laboratories and stored over molecular sieves (4 Å) at rt. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ (unless otherwise mentioned) on either a Bruker DRX-400 MHz spectrometer operating at 400 and 100 MHz, respectively; or a Bruker Avance-500 MHz spectrometer operating at 500 and 126 MHz, respectively, and references to residual $CHCl_3$ peaks (7.26 and 77.0 ppm for ^1H and ^{13}C, respectively). High resolution mass spectrometry (HRMS) and FAB spectra were performed by the Mass Spectrometry Laboratory at the University of Kansas using a VG Instrument ZAB double-focusing mass spectrometer. Inductively coupled plasma mass spectrometry (ICPMS) was performed using a VG PlasmaQuad II+XS inductively coupled plasma mass spectrometer and run against calibration standards (1, 5, 10, 50 and 100 ppb) which were made from commercial Ru stock solution (provided in 10% HCl) by diluting with distilled 6 N nitric acid to the same acid strength as the samples. Prior to analysis, samples were weighed (~5 mg) into screw-top glass vials and 0.3 mL 4:1 H_2SO_4/35% aq H_2O_2 was added. *Caution: this mixture is extremely corrosive*. The 35% aq H_2O_2 should be added extremely slowly with the temperature of the mixture not allowed to rise above 50–60 °C. Once dissolution was complete (1–2 days), the samples were dissolved in 3 mL of distilled 6 N HNO_3 acid, capped, and placed on a 50 °C hot plate for 1–2 days. The samples were then cooled and transferred to acid-cleaned high-density polyethylene bottles, sonicated for one hour, and diluted to a total volume of approximately 100 mL with distilled acid and distilled-deionized water to a final acid concentration of about 2%.

4.1.1. 4-(Bicyclo[2.2.1]hept-5-en-2-yl)benzene-1-sulfonyl chloride (7). A flask was charged with $SOCl_2$ (85 mL, 891 mmol) and cooled with an ice bath. Sodium 4-styrenesulfonate (26.37 g, 128 mmol) was added portion-wise with heavy stirring over 1 h. DMF (35 mL) was added slowly and the mixture warmed to RT. After 6 h the flask was placed in a refrigerator overnight. The cold mixture was then carefully poured onto ~800 mL of ice. The mixture was extracted with Et_2O, and evaporated. The residue was dissolved in toluene (60 mL), freshly cracked cyclopentadiene (~10 mL) was added, and the solution heated to reflux. Fresh cyclopentadiene was added in 10 mL increments every hour for 5 h. After the last addition the mixture was kept at reflux for 2 h. After cooling to RT, the reaction was concentrated under reduced pressure. Flash chromatography [heptane (to remove dicyclopentadiene) and then 10:1 heptane/EtOAc, all mixed fractions were resubjected to flash chromatography] afforded **7** (24.52 g, 71%) as a slightly yellow solid (8:1 *endo*/*exo* mixture). TLC (5:1 heptane/EtOAc) R_f 0.11; IR (thin film) 3059, 2968, 1589, 1375, 1175 cm^{-1}.

Major *endo* isomer: ^1H NMR (400 MHz, $CDCl_3$) 7.87 (d, 2H, $J=8.1$ Hz), 7.35 (d, 2H, $J=8.5$ Hz), 6.32 (dd, 1H, $J=5.6$, 3.1 Hz), 5.76 (dd, 1H, $J=5.6$, 2.8 Hz), 3.49 (ddd, 1H, $J=8.6$, 4.0, 4.0 Hz), 3.12 (br s, 1H), 3.02 (br s, 1H), 2.26 (ddd, 1H, $J=12.7$, 9.4, 3.8 Hz), 1.56 (br d, 1H, $J=8.3$ Hz), 1.51 (br d, 1H, $J=8.1$ Hz), 1.33 (ddd, 1H, $J=11.9$, 4.4, 2.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) 154.0, 141.4, 138.0, 132.1, 129.2, 126.4, 50.3, 48.8, 44.0, 43.2, 33.0.

Minor *exo* isomer: ^1H NMR (400 MHz, $CDCl_3$) 7.94 (d, 2H, $J=8.0$ Hz), 7.49 (d, 2H, $J=8.5$ Hz), 6.27 (dd, 1H, $J=5.6$, 3.0 Hz), 6.22 (dd, 1H, $J=5.8$, 2.8 Hz), 3.02 (br s, 1H), 2.97 (br s, 1H), 2.81 (dd, 1H, $J=7.4$, 7.4 Hz), 2.26 (ddd, 1H, $J=12.7$, 9.4, 3.8 Hz), 1.56 (br d, 1H, $J=8.3$ Hz), 1.51 (br d, 1H, $J=8.1$ Hz), 1.33 (ddd, 1H, $J=11.9$, 4.4, 2.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) 155.2, 141.3, 137.7, 136.8, 128.7, 126.9, 47.8, 45.7, 44.1, 42.3, 33.9.

4.1.2. Formation of oligomeric sulfonyl chloride (8). A flask was charged with **7** (8.5814 g, 31.9 mmol) and CH_2Cl_2 (100 mL) was added. The mixture was degassed with argon for 20 min. Catalyst **2G** was added (895 mg, 1.05 mmol) and the solution was heated to 50 °C. The reaction was monitored by TLC (8:1 heptane/EtOAc) and upon completion (about 30 min), the solution was cooled to rt and 20 mL ethyl vinyl ether (EVE) was added. The mixture was stirred for 1 h and then added to 3 L heptane via cannula with stirring. The precipitate was allowed to settle and the supernatant was then decanted through a fritted glass funnel. The precipitate was washed with three 500 mL portions of 10:1 heptane/$CHCl_3$ followed by heptane. Oligomer **8** (8.6396 g, 99%) was collected as a free-flowing, light grey solid: IR (thin film) 3059, 2943, 1589, 1411, 1373, 1173, 1084, 972, and 837 cm^{-1}.

4.1.3. Formation of oligomeric sulfonyl azide (9). To a mixture of **8** (1.0124 g, 3.77 mmol) and Hex_4NCl (35.9 mg, 0.0826 mmol) in THF (10 mL), was added NaN_3 (394.3 mg, 6.07 mmol). Caution: NaN_3 should not be measured out with metal utensils. The end of a glass pipette was always used to weigh the necessary amount. The heterogeneous mixture was stirred at rt for 15 h. The reaction was then added to a stirred mixture of H_2O/MeOH (70 mL/30 mL). The precipitate was filtered with a coarse glass frit and washed with H_2O, MeOH, and heptane to afford oligomer **9** (1.0745 g, 99%) as a brown solid. Caution: while we have had no problems with handling oligomer **9**, safety shields should be utilized when handling large quantities: IR (thin film) 3051, 2943, 2125, 1593, 1371, 1169, 1088 cm^{-1}.

4.2. General procedure for diazo transfer reaction with OSA

An oven-dried vial was charged with the active methylene compound (1 equiv), and KO*t*-Bu (1.5 equiv) and dissolved in CH_2Cl_2 (0.2 M). Oligomer **9** (1.5–2 equiv) was added and the mixture stirred at rt and monitored by TLC. When the reaction was complete, EtOAc (1 mL) was added

and the mixture filtered through a SPE cartridge containing ~650 mg silica. The cartridge was washed with EtOAc (4×1 mL). The filtrate was evaporated under reduced pressure to afford pure diazo compound.

4.3. Characterization of diazo transfer products 11–15

4.3.1. Diethyl (1-diazo-2-oxopropyl)phosphonate (11). The general procedure above was followed starting with diethyl (2-oxopropyl)phosphonate (200 μL, 1.04 mmol), KO*t*-Bu (131.4 mg, 1.17 mmol), and **9** (433.5 mg, 1.56 mmol), to afford **11** (224.5 mg, 97%) as an orange oil: IR (thin film) 2986, 2123, 1659, 1267, 1018 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 4.21 (dq, 4H, J=7.0, 8.4 Hz), 2.28 (s, 3H), 1.39 (dt, 6H, J=7.1, 0.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) 190.1 (J_{CP}=13.8 Hz), 63.4 (J_{CP}=5.6 Hz), 27.2, 16.1 (J_{CP}=6.8 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) −12.49.

4.3.2. *t*-Butyl 2-diazo-3-oxobutanoate (12). The general procedure above was followed starting with *t*-butyl acetoacetate (45 mg, 0.284 mmol), KO*t*-Bu (51.6 mg, 0.460 mmol), and **9** (120.4 mg, 0.433 mmol) to afford **12** (46 mg, 88%) as a yellow-orange oil:[10c] IR (thin film) 2980, 2934, 2131, 1659, 1651 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 2.45 (s, 3H), 1.52 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) 190.5, 160.5, 83.1, 28.2, 28.1.

4.3.3. 2-Diazo-5,5-dimethyl-1,3-cyclohexanedione (13). The general procedure above was followed starting with 5,5-dimethyl-1,3-cyclohexanedione (33.1 mg, 0.236 mmol), KO*t*-Bu (45.1 mg, 0.402 mmol), and **9** (99.3 mg, 0.357 mmol) to afford **13** (29.5 mg, 75%) as a pale yellow solid: mp 103–105 °C (lit.[25] 105–107 °C), IR (thin film) 2962, 2137, 1643, 1312, 1277 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 2.44 (s, 4H), 1.12 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) 189.8, 50.5, 31.1, 28.3.

4.3.4. Di-*t*-butyl 2-diazomalonate (14). The general procedure above was followed starting with di-*t*-butyl malonate (46.3 mg, 0.214 mmol), KO*t*-Bu (38.8 mg, 0.346 mmol), and **9** (95.9 mg, 0.345 mmol) to afford **14** (38.3 mg, 74% containing 7% starting material) as a yellow-orange oil: IR (thin film) 2980, 2133, 1747, 1693 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 1.50 (s); ^{13}C NMR (125 MHz, $CDCl_3$) 160.3, 82.6, 28.2.

4.3.5. Ethyl 2-diazo-3-oxo-3-phenylpropanoate (15). The general procedure above was followed starting with ethyl benzoylacetate (39.7 mg, 0.207 mmol), KO*t*-Bu (43.3 mg, 0.386 mmol), and **9** (99.6 mg, 0.359 mmol) to afford **15** (40.5 mg, 90%) as a yellow-orange oil: IR (thin film) 3061, 2984, 2143, 1728, 1631 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.66–7.61 (m, 2H), 7.56–7.51 (m, 1H), 7.46–7.40 (m, 2H), 4.24 (q, 4H, J=7.1 Hz), 1.26 (t, 6H, J=7.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) 186.9, 161.0, 137.1, 132.2, 128.3, 127.8, 61.6, 14.1.

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PEG-supported pyridylthioesters for racemization-free amide synthesis: a reagent that allows simultaneous product formation and removal from the polymer

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Abstract—Pyridylthioesters anchored to a modified poly(ethylene glycol) of M_w 5000 Da have been prepared in high yields. The thioesters were employed as a convenient starting material for the liquid-phase synthesis of various enantiomerically pure amides. This new methodology allowed to perform simultaneously the reaction with the poly(ethylene glycol)-supported reagent and the traceless removal of the final product from the polymer support in a single step. The products were obtained in high yield and purity.

1. Introduction

In the early 1990s the first examples of combinatorial organic synthesis led to a renaissance of the interest in synthetic methodologies on polymer supports.[1] In the last decade the number of publications in the field of combinatorial synthesis of relatively small organic molecules has been growing exponentially and today solid-phase organic synthesis (SPOS) is routinely used for the preparation of combinatorial libraries of low molecular weight organic molecules.[2]

Poly(ethylene glycol)s (PEGs) have emerged as very convenient supports for the synthesis of a variety of small organic molecules.[3] PEGs are inexpensive and commercially available polymers[4] that can readily be functionalized with different spacers and linkers.[5] Provided that their M_w is >2000 Da, PEGs are soluble in many, mostly polar solvents (including water) and insoluble in a few nonpolar solvents (hexanes, diethyl ether, *tert*-butyl methyl ether). Because of this solubility profile, PEG-based supports combine the advantageous features of homogeneous solution chemistry (high reactivity, lack of diffusion phenomena, analytical simplicity) and of solid-phase methods (ready isolation and purification of products).[6] Consequently, syntheses and immobilization of several organic molecules on PEGs have been extensively reported over the last few years.[7]

Recently our group has been involved in the synthesis and development of poly(ethylene glycol)-supported catalysts.[8] Achiral[9] and chiral organic catalysts,[10] as well as chiral organometallic species[11] have been immobilized on properly modified PEG derivatives and their catalytic activity investigated. The synthesis of PEG-anchored *N*-aryl imines, their conversion into differently substituted, supported β-lactams[12] and tetrahydroquinolines,[13] and finally the traceless removal of these products from the polymer support have also been studied.

On the basis of this experience we became convinced that the success of a polymer-supported synthesis strategically depends on the development of suitably modified new polymeric backbones. In particular the choice of the structural unit which temporarily connects the solid support and the substrate under manipulation (the so-called 'linker') is crucial.[14] The ideal linker must tolerate the conditions employed to elaborate the substrate, but it must cleave under mild conditions without affecting neither chemically nor stereo chemically the product's integrity. For the reversible attachment of special functional groups, known anchors have often to be modified and optimized or, when necessary, must be created de novo.[15]

Recently an increasing attention has been devoted to the development of 'traceless' linkers to join the desired

Keywords: Poly(ethylene glycol); Mesylate derivative; Pyridylthioester.
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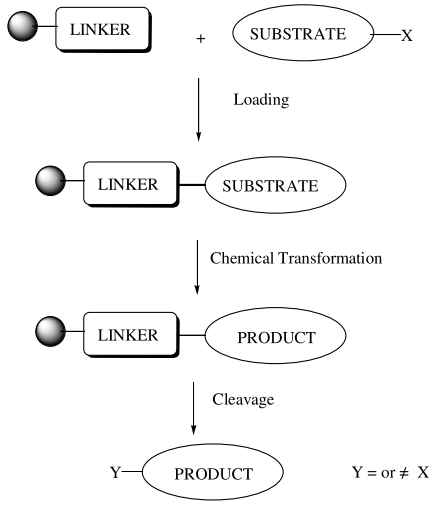


Figure 1. Schematic representation of the synthetic sequence in polymer-supported organic synthesis.

synthetic intermediates to the solid support. With these linkers the cleavage can be accomplished without leaving a residue or trace of the linker on the final product[16] (Fig. 1).

Another popular strategy in the very active field of the study and optimization of novel linkers, is the so-called 'safety-catch' linking methodology.[17] According to this strategy the linker employed is stable under different reaction conditions until it is activated for the removal of the product.[18] Safety-catch linkers may facilitate the use of a wider range of reaction conditions but at the cost of one additional activation step.

Here, we report a new methodology that allows to perform simultaneously a chemical transformation of the polymer supported substrate and the traceless cleavage of the product (Fig. 2). A single synthesis-removal step delivers the product in solution while leaving the polymer ready for recycling after an activation step.

2. Results and discussion

The functionalization of the polymeric support was performed as follows. The monomethylether of PEG with a M_w of 5000 Da (MeOPEG) was easily converted into mesylate **1** that was reacted with the cesium salt of the commercially available 3-(4-hydroxyphenyl)-1-propanol (3 mol equiv, *N*,*N*-dimethylformammide, 48 h) to afford the corresponding polymer supported alcohol. This was

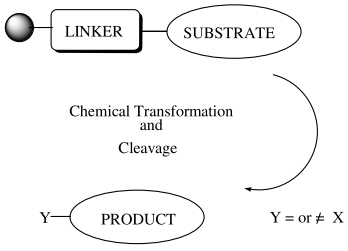
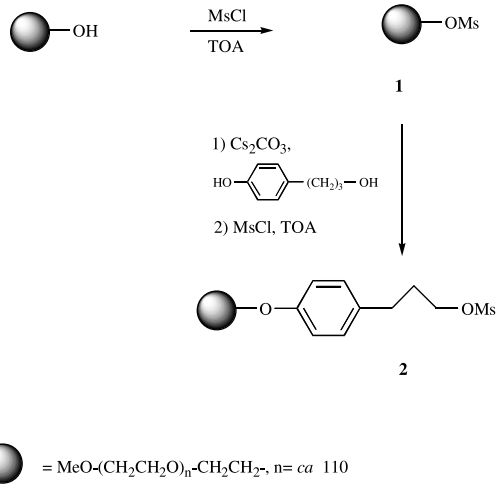


Figure 2. Schematic representation of the novel methodology.



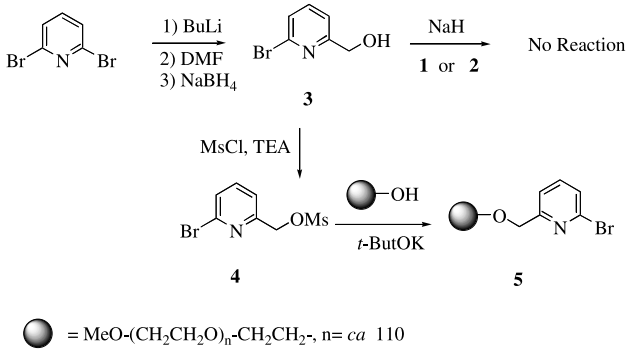
Scheme 1. Synthesis of functionalized PEG derivatives **1** and **2**.

transformed into the mesylate derivative **2** in 95% overall yield over three steps[12] (Scheme 1).

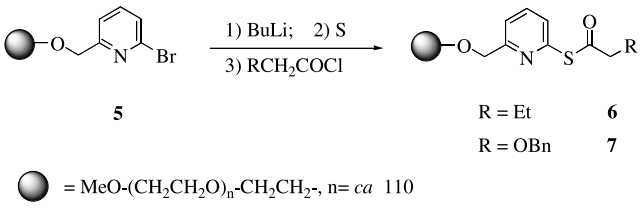
The immobilization of a functionalized pyridine unit onto the polymer was then attempted. 6-Bromo-2-hydroxymethylpyridine **3** was easily prepared starting from the commercially available 2,6-dibromopyridine by lithiation with *n*-butyllithium, formylation with DMF and reduction with $NaBH_4$ (91% overall yield). Unfortunately, any attempt to react the sodium salt of alcohol **3** (prepared from **3** with NaH) with mesylate **1** or **2** were unsuccesfull.[19]

On the contrary, reaction of the mesylate **4**, obtained in 98% yield from **3**,[20] with MeOPEG carried out in the presence of potassium *t*-butoxide in dry toluene allowed to obtain the poly(ethylene glycol)-supported 6-bromopyridyl derivative **5** in 91% yield (Scheme 2).

The most straightforward transformation of a 2-bromopyridine into the corresponding thioester involves lithiation at position 2 by lithium–halogen exchange followed by quenching with sulphur and in situ reaction with an acyl chloride. However, when this sequence was performed on bromide **5** in ethereal solvents the very low solubility of PEG in these reaction media prevented any product formation. Therefore, on the base of Peterson's work,[21] we decided to employ dichloromethane as reaction solvent. We were very pleased to find that reaction of **5** with butyllithium in dry CH_2Cl_2 at −78 °C, followed by



Scheme 2. Synthesis of poly(ethylene glycol)-supported pyridyl unit **5**.



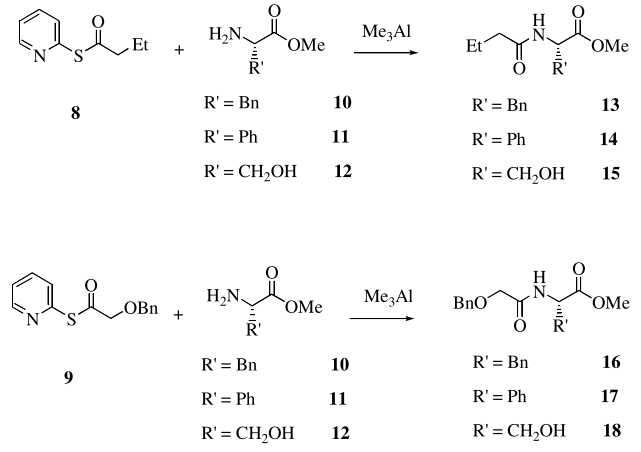
Scheme 3. Synthesis of poly(ethylene glycol)-supported pyridylthioesters **6** and **7**.

quenching with sulfur and trapping of the intermediate thiolate with butanoyl chloride afforded the PEG-supported 2-pyridylthiobutanoate **6** in an excellent 87% overall yield. (Scheme 3). Similarly, by lithiation of **5**, reaction first with sulfur and then with benzyloxyacetyl chloride, polymer-supported pyridylthioester **7** was synthesized in 91% yield.[22]

The availability of the PEG-supported thioesters **6** and **7** allowed us to investigate the possibility of performing in a single step a synthesis/removal process.[23] Thioesters are activated carboxylic acid derivatives that have found widespread application as acylating agents in synthetic chemistry acting as precursors of carbonyl compounds, acids, esters, lactones, amides, lactams, and heterocycles.[24,25]

We decided to employ our PEG-supported thioesters in some amide bond forming reactions, where it is essential to prevent base-catalysed racemization during the coupling process. In particular, the reaction of PEG-supported pyridylthioesters **6** and **7** with differently substituted chiral α-amino esters in the presence of Me_3Al was studied.[26,27]

For sake of comparison, the condensation between thioesters **8** and **9** (the nonsupported equivalents of **6** and **7**) and the chiral α-amino esters, was also performed as test reactions (Scheme 4). Condensation of 2-pyridyl-thiobutanoate **8** in the presence of trimethylaluminum in dry dichloromethane with (*S*)-phenylalanine methyl ester **10** afforded the corresponding amide **13** in 71% yield. Analogously, the reactions under the same experimental conditions of **8** with (*S*)-phenylglycine methyl ester **11** and (*S*)-serine methylester **12** gave the corresponding products **14** and **15** in 47 and 23% yield, respectively. Better yields were obtained in the condensation between the same aminoesters and pyridylthio-2-benzyloxyacetate **9**; in this case the reaction with **10**, **11** and **12** afforded the corresponding products **16**, **17** and **18** in 84, 51 and 71% yield, respectively.



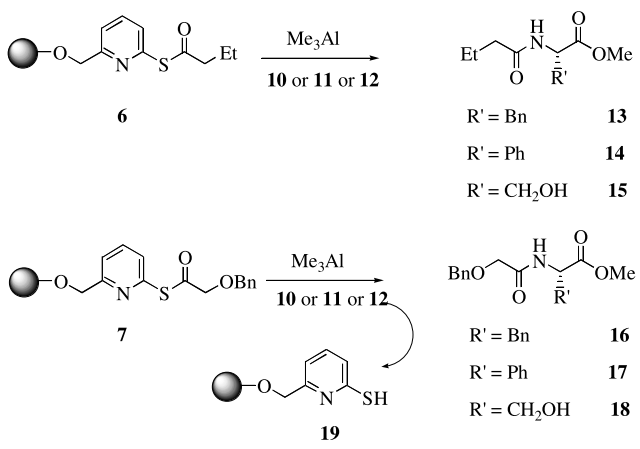
Scheme 4. Reaction of nonsupported pyridylthioesters **8** and **9**.

The same reaction starting from the PEG-supported pyridylthioesters were then studied (Scheme 5). The dimethylaluminum amide of (*S*)-phenylalanine methylester (2 mol/equiv) reacted with the poly(ethylene glycol)-supported pyridylthioester **6** (1 mol/equiv) in dichloromethane to afford, after 24 h at room temperature, the product **13** in 63% yield. After the work up, the organic phase was concentrated and poured into a diethyl ether solution. The precipitated polymer was filtered off, and the organic solvent simply evaporated to give the reaction product.[28] Starting always from **6**, a similar procedure allowed to obtain the amide **14** and **15**, derived from reaction of (*S*)-phenylglycine and (*S*)-serine derivatives, in 33 and 19% yield.

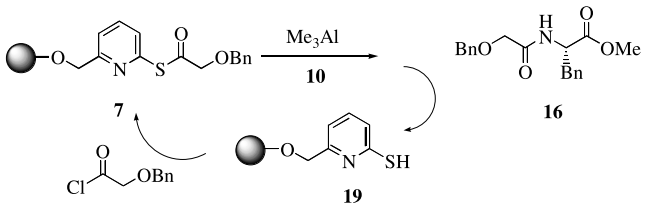
PEG-anchored thioester **7** gave better results than **6**, exactly like the nonimmobilized thioester **9** did in comparison with **8**. Compound **16**, the product of the reaction of **7** with phenylalanine derivative, was isolated in 77% yield, that was only marginally lower than that obtained starting from the nonsupported derivative **9** (84% yield). Analogously, starting from **7** compounds **17** and **18** were synthesized in 35 and 43% yield, respectively. It is worth mentioning that these are highly functionalized molecules; for example different functional groups as an amide, an ester, a free primary alcohol and another primary but protected alcohol are all present in **18**. Noteworthy, all the products **13**-**18** were obtained as enantiomerically pure compounds, in a racemization-free methodology.[29]

Another point of interest is the possibility to recover and recycle the polymer-supported reagent. For example, from the reaction of **9** with phenylalanine derivative **10**, besides product **16**, the PEG-supported 2-mercaptopyridyl derivative **19** was recovered by filtration in 91% yield (Scheme 6).

Starting from **19** the poly(ethylene glycol)-anchored benzyloxy-pyridylthioacetate **7** was easily regenerated by reaction with benzyloxyacetyl chloride in the presence of a



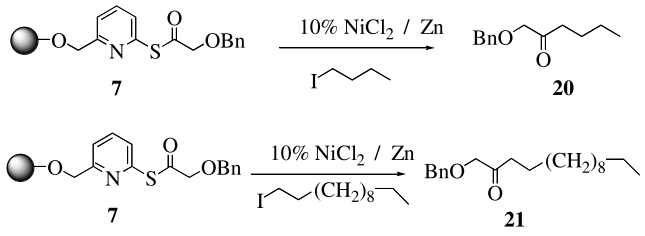
Scheme 5. Reaction of PEG-supported pyridylthioesters **6** and **7**.



Scheme 6. Recycle of the PEG-supported reagent.

base and employed in a new condensation with **10** that afforded the product **16** in a comparable yield (75% vs 77%).

Finally we tested the polymer-supported thioester also in another reaction. We were attracted by Seki's[30] and Mukaiyama's[31] work, where a iodo compound in the presence of an excess of zinc, under catalysis of nickel (II) chloride, was coupled to a pyridylthioester to afford a ketone. We decided to study this reaction with the PEG-supported pyridylthioester **7** (Scheme 7).



Scheme 7. Nickel catalysed synthesis of ketones **20** and **21**.

To the polymer-immobilized thioester **7** in dry *N*,*N*-dimethylformammide (DMF), iodo-butane, zinc and a catalytic amount of nickel chloride were added; the reaction mixture was allowed to stir for 20 h at room temperature. After work up with water and diethyl ether the evaporation of the organic phase afforded the expected ketone **20** in 81% yield. Similarly, the long chain-ketone **21** was obtained from the reaction with iodododecane.

In conclusion, a new synthesis of soluble polymer-supported pyridylthioesters, useful starting materials for several reactions in liquid phase synthesis has been developed. A new methodology allowed to perform at the same time the reaction of the poly(ethylene glycol)-supported reagent and the traceless removal of the final product from the polymer support in a single step. This synthetic procedure was successfully tested in two different reactions, the synthesis of various enantiomerically pure amides and a nickel-catalyzed preparation of ketones. The recovery, the regeneration and the recycle of the polymer-supported reagent was also realized.

3. Experimental

3.1. General methods

^{1}H NMR spectra were recorded at 300 MHz in chloroform-*d* ($CDCl_3$) unless otherwise stated, and were referenced to tetramethylsilane (TMS) at 0.00 ppm. ^{13}C NMR spectra were recorded at 75 MHz and were referenced to 77.0 ppm in $CDCl_3$. Optical rotations were measured at the Na-D line in a 1 dm cell at 22 °C. IR spectra were recorded on thin film or as solution in CH_2Cl_2.

All the PEG samples were melted at 80 °C under vacuum for 60 min before use to remove traces of moisture. After reaction, PEG-supported product purification involved evaporation of the reaction solvent in vacuum and addition of the residue dissolved in a few mL of CH_2Cl_2 to diethylether (40 mL/g of polymer), which was stirred and cooled at 0 °C. After 20 min stirring at 0 °C, the obtained suspension was filtered through a sintered glass filter, and the solid repeatedly washed on the filter with diethylether (up to 80 mL/g of polymer, overall).

Yield and purity determination of PEG-supported compounds. The yield of the PEG-supported compounds were determined by weight with the assumption that M_w is 5000 Da for the PEG fragment. The M_w actually ranged from 4500 to 5500. The indicated yields were for pure compounds. The purity of these compounds was determined by ^{1}H NMR analysis in $CDCl_3$ at 300 MHz with pre-saturation of the methylene signals of the polymer centered at $\delta=3.63$. In recording the NMR spectra, a relaxation time of 6 s and an acquisition time of 4 s were used to ensure complete relaxation and accuracy of the integration. The relaxation delay was selected after T_1 measurements. The integration of the signals of the PEG CH_2OCH_3 fragment at $\delta=3.30$ and 3.36 were used as internal standard. The estimated integration error was +5%.

3.2. Synthesis of pyridyl derivatives

PEG derivative **1** was prepared by a synthesis developed in our group.[12] Products **3** and **4**[20] are known compounds; product **14** is also known;[32] product **14** is known also as racemic compound.[33]

3.2.1. Synthesis of PEG-mesylate 2. To a solution of mesylate **1** (9.00 g, 1.80 mmol) in dry DMF (20 mL) stirred under nitrogen, Cs_2CO_3 (1.94 g, 5.94 mmol) and 3-(4-hydroxy-phenyl)-1-propanol (0.82 g, 5.40 mmol) were added. The mixture was stirred at room temperature for 40 h and concentrated under vacuum to half of the original volume. Purification by precipitation with diethyl ether (40 mL/g of polymer) afforded the corresponding alcohol (8.85 g, 96% yield).

^{1}H NMR: 1.83 (m, 2H, CH_2–*CH_2*–CH_2), 2.67 (t, $^3J_{H,H}$= 7.4 Hz, 2H, Ar-*CH_2*–CH_2–CH_2), 3.38 (s, 3H, O*Me*), 4.10 (t, $^3J_{H,H}=5.0$ Hz, 2H, Ar-O–*CH_2*–CH_2–PEG), 6.82 (B part of a AB system, $^3J_{H,H}=8.5$ Hz, 2H, *H ortho* to O in aromatic ring), 7.07 (A part of a AB system, $^3J_{H,H}=8.5$ Hz, 2H, *H meta* to O in aromatic ring). This intermediate[12] was then converted into mesylate **2**. To a solution of the PEG-alcohol (6.00 g, 1.2 mmol) in dichloromethane (30 mL), mesyl chloride (3.6 mmol, 0.29 mL) and trioctylamine (3.96 mmol, 1.72 mL) were added. The mixture was stirred at room temperature for 24 h. Purification by precipitation with diethyl ether (40 mL/g of polymer) afforded the corresponding mesylate **2** (6.01 g, 99% yield). 2.73 g, yield 91%). ^{1}H NMR: 1.93 (m, 2H, CH_2–*CH_2*–CH_2), 2.60 (t, $^3J_{H,H}=7.5$ Hz, 2H, Ar-*CH_2*–CH_2–CH_2), 3.07 (s, 3H,

OSO_2Me), 3.35 (s, 3H, O*Me*), 4.05 (t, $^3J_{H,H}=5.0$ Hz, 2H, Ar-O–CH_2–CH_2–PEG), 4.25 (t, $^3J_{H,H}=5.2$ Hz, 2H, –CH_2–OSO_2Me), 6.87 (B part of a AB system, $^3J_{H,H}=8.0$ Hz, 2H, *H ortho* to O in aromatic ring), 7.15 (A part of a AB system, $^3J_{H,H}=8.0$ Hz, 2H, *H meta* to O in aromatic ring).

3.2.2. Synthesis of PEG-derivative 5. To a solution of poly(ethylene glycol) monomethylether (3.00 g, 0.60 mmol) in dry toluene (20 mL) stirred under nitrogen, potassium *t*-butoxide (80 mg, 0.72 mmol) was added. The mixture was warmed up to 60 °C and stirred at that temperature for 3 h. A solution of mesylate **4** (479 mg, 1.8 mmol) in toluene (3 mL) was then added and all the reaction mixture was allowed to stir at 65 °C for 48 h. The solvent was then evaporated under vacuum, and the residue was solved into CH_2Cl_2 (30 mL). This organic phase was washed with water, dried over sodium sulfate, filtered, concentrated under vacuum, and precipitated with diethyl ether (see above). The product was isolated by filtration. (2.73 g, yield 91%). ^{1}H NMR: 3.38 (s, 3H, O*Me*), 3.80 (t, $^3J_{H,H}=6$ Hz, 2H, CH_2–O–EG–Me), 4.68 (s, 2H, Py-CH_2–O), 7.31 (d, $^3J_{H,H}=9$ Hz, 1H, H_5 Py), 7.46 (d, $^3J_{H,H}=9$ Hz, 1H, H_3 Py), 7.53 (t, $^3J_{H,H}=9$ Hz, 1H, H_4 Py).

3.2.3. Synthesis of PEG-supported pyridylthioesters 6 and 7. To a solution of poly(ethylene glycol) monomethylether (2.5 g, 0.48 mmol) in dry CH_2Cl_2 (20 mL) stirred under nitrogen and cooled to −78 °C, butyllithium (0.39 mL of a 1.5 M solution of butyllithium in hexanes, 0.58 mmol) was slowly added by syringe. The suspension was allowed to stir at −78 °C for 45 min, then sulfur (0.186 g, 5.8 mmol) was added; the reaction mixture was stirred at that temperature for 15 min, then at 0 °C for other 15 min and finally at room temperature for other 90 min. Then a solution of the acyl chloride (0.97 mmol in 5 mL of dichloromethane) was added and the reaction mixture was allowed to stir overnight at room temperature. Na HCO_3 satd sol was added and the phases separated. The organic phase was dried over sodium sulfate, filtered, concentrated under vacuum, and precipitated with diethyl ether (see above). The product was isolated by filtration.

Product **6**. (2.3 g, yield 87%). ^{1}H NMR: 1.10 (t, $^3J_{H,H}=7$ Hz, 3H, CH_3–CH_2CO), 2.35 (q, $^3J_{H,H}=7$ Hz, 2H, CH_3–CH_2CO), 3.38 (s, 3H, O*Me*), 3.80 (t, $^3J_{H,H}=6$ Hz, 2H, CH_2–O–EG–Me), 4.65 (s, 2H, Py-CH_2–O), 7.31 (d, $^3J_{H,H}=8$ Hz, 1H, H_5 Py), 7.41 (d, $^3J_{H,H}=8$ Hz, 1H, H_3 Py), 7.49 (t, $^3J_{H,H}=8$ Hz, 1H, H_4 Py).

Product **7**. (2.41 g, yield 91%). ^{1}H NMR: 3.38 (s, 3H, O*Me*), 3.80 (t, $^3J_{H,H}=6$ Hz, 2H, CH_2–O–EG–Me), 4.10 (s, 2H, CO–CH_2–O), 4.60 (s, 2H, Ph-CH_2–O), 4.70 (s, 2H, Py-CH_2–O), 7.25–7.35 (m, 5H, phenyl), 7.31 (d, $^3J_{H,H}=8$ Hz, 1H, H_5 Py), 7.43 (d, $^3J_{H,H}=8$ Hz, 1H, H_3 Py), 7.53 (t, $^3J_{H,H}=8$ Hz, 1H, H_4 Py).

3.3. Synthesis of amides 13-18

With nonsupported reagents. To a solution of pyridylthioester (1 mmol) in dry dichloromethane (5 mL) at 0 °C, the amino-ester (2 mmol) was added. After a few minutes a 2 M toluene solution of trimethylaluminum (4 mmol) was added and the reaction mixture was allowed to stir at 0 °C for 1–6 h. *t*-Butanol (a few drops) was added, then the reaction solution was acidified by addition of 5% HCl to pH 4–5. Water was added, the phases separated and the aqueous phase extracted twice with CH_2Cl_2. The combined organic phases were washed with water, dried over sodium sulfate, filtered, concentrated under vacuum, to give the crude product that was purified by flash chromatography with hexanes:AcOEt mixtures as eluant.

With supported reagents **6** and **7**. To a solution of PEG-supported pyridylthioester (0.4 mmol) in dry dichloromethane (4 mL) at 0 °C, the amino-ester (0.8 mmol) was added. After a few minutes a 2 M toluene solution of trimethylaluminum (1.6 mmol) was added and the reaction mixture was allowed to stir at 0 °C for 3–12 h. *t*-Butanol (a few drops) was added, then the reaction solution was acidified by addition of 5% HCl to pH 4–5. Water was added, the phases separated and the aqueous phase extracted twice with CH_2Cl_2. The combined organic phases were washed with water, dried over sodium sulfate, filtered, concentrated under vacuum, and poured into diethyl ether (100 mL). The PEG-derivative **19** was recovered by filtration, while the evaporation of the organic phase afforded the crude product that was purified by a filtration onto a short plug of silica gel with hexanes:AcOEt mixtures as eluant.

3.3.1. *N*-Butanoyl-(*S*)-phenylalanine methylester 13. Thick oil; $[\alpha]_D^{22}$ 65.6 (*c* 1.2 in $CHCl_3$). IR: 3408, 1747, 1686 cm^{-1}. ^{1}H NMR: 0.90 (t, $^3J_{H,H}=7$ Hz, 3H, CH_3–CH_2–CH_2–CO), 1.55 (m, 2H, CH_3–CH_2–CH_2–CO), 2.05 (t, $^3J_{H,H}=7$ Hz, 2H, CH_3–CH_2–CH_2–CO), 3.0–3.08 (m, 2H, CH_2-Ph), 3.65 (s, 3H, *OMe*), 4.85 (dd, $^3J_{H,H}=6$, 8 Hz, 1H, *CH*–NHCO), 5.90 (bs, 1H, *NH*), 7.01 (m, 2H, phenyl), 7.11–7.31 (m, 3H, phenyl). ^{13}C NMR: δ 172.6, 172.2, 135.95, 129.2, 128.5, 127.0, 52.9, 52.2, 38.5, 38.0, 18.9, 13.6. M_w 249.31 Da. Anal. Calcd for $C_{14}H_{19}NO_3$. C, 67.45; H, 7.68; N, 5.62. Found: C, 67.29; H, 7.79; N, 5.71.

3.3.2. *N*-Butanoyl-(*S*)-phenylglycine methylester 14.[32,33] Thick oil; $[\alpha]_D^{22}$ 86.7 (*c* 0.2 in $CHCl_3$). IR: 3408, 1744, 1666 cm^{-1}. ^{1}H NMR: 0.91 (t, $^3J_{H,H}=8$ Hz, 3H, CH_3–CH_2–CH_2–CO), 1.60 (m, 2H, CH_3–CH_2–CH_2–CO), 2.20 (t, $^3J_{H,H}=8$ Hz, 2H, CH_3–CH_2–CH_2–CO), 3.70 (s, 3H, *OMe*), 5.60 (d, $^3J_{H,H}=6$ Hz, 1H, *CH*–NHCO), 7.01–7.40 (m, 5H, phenyl).

3.3.3. *N*-Butanoyl-(*S*)-threonine methylester 15. Thick oil; IR: 3408, 1747, 1686 cm^{-1}. ^{1}H NMR: 0.98 (t, $^3J_{H,H}=7$ Hz, 3H, CH_3–CH_2–CH_2–CO), 1.65 (m, 2H, CH_3–CH_2–CH_2–CO), 2.15 (t, $^3J_{H,H}=7$ Hz, 2H, CH_3–CH_2–CH_2–CO), 3.65 (s, 3H, *OMe*), 3.95 (m, 2H, CH_2OH), 4.70 (m, 1H, *CH*–NHCO), 7.45 (bs, 1H, *NH*). ^{13}C NMR: δ 173.7, 171.0, 63.8, 54.8, 52.9, 38.5, 19.1, 13.8. M_w 189.21 Da. Anal. Calcd for $C_8H_{15}NO_4$. C, 50.78; H, 7.99; N, 7.40. Found: C, 50.79; H, 7.89; N, 7.71.

3.3.4. *N*-Benzyloxyacetyl-(*S*)-phenylalanine methylester 16. Thick oil; $[\alpha]_D^{22}$ 8.476 (*c* 1.15 in $CHCl_3$). IR: 3412, 1744, 1681 cm^{-1}. ^{1}H NMR: 3.0–3.08 (m, 2H, CH_2-Ph), 3.65 (s, 3H, *OMe*), 3.90 (s, 2H, CO–CH_2–O), 4.55 (B part of an AB system, $^3J_{H,H}=12$ Hz, 1H, O–CH_2Ph), 4.60 (A part of an AB system, $^3J_{H,H}=12$ Hz, 1H, O–CH_2Ph), 4.85 (dd,

$^3J_{H,H}$=6, 8 Hz, 1H, *CH*–NHCO), 5.90 (bs, 1H, *NH*), 7.05–7.35 (m, 10H, phenyl). ^{13}C NMR: δ 171.5, 169.2, 136.6, 135.6, 129.1, 128.5, 128.4, 128.0, 127.7, 127.0, 73.3, 68.0, 52.3, 52.2, 37.8. M_w 327.37 Da. Anal. Calcd for $C_{19}H_{21}NO_4$. C, 69.71; H, 6.47; N, 4.28. Found: C, 69.79; H, 6.49; N, 4.31.

3.3.5. *N*-Benzyloxyacetyl-(*S*)-phenylglycine methylester 17. Thick oil; $[\alpha]_D^{22}$ 81.6 (*c* 1.1 in $CHCl_3$). IR: 3410, 1734, 1671 cm^{-1}. ^{1}H NMR: 3.70 (s, 3H, *OMe*), 3.92 (s, 2H, CO–*CH*$_2$–O), 4.50 (B part of an AB system, $^3J_{H,H}$=11 Hz, 1H, O–*CH*$_2$Ph), 4.55 (A part of an AB system, *J*=11 Hz, 1H, O–*CH*$_2$Ph), 5.55 (d, $^3J_{H,H}$=8 Hz, 1H, *CH*–NHCO), 7.10–7.35 (m, 10H, phenyl); 7.50 (d, $^3J_{H,H}$=8 Hz, 1H, *NH*). ^{13}C NMR: δ 171.2, 169.2, 136.8, 136.4, 129.1, 128.7, 128.4, 128.1, 73.8, 69.4, 55.9, 52.9. M_w 313.35 Da. Anal. Calcd for $C_{18}H_{19}NO_4$. C, 68.99; H, 6.11; N, 4.47. Found: C, 68.91; H, 6.10; N, 4.51.

3.3.6. *N*-Benzyloxyacetyl-(*S*)-threonine methylester 18. Thick oil; $[\alpha]_D^{22}$ 11.95 (*c* 0.4 in $CHCl_3$). IR: 3410, 1737, 1686 cm^{-1}. ^{1}H NMR: 3.70 (s, 3H, *OMe*), 3.90 (m, 2H, *CH*$_2$*OH*), 3.98 (s, 2H, CO–*CH*$_2$–O), 4.51 (B part of an AB system, *J*=10 Hz, 1H, O–*CH*$_2$Ph), 4.56 (A part of an AB system, *J*=10 Hz, 1H, O–*CH*$_2$Ph), 4.80 (m, 1H, *CH*–NHCO), 7.21–7.31 (m, 5H, phenyl), 7.50 (bs, 1H, *NH*). ^{13}C NMR: δ 170.5, 170.0, 136.5, 128.6, 128.3, 128.0, 73.7, 69.2, 63.3, 54.3, 52.8. M_w 267.28 Da. Anal. Calcd for $C_{13}H_{17}NO_5$. C, 58.42; H, 6.41; N, 5.24. Found: C, 58.39; H, 6.39; N, 5.21.

3.4. Regeneration of 7 starting from 19

To a solution of the PEG-derivative **19** recovered from a previous reaction (0.4 mmol) in dichloromethane (5 mL) trioctylamine (1 mmol) and then benzyloxyacetyl chloride (0.8 mmol) were added at room temperature. The reaction mixture was allowed to stir overnight, then it was concentrated and poured into a diethyl ether solution. The precipitated polymer was recovered by filtration and showed NMR spectra identical to those of product **7**, previously prepared starting from **5**.

3.5. Synthesis of ketones 20 and 21

In typical procedure, to a solution of PEG-supported pyridylthioester (0.2 mmol) in dry dimethylformammide (2 mL) at room temperature, zinc (3 mmol), nickel chloride (0.2 mmol) and the iodoalkane (2 mmol) were added. Then the reaction mixture was allowed to stir at room temperature overnight, then it was filtered and water and diethyl ether were added. The organic phase was separated, dried over sodium sulfate, filtered, concentrated under vacuum to afford the crude product that was purified by a filtration onto a short plug of silica gel with hexanes:AcOEt mixtures as eluant.

3.5.1. 1-Benzyloxy-hexan-2-one 20. Oil; IR: 1724 cm^{-1}. ^{1}H NMR: 0.98 (t, $^3J_{H,H}$=8 Hz, 3H, *CH*$_3$–CH$_2$–CH$_2$–CH$_2$–CO), 1.35 (m, 2H, CH$_3$–*CH*$_2$–CH$_2$–CH$_2$–CO), 1.65 (m, 2H, CH$_3$–CH$_2$–*CH*$_2$–CH$_2$–CO), 2.20 (t, $^3J_{H,H}$=7 Hz, 2H, CH$_3$–CH$_2$–CH$_2$–*CH*$_2$–CO), 4.02 (s, 2H, CO–*CH*$_2$–O), 4.70 (s, 2H, O–*CH*$_2$Ph), 7.20–7.45 (m, 5H, phenyl).

3.5.2. 1-Benzyloxy-tetradecan-2-one 21. Oil; IR: 1721 cm^{-1}. ^{1}H NMR: 1.02 (t, $^3J_{H,H}$=8 Hz, 3H, *CH*$_3$–CH$_2$–), 1.30–1.55 (m, 20H, alifatic chain *CH*$_2$–), 2.25 (m, 2H, –*CH*$_2$–CO), 4.10 (s, 2H, CO–*CH*$_2$–O), 4.65 (s, 2H, O–*CH*$_2$Ph), 7.30–7.45 (m, 5H, phenyl).

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28. The crude reaction product was often pure enough to be analyzed directly by NMR spectroscopy. However, a filtration through a short plug of silica gel of the crude reaction mixture afforded analytical pure products. Low yielding reaction products, like **14** or **15**, were purified by a standard flash chromatography (hexanes/ethylacetate 60:40 mixture as eluant).
29. For example, for product **14** optical rotation was measured and a $[\alpha]_D = 131$ (*c* 8 in $CHCl_3$) was found (lit. $[\alpha]_D = 136$ (*c* 9 in $CHCl_3$)).[32]
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Reversible microencapsulation of pybox–Ru chiral catalysts: scope and limitations

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Abstract—Chiral Pybox–Ru catalysts can be microencapsulated into linear polystyrene as a method to recover and recycle the valuable catalyst. These catalysts allow 60–68% yields to be achieved with enantioselectivities in the range 75–85% ee in the benchmark cyclopropanation reaction between styrene and ethyl diazoacetate. The catalyst is soluble in the reaction solvent and is re-encapsulated at the end of the reaction. The great advantage of this methodology is that the chiral ligand does not need to be modified, but the recycling is highly solvent dependent—in contrast with the catalysts immobilized through covalent bonds.

1. Introduction

Immobilization on organic polymers is one of the most widely used strategies to support chiral catalysts and is a way to make them recoverable and reusable—with the associated practical advantages.[1] The chiral catalyst can be linked to the polymeric support either through strong bonds/interactions (e.g., covalent bond or electrostatic interaction) or through weak interactions. Covalent bonding is by far the most common method,[2] but has the drawback of requiring chemical modification of the chiral ligand to introduce additional functionality to form the covalent bond with the support. This requirement makes the preparation of the catalyst more difficult, which is often a serious limitation for the industrial application of the immobilized chiral catalysts,[3] in contrast with the recent applications described for analogous non-chiral systems.[4]

In terms of immobilization through weak interactions, a number of examples have been described for the entrapment of chiral catalysts within polymers, either in cross-linked polymers[5] or in linear polymers to give microcapsules.[6,7] In both cases, the preparation of the catalyst is rather simple and this method does not require any modification of the chiral ligand.

Our group is working in the field of chiral catalyst immobilization, with special emphasis on oxazoline-containing ligands[8] —particularly pyridinebis(oxazoline) ligands (pybox). The immobilization of these systems through covalent bonding to organic polymers was assessed in two ways: polymerization and grafting (Fig. 1). The polymerization method involves functionalization of the chiral pybox with a group that can polymerize with other monomers, such as styrene.[9] In this case the synthetic effort is double because the polymerizable ligand and the polymeric support with a suitable morphology must be considered. In the case of grafting (Fig. 1), well-characterized, commercially available supports can be used, so the synthetic effort for this method is restricted to the modified chiral ligand.[10]

Given the attractiveness of the microencapsulation methodology (Fig. 2) we decided to investigate this area with the same types of catalysts to evaluate the advantages and disadvantages of this system in comparison with the methods involving ligand-support covalent bonding.

2. Results and discussion

One important limitation of the microencapsulation method is compatibility with the solvent. Indeed, cyclopropanation

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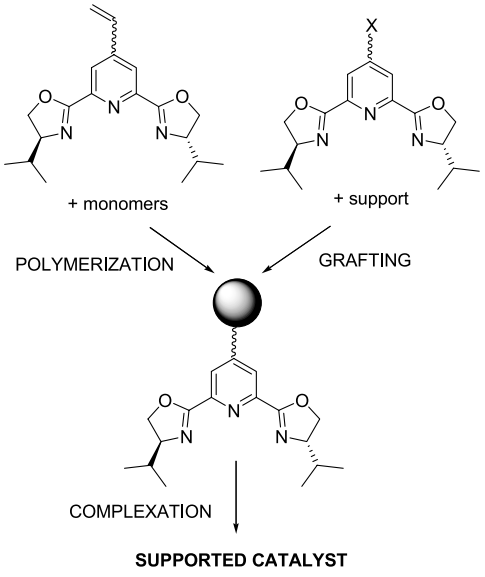


Figure 1. Polymerization and grafting methods for pybox immobilization.

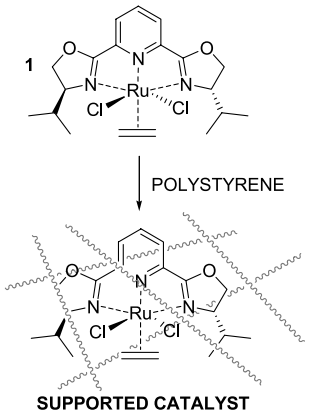


Figure 2. Microencapsulation of pybox–Ru chiral catalyst.

reactions with pybox–Ru catalysts are usually carried out in dichloromethane, a solvent in which linear polystyrene is soluble. We therefore envisaged microencapsulation as a reversible method for immobilization. The catalyst and support will be soluble in the reaction medium (homogeneous catalysis) but can be recovered by re-encapsulation at the end of the reaction.[11]

The pybox–Ru complex **1** was prepared from pybox ligand and $[Ru(p\text{-cymene})Cl_2]_2$ in an ethylene atmosphere using the method described by Nishiyama et al.[12] Ethylene plays an important role in the stability and efficiency of the catalyst[7] as it protects the ruthenium centre from other strongly coordinating molecules such as oxygen. A solution of pybox–Ru complex in dichloromethane was added to a solution of the linear polystyrene in warm cyclohexane and the solvents were slowly evaporated. The Ru content was determined by plasma emission spectroscopy and, in the fresh catalysts, was slightly lower than the theoretical value (0.225–0.230 mmol/g vs 0.258 mmol/g). FTIR (Fig. 3) shows the presence of the Ru catalyst in the solid.

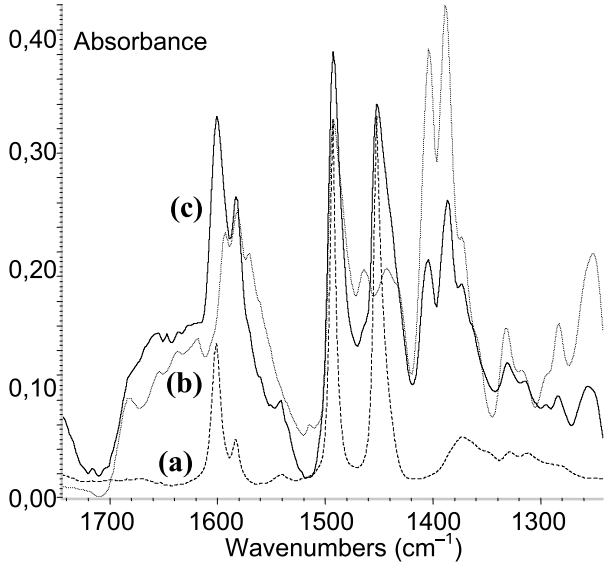
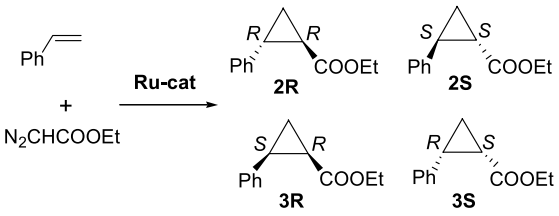


Figure 3. FTIR spectra of the polystyrene matrix (a), the Ru–pybox complex (b), and the microencapsulated the Ru–pybox complex (c).

The asymmetric cyclopropanation reactions between styrene and ethyl diazoacetate (Scheme 1) were carried out in dichloromethane, with only one exception (MC3). Under these conditions the encapsulated catalyst was completely soluble in the reaction medium and behaved as a homogeneous catalyst. However, the addition of a solvent such as hexane or cyclohexane led to the formation and hardening of the capsules, which were filtered off, washed and reused. The reaction conditions, results and recycling method are collected in Table 1. One set of experiments in the homogeneous phase (Hom in Table 1) was conducted under the same conditions for the sake of comparison.



Scheme 1. Asymmetric cyclopropanation reaction.

Comparison of MC1 and the homogeneous test clearly shows that the use of polystyrene increases the recyclability of the complex, which maintains good yield and enantioselectivity up to the fourth run. However, a small amount of Ru is lost in each recycle, as shown by the colour of the washings. However, the amount leached in each batch is so small that it cannot be accurately analyzed, meaning that it must be less than 5%. The analysis of joint mother liquors after four batch reactions shows an overall loss of Ru of about 15% (0.01 mmol). The worst property of this type of complex is its mechanical weakness—the solid is ground by the magnetic stirrer and is almost completely destroyed after four runs. An interesting aspect is the higher stability of this catalyst in comparison with the homogeneous one. All of the recycling operations were carried out in air without loss of activity or selectivity, in contrast with the grafted catalysts.[10] Despite this finding, all recycling operations in

Table 1. Asymmetric cyclopropanation reactions with microencapsulated catalysts

Experiment	Solvent (mL)[a]	Run	Yield %[b,c]	*trans*/*cis*[b]	%ee *trans*[b]	%ee *cis*[b]	Hexane addition[d]	Evaporation[d]	Washing solvent and temperature[d]
Hom[e]	DCM (5+1)	1	49	88/12	81	52	15 mL	Yes	Hex (6×12 mL) rt
		2	50	90/10	84	63			
		3	13	87/13	74	41			
MC1	DCM (5.4+1)	1	46	85/15	75	37	No	Yes	CHex (6×15 mL) rt
		2	63	87/13	85	45			
		3	63	88/12	83	47			
		4	48	88/12	84	45			
MC2	DCM (10+2)	1	36	88/12	78	43	15 mL	Yes	Hex (6×12 mL) −20 °C
		2	37	88/12	83	48			
		3	29	87/13	75	40			
		4[f]	11	77/23	45	10			
MC3	CHex (10+2)	1	31	94/6	85	68	No	Yes	CHex (6×15 mL) rt
		2	12	91/9	66	35			
MC4	DCM (10+2)	1	44	88/12	84	50	15 mL	Yes	Hex (6×10 mL) 0 °C
		2	41	89/11	86	61			
		3	25	88/12	84	54			
MC5	DCM (2+0.5)	1	42	88/12	81	50	20 mL	No	Hex (5×10 mL) 0 °C
		2	51	88/12	82	43			
		3	32	86/14	75	40			
		4	8	76/24	23	5			
MC6	DCM (2+0.5)	1	62	88/12	83	52	20 mL	No	Hex (5×10 mL) −20 °C
		2	68	86/14	80	35			
		3	61	87/13	73	30			
		4	18	72/28	20	2			
Grafted[f,g]	DCM	1	38	86/14	77	43			
		2	47	88/12	83	54			
		3	41	88/12	81	50			
		4	36	84/16	56	23			
Polym[h]	DCM	1	52	88/12	85	54			
		2	67	90/10	91	67			
		3	70	90/10	89	64			
		4	68	90/10	87	63			
		5	32	88/12	74	63			

[a] DCM=dichloromethane; Chex=cyclohexane; Hex=hexane. The two different quantities indicate the amount solvent used to dissolve the catalyst and styrene and to dilute ethyl diazoacetate, respectively.
[b] Determined by gas chromatography. **2R** and **3R** are the major products.
[c] In all cases complete disappearance of ethyl diazoacetate is observed, therefore yields reflect chemoselectivity rather that catalyst activity.
[d] Steps in recycling of the catalyst: addition of hexane to the reaction mixture, evaporation of the solvents and washing the solids with solvent at different temperatures. The combined solutions were analyzed to determine the results and the resulting solid was reused under the same conditions.
[e] Homogeneous reaction. Non-encapsulated catalyst.
[f] Run not carried out under inert atmosphere.
[g] 4-Vinylpybox immobilized on Merrifield's resin. Data from Ref. 10.
[h] 4-Vinylpybox polymerized with styrene and divinylbenzene. Data from Ref. 10.

the other experiments were carried out under an inert atmosphere. In recovered catalysts ethylene must be replaced by other molecule, most probably the reacting alkene—styrene in this case—as it has been recently shown in a theoretical study on the mechanism of this reaction.[13]

An increase in the amount of reaction solvent seemed to have a slightly negative effect on the yield, and cyclohexane (MC3) proved more detrimental than dichloromethane. In experiment MC2 hexane was added to the reaction mixture to harden the capsules prior to evaporation and washing. In this way recycling is experimentally easier and more efficient. The fourth run was carried out without an inert atmosphere in order to assess the stability of the system in air. The poor result, both in terms of activity and stability, shows that the enhanced stability is not effective when the catalyst is under reaction conditions, probably because it is homogeneous in nature.

The stability of the catalyst is improved by recovering it at 0 °C instead of −20 °C, probably due to a more efficient extraction of the reaction products and by-products. In fact, complexation of ruthenium by maleate and fumarate may contribute to catalyst deactivation. Another method to increase the mechanical stability is the use of orbital shaking instead of stirring in the experiments from MC4.

In another set of experiments, the amount of dichloromethane was markedly reduced in order to allow the collapse of the capsules without the need for evaporation. This method works effectively but a significant loss of activity and enantioselectivity was observed in the fourth run. In this case the collapse and extraction at lower temperature (MC6) improve the yield with no significant modification of the enantioselectivity, but again the cyclopropane yields noticeably decrease after the third run.

The results and stability of the microencapsulated catalysts were compared with those prepared by grafting 4-mercaptopybox or by polymerization of 4-vinylpybox.[10] In both cases the catalysts covalently linked to the polymeric support show enhanced stability—both chemical

and mechanical. The grafted catalyst leads to slightly lower yields than the microencapsulated one and has comparable enantioselectivity, which begins to drop in the fourth run. In contrast, the polymerized catalyst is as good as the microencapsulated one, with higher enantioselectivity and better recoverability—as shown by the excellent results in the fourth run and the moderate loss of activity and enantioselectivity only in the fifth run. Although polymerization is the best method for the immobilization of the pybox–Ru system, microencapsulation is an interesting alternative to grafting owing to its simplicity and similar performance.

3. Conclusions

Microencapsulation allows the reversible immobilization of enantioselective pybox–Ru catalysts. In this way the solid catalyst is solubilized under the reaction conditions and can be re-encapsulated at the end of the reaction. When compared with the grafting and polymerization methods for covalent bonding to the polymeric support, the microencapsulation technique shows some advantages, for example, it is not necessary to modify the chiral ligand and this leads to an easier preparation. On the other hand, microencapsulation leads to less stable catalysts in terms of mechanical attrition and leaching, making recovery and reuse more difficult. In conclusion, microencapsulation is an interesting methodology that should be taken into account when a chiral immobilized catalyst has to be designed for a given application. This approach requires almost no supplementary synthetic effort in comparison with the polymerization or grafting techniques, although for this particular case the grafted catalyst performs better, and it would be interesting to assess this method in immobilization work.

4. Experimental

4.1. Preparation of microencapsulated catalysts

Ethylene was bubbled for 1 h into a solution of 2,6-[4′-(*S*)-isopropyloxazolin-2′-yl]pyridine (400 mg, 1.33 mmol) and $[RuCl_2(p\text{-cymene})]_2$ (408 mg, 0.67 mmol) in anhydrous dichloromethane (15 mL). After purging with nitrogen, the solution was added to *n*-heptane (HPLC grade, 100 mL) and the resulting solid was collected by filtration and dried under vacuum. Yield of **1** 550 mg (82%).

A suspension of linear polystyrene (MW = 280,000, 246 mg) in anhydrous cyclohexane (20 mL) was heated at 45 °C for 90 min until complete dissolution. A solution of complex **1** (36.7 mg, 0.073 mmol) in anhydrous dichloromethane in (1.5 mL) was added and the resulting solution was stirred at 30 °C for 1 h. The solvent was evaporated at room temperature under reduced pressure and the solid was used without further treatment.

4.2. Asymmetric cyclopropanation reactions

A solution of styrene (0.57 mL, 5 mmol) in the corresponding anhydrous solvent (see Table 1) was added to the immobilized catalyst (ca. 0.06 mmol). A solution of ethyl diazoacetate (114 mg, 1 mmol) in the same solvent was slowly added (6 h). The solution was shaken for an additional period of 17 h. The catalyst was collapsed by the addition of hexane or cyclohexane. The exact method is described in Table 1. The solid catalyst was washed with the same solvent and the combined organic solutions were analyzed by gas chromatography. The dried solid catalyst was reused several times under the same conditions.

Acknowledgements

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Polystyrene-supported amino alcohol ligands for the heterogeneous asymmetric addition of phenyl zinc reagents to aldehydes

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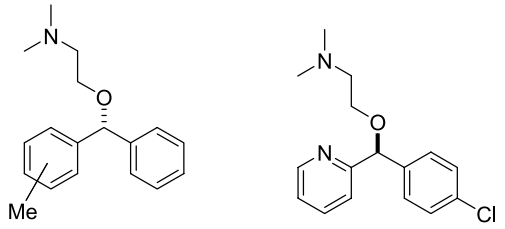
Abstract—A family of polystyrene-supported amino alcohols, characterized by a high catalytic activity in alkyl transfer from zinc to formyl groups has been successfully tested in the enantioselective addition of phenyl zinc reagents to aldehydes to afford chiral diarylmethanols. Enantioselectivities higher than 90% (mean ee 90.5%; eight examples) are recorded with aromatic aldehydes in what represents the first successful use of heterogeneous, polymeric reagents for enantiocontrol in the phenylation of aldehydes.

1. Introduction

Enantiomerically pure diarylmethanols are important building blocks for biologically active compounds.[1] For example, (*R*)-neobenodine, (*R*)-orphenadrine, or (*S*)-carbinoxamine (Fig. 1) have been used for a long time as muscle relaxants or antihistaminics.[2] However, their preparation by asymmetric synthesis is challenging, because the asymmetric reduction of the appropriate diaryl ketone is usually hampered by low ee's due to the steric and electronic similitudes between both aryl groups.[3] Then, the enantioselective addition of an aryl fragment to an aldehyde (where all groups are easily distinguishable by the catalyst) appears as the most convenient way to gain access to these structural motifs.[4]



p-Me: (*R*)-neobenodine
o-Me: (*R*)-orphenadrine

(*S*)-carbinoxamine

Figure 1. Some pharmaceutically active diarylmethanols.

Diphenylzinc could be in principle a suitable reagent for this task, but it has the problem that the uncatalyzed background addition to aldehydes is a significant competing reaction with deletereous effects on the enantiomeric purity of the resulting diarylmethanols. In any case, since the pioneering work by Fu in 1997,[5] several efficient homogeneous catalytic systems for the enantioselective addition of diphenylzinc to aldehydes have been successfully developed relying in two basic strategies: the use of diluted reaction conditions to increase the rate difference between the catalyzed and the uncatalyzed processes,[6] or the in situ formation of a less reactive, mixed EtPhZn species extensively studied by Bolm.[7]

Over the last years, our research group has been involved in a project devoted to the synthesis of highly modular, synthetic yet enantiopure β-amino alcohol ligands using the Sharpless epoxidation of allyl alcohols or the Jacobsen epoxidation of arylethylenes as the ultimate source of chirality.[8] The modular nature of these species has allowed the simultaneous optimization of their catalytic activity and enantioselectivity in different processes such as alkyl transfer to carbonyls[8,9] and imines,[10] oxazaborolidine-mediated reduction of ketones,[11] transfer hydrogenation of ketones,[12] and allylic alkylation.[13] Among these ligands, readily available 2-piperidino-1,1,2-triphenylethanol (**1**)[8b] depicts an excellent enantioselectivity/activity profile for

Keywords: Heterogenous reaction; Ligand immobilization; Enantioselective synthesis; Aldehyde arylation.
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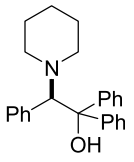
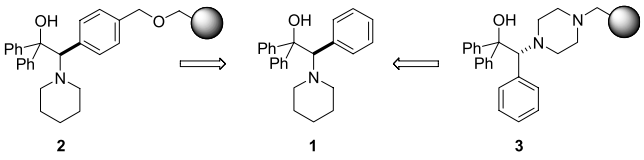
alkyl transfer to aldehydes[8b,14] and has also been found to be a most efficient mediator for the enantioselective phenyl transfer to these substrates,[15] enantioselectivities of 91–99% being achieved with only 1.5 mol% of **1** in reactions that typically require less than 1 h for completion.



1

From a general perspective, homogeneous catalysis has notably contributed to the clean and efficient production of chiral compounds as single enantiomers. Homogeneous catalytic processes, however, are usually performed in a batch manner, and work-up stages required for product isolation and catalyst recovery are detrimental to their overall sustainable characteristics. To solve this problem, covalent anchoring of properly functionalized ligands to polymeric supports has been widely applied.[16] While this method can ultimately allow performing catalytic enantioselective reactions in a continuous mode, it is usually accompanied by a decrease in catalytic activity and enantioselectivity with respect to structurally referable, homogeneous ligands. Within this approach, attention has been paid to the enantioselective arylation of aldehydes, but only partial success has been achieved. In 1999, Pu and co-workers used a soluble, rigid BINOL polymer to perform the catalytic asymmetric addition of $ZnPh_2$ to aldehydes under much diluted conditions, achieving ee's up to 92% (Fig. 2). However, a high catalyst loading (40 mol%) was needed to drive the reaction to completion, and some of the main advantages associated to the use of polymer-supported ligands (easy recovery and reuse) were absent from this approach.[6b] Later on, Bolm immobilized a ferrocenyloxazoline ligand onto polymeric supports and studied the enantioselective phenyl transfer to *p*-chlorobenzaldehyde. When the ligand was bound to an insoluble trityl chloride resin, the polymer proved to be unsuitable for the catalysis of the asymmetric process, and only racemic product was obtained. On the other hand, when the ligand was bound to a soluble MeO–PEG resin, the resulting catalyst led to the addition product with high enantioselectivity.[17] It is clear from these results that low activity, insoluble resins fail to induce the enantioselective reaction at a sufficient rate to compete with the rather fast,[15] uncatalyzed background reaction, and that very active ligands should be designed to achieve high enantiocontrol levels in this class of heterogeneous reaction.

Using the highly active ligand (*R*)-2-piperidino-1,1,2-triphenylethanol (**1**),[8b] as the basis of our design,[18] we have developed polystyrene supported amino alcohols **2**[19] and **3**,[20] and have introduced for their designation the term tail-tied ligands. Gratifyingly enough, both the catalytic activity and the enantioselectivity exhibited by **2** and **3** are among the highest ever recorded for supported ligands, and this fact converts them into qualified candidates for the achievement of enantiocontrol in the phenylation of aldehydes.



2 **1** **3**

We wish to report here the preparation of a new tail-tied ligand (**5**), a regioisomer of **2** and **3**, conceptually derived from the highly active and enantioselective amino alcohol

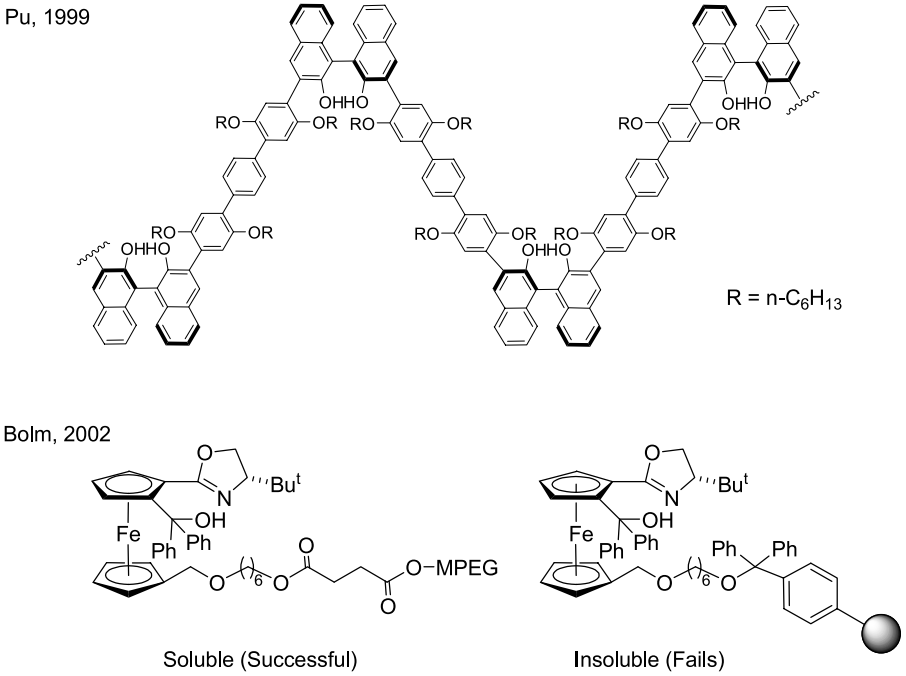
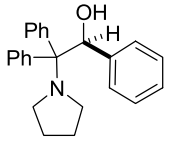


Figure 2. Soluble and insoluble polymer-supported ligands employed in the enantioselective phenylation of aldehydes.

4,[8c] and its evaluation in the enantioselective ethylation of aldehydes. In addition, the evaluation of **2**, **3**, and **5** in the enantioselective phenylation reaction leading to the identification of the first insoluble, polymeric ligands successful in the considered reaction is also reported.



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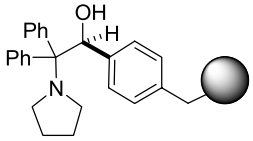

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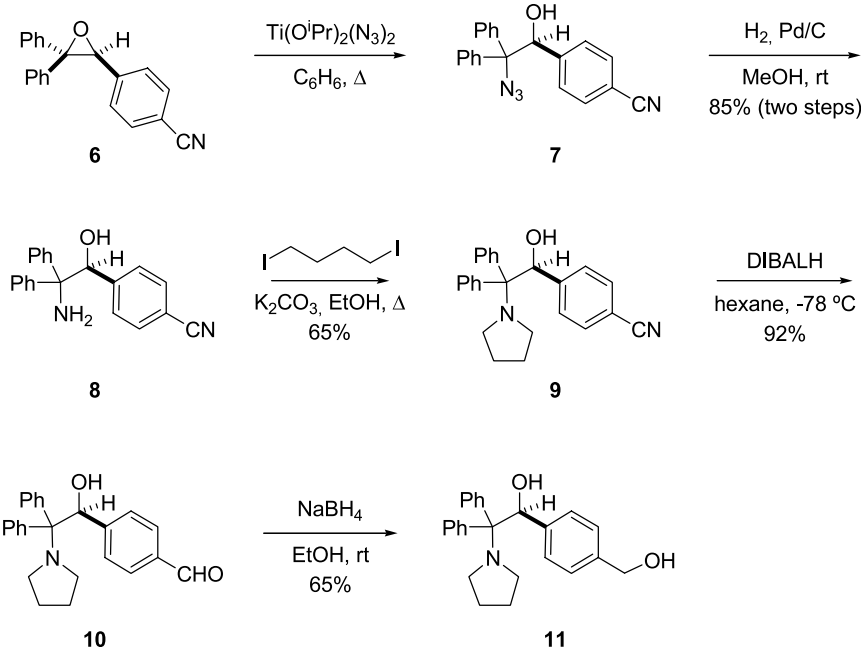
2. Results and discussion

2.1. Synthesis and anchoring to Barlos' resins of (*S*)-1-(4-(hydroxymethyl)phenyl)-2,2-diphenyl-2-(pyrrolidin-1-yl)-ethanol

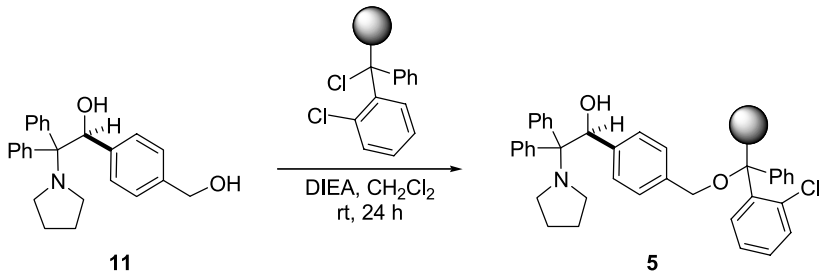
As we have already mentioned, a primary goal in the present research was the synthesis of resins **5** which, on one side, possess the characteristic of the ligand being anchored to the polymeric support through a position remote from the active center and, on the other side, exhibit a functional group arrangement opposite to the one present in **2** and **3**. We have previously shown[8c–d] that the regiochemistry of the ring-opening of triarylethylene oxides with nitrogen nucleophiles can be exclusively directed to the more substituted carbon by the use of diisopropoxytitanium diazide,[21] although some additional functional group manipulation can be required. According to this strategy (Scheme 1), the known epoxide **6**, that is readily available in enantiomerically pure form (>99.9% ee) by Jacobsen epoxidation[22] and recrystallization from hexane, would be the starting material for the synthesis. It is interesting to note that **6** is also the starting material for the preparation of the supported ligand **2**.

When enantiomerically pure (*S*)-**6** was treated with diisopropoxytitanium diazide in benzene at reflux, a totally regioselective ring-opening took place leading to azido-alcohol (*S*)-**7**, arising from attack to the more heavily substituted carbon of the epoxide. The crude azidoalcohol was directly submitted to hydrogenolysis in methanol (1 atm H_2; Pd/C) to afford amino alcohol **8** in 85% overall yield.

It is interesting to note that the amino group of **8** offers a good possibility for structural diversity, since many different groups could be installed on it by alkylation, cyclialkylation, and reductive amination processes.[8c] In the present case, the planned pirrolidine ring was constructed by cyclialkylation with 1,4-diiodobutane in ethanol at reflux in the presence of potassium carbonate. To achieve a good yield in this reaction, it was necessary to maintain in the reaction medium an excess of 1,4-diiodobutane during the whole reaction time. In this way, a 65% yield of **9** was obtained after 72 h, with periodical addition of alkylating agent (up to 7 equiv). Finally, the cyano group in **9** was reduced to hydroxymethyl through a two-stage process: First, the aldehyde **10** was obtained in 92% yield by treatment of **9** with DIBALH at −78 °C in hexane/ether solution; then, the primary alcohol **11** was formed (65% yield) by reduction of **10** with sodium borohydride in ethanol at room temperature. For the anchoring of **11** to polymeric supports, a chlorotritylated polystyrene resin (Barlos' resin)[23] was selected as the most convenient alternative[24] (Scheme 2). Starting from a Barlos' resin with f_o: 1.60, and using the standard anchoring conditions (Scheme 2), a functionalized resin 5, with *f*: 0.90 (calculated by nitrogen elemental analysis with the formula; *f*: 0.714[%N]) was obtained. Since f_{max} for this particular resin is 1.06[19] the yield of the anchoring process turns out to be 85%.



Scheme 1. Enantioselective synthesis of amino alcohol **11**, the precursor of resin **5**.



11 5

Scheme 2. Anchoring of amino alcohol **11** to a Barlos' resin.

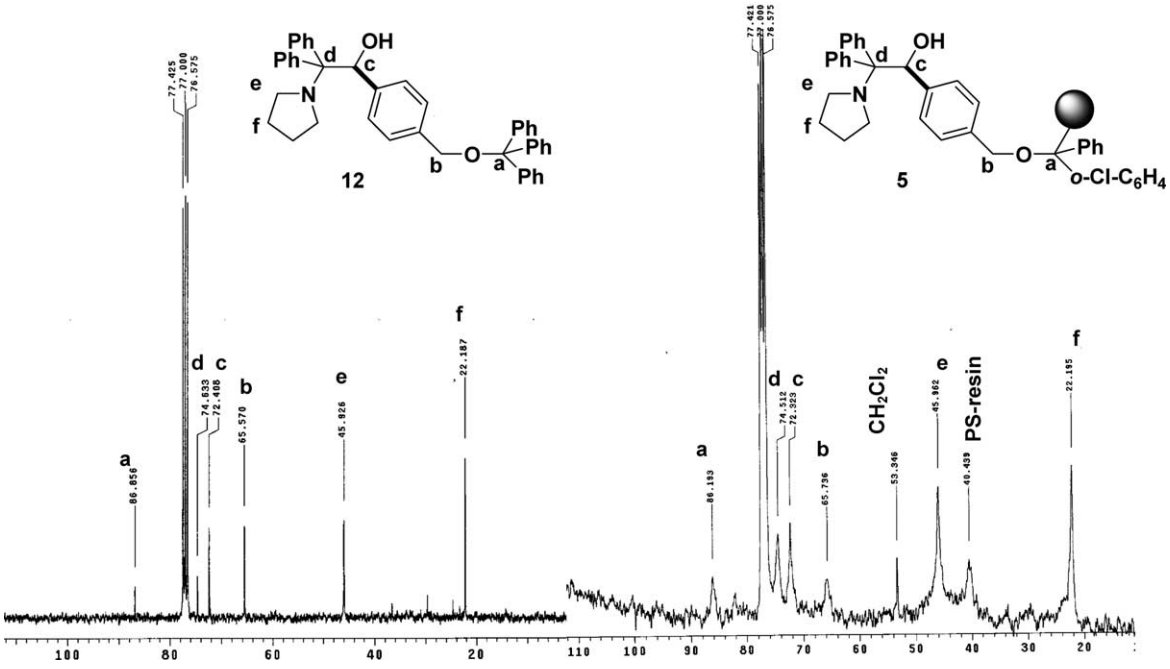


Figure 3. Monitoring of the anchoring of amino alcohol **11** to a Barlos' resin by gel phase ^{13}C NMR. The NMR spectrum of the model compound **12** is included for comparison.

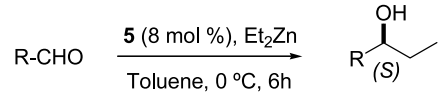
The progress of the anchoring process can be easily monitored by gel-phase ^{13}C NMR.[25] For comparison purposes, the trityl-protected amino alcohol **12** was easily prepared by treatment of **11** with *N*-tritylpyridinium tetrafluoroborate in acetonitrile. The diagnostic region of the ^{13}C NMR spectra of both compounds (**12** in solution; **5** in gel) is represented in Figure 3.

2.2. Evaluation of resin 5 as a ligand for enantioselective ethylation and phenylation of aldehydes

Resin **5** was initially tested in the enantioselective addition of diethylzinc to aldehydes (**13**). A representative set of aldehydes **13a–h**, mostly containing difficult substrates (aliphatic, α,β-unsaturated), was selected, and the ethylation reaction leading to 1-propanols **14a–h** was performed in toluene at 0 °C, in the presence of a 8 mol% of **5**. The results of these additions have been summarized in Table 1.

As it can be seen, resin **5** provides high conversion numbers for the ethylation of aromatic aldehydes (**13a–c**) and for aliphatic and α,β-unsaturated aldehydes not fully substituted at the α position (**13e–f** and **13d**, respectively). With

Table 1. Enantioselective ethylation of aldehydes **13a–h** mediated by resin **5** (8 mol%)

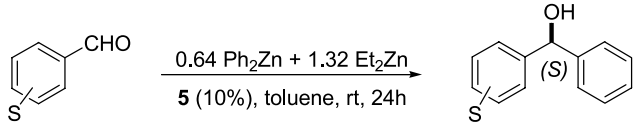


13 14

Starting aldehyde	Conv (%)	ee (%)
o-Methoxybenzaldehyde (**13a**)	95	86
m-Tolualdehyde (**13b**)	90	90
p-Fluorobenzaldehyde (**13c**)	94	84
Cinnamaldehyde (**13d**)	89	71
Heptanal (**13e**)	93	90
3-Phenylpropanal (**13f**)	94	89
2-Ethylbutanal (**13g**)	50	91
α-Methylcinnamaldehyde (**13h**)	55	89

respect to enantioselectivity, good results are obtained for aromatic aldehydes. However, the most noteworthy enantioselectivities are those obtained with aliphatic and α,β-unsaturated aldehydes, where many homogeneous and heterogeneous ligands fail. Encouraged by these results, we decided to test the use of resin **5** for the enantioselective phenylation reaction leading to diarylmethanols **15**. The phenyl transferring system developed by Bolm and co-workers,[7] that involves the use of a Ph_2Zn/Et_2Zn mixture and has provided excellent results in the enantioselective phenylation mediated by the monomeric ligand **1** was also used in this case.[15] The reactions were initially tested on a limited set of aromatic aldehydes (**13i–13l**) by using a 10% molar amount of catalyst. Since our primary interest was on enantioselectivity, no attention was paid to optimization of reaction time. The results of this study have been summarized in Table 2.

Table 2. Enantioselective phenylation of aldehydes **13i–l** mediated by resin **5** (10 mol%)



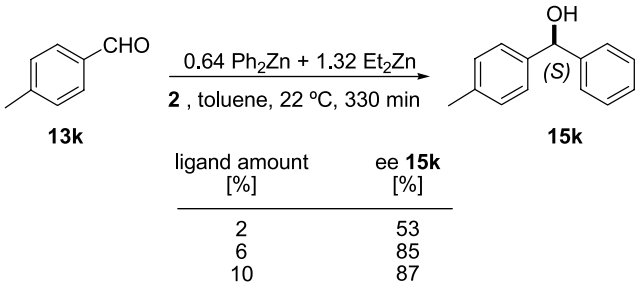
13i-l **15**

Starting aldehyde	Conv (%)	ee (%)
o-Fluorobenzaldehyde (**13i**)	90	43
o-Tolualdehyde (**13j**)	99	38
p-Tolualdehyde (**13k**)	99	48
m-Methoxybenzaldehyde (**13l**)	99	42

A first aspect of these results to be highlighted is that the heterogeneous ligand **5** is able to induce enantioselectivity in the phenylation reaction, albeit to a moderate level. It thus appears that the strategy of structural modification of ligands known to be very active and enantioselective to allow anchoring to a polymeric matrix without perturbing the catalytic center (tail-tied ligands) can provide a solution for the problem of the enantioselective phenylation of aldehydes with heterogeneous ligands. In any case, when the behavior of the polymer-supported ligand **5** is compared with that of its homogeneous counterpart **4**,[8c] it becomes evident that in this case the anchoring process provokes some decrease in the enantioselectivity characteristics of the homogeneous ligand. As we have previously shown,[19–20] this is not the case for polymer-supported ligands **2** and **3**, conceptually derived from amino alcohol **1**. In view of the results obtained in the preliminary evaluation of resin **5**, its use as a catalytic ligand for the catalytic enantioselective phenylation of aldehydes was abandoned. Alternatively, the evaluation of resins **2** and **3** with the same purpose was undertaken.

2.3. Evaluation of resin 2 as a ligand for enantioselective phenylation of aldehydes

According to precedents in the enantioselective ethylation of aldehydes with this family of polymer-supported ligands, a resin with a rather high cross-linking level (2% DVB) and a functionalization level (f) of 0.35 mmol ligand/g was used in this study. The optimal molar amount of resin was determined first, working on *p*-tolualdehyde (**13k**) and performing the reactions in toluene (for optimal resin swelling) at room temperature (Scheme 3).



Scheme 3. Optimization of ligand amount in the phenylation of *p*-tolualdehyde mediated by resin **2**.

It was already clear from these experiments that **2** was a much better ligand than **5** for the asymmetric phenyl transfer reaction. With respect to the optimal amount of ligand, it was decided to perform the reaction with a 10% molar amount of **2** in order to secure the highest possible enantioselectivity in the shortest reaction time. It is important to recall here that this level of ligand loading is the usual one in phenyl transfer reactions with homogeneous, monomeric ligands.

Next, the phenyl transfer reaction was performed on a representative family of aldehydes under the optimized conditions. To test the preparative merits of the procedure, the diarylmethanol products **15** were isolated and quantified after each reaction. Results arising from this study have been summarized in Table 3, where the enantioselectivities recorded with the homogeneous ligand **1** under identical experimental conditions have also been included for comparison.

Table 3. Enantioselective phenylation of aldehydes mediated by resin **2** (10 mol%)

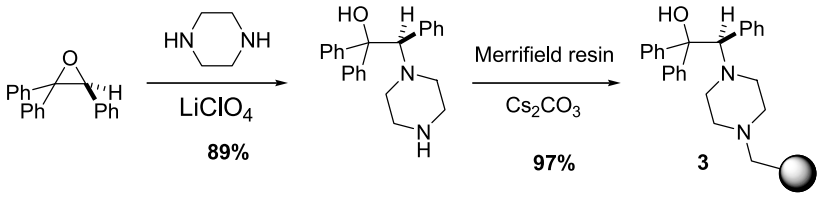
Starting aldehyde	Yield (%)	ee (%)	ee with **1** (%)
α-Methylcinnamaldehyde (**13h**)	75	87	94[a]
o-Fluorobenzaldehyde (**13i**)	99	85	98
o-Tolualdehyde (**13j**)	98	91	99
p-Tolualdehyde (**13k**)	96	87	98
m-Methoxybenzaldehyde (**13l**)	74	90	—
Pivalaldehyde (**13m**)	78	80	92
Biphenyl-4-carbaldehyde (**13n**)	86	91	97
2-Naphthaldehyde (**13o**)	81	90	96

[a] Reaction in toluene at 0 °C.

As it can be readily seen, high yields of diarylmethanols **15** are obtained in the phenyl transfer reaction mediated by resin **2**. Even more importantly, a uniformly high enantioselectivity is recorded in the reactions, the mean ee of the resulting products **15** being 87.6%.

2.4. Evaluation of resin 3 as a ligand for enantioselective phenylation of aldehydes

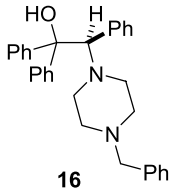
While it is clear that resin **2** depicts a very interesting profile as a ligand for the catalytic enantioselective phenyl transfer to aldehydes, it is also true that its synthesis (as in the case of



Scheme 4. Two-step assembly of ligand **3** from its precursors.[22]

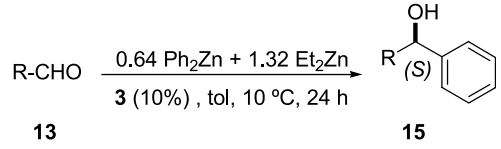
resin **5**) from commercial precursors is rather lengthy. This observation, that could be of practical interest if the application of these resins at a larger scale was considered, boosted the development of resin **3**, that can be straightforwardly assembled from its fragments: enantiomerically pure triphenylethylene oxide, piperazine, and a Merrifield resin, as shown in Scheme 4.[20]

In addition to the ease of its preparation, resin **3** was shown to be a most efficient ligand for the enantioselective ethyl transfer to aldehydes, with catalytic activity and enantioselectivity that did not show any decrease with respect to the referable, homogeneous ligand **16**.[20,26]



According to these precedents, resin **3** was an ideal candidate for a successful ligand in enantioselective phenyl transfer to aldehydes. As in the case of **2**, a preliminary screening confirmed these expectations (Table 4).

Table 4. Preliminary screening of resin **3** (10 mol%) in the enantioselective phenylation of aldehydes



Starting aldehyde	ee (%)
α-Methylcinnamaldehyde (**13h**)	90
o-Fluorobenzaldehyde (**13i**)	84
o-Tolualdehyde (**13j**)	91
m-Methoxybenzaldehyde (**13l**)	89
Pivalaldehyde (**13m**)	89
2-Naphthaldehyde (**13o**)	90

Next, some key parameters related to the use of **3** in the reaction were optimized. On the first place, since it is known that phenyl transfer from zinc to carbonyl groups usually presents an isoinversion temperature,[27] and the temperature for optimal enantioselectivity had been previously established as 10 °C working with ligand **1** in the addition to *p*-tolualdehyde (**13k**),[15] the optimization was repeated for ligand **3** working on the same substrate. By using a 5% molar amount of **3** in reactions at 0, 10, and 23 °C, the corresponding diarylcarbynol **15k** was obtained with enantiomeric purities of 92, 94, and 91%, respectively. It is thus confirmed that, at least for **13k**, 10 °C represents the optimal temperature for reaction. To simultaneously gain information on the kinetics of the process at different temperatures, the forementioned experiments were performed with continuous monitoring of the reaction progress by in situ FTIR spectroscopy. This was done with an immersible DiComp ATR diamond probe, and the disappearance of the band corresponding to the carbonyl group of **13k** was analyzed. We have represented in Figure 4 the evolution of this band in the experiments at 0, 10, and 23 °C in the presence of 5 mol% of **3**.

Two aspects of this graph deserve a comment: On one hand, the important acceleration experienced by the reaction when the temperature increases from 0 to 10 °C, that has necessarily to obey to a combination of physical (mass transport) and chemical (kinetic) factors. On the other hand, the high catalytic activity exhibited by **3** at 10 °C or above, that leads to complete conversion in only 50 min. Keeping in mind the possibility of a future use of **3** in a continuous flow system, we also wanted to test if reaction time could be further reduced if catalyst loading was increased. To this end, the reaction at 23 °C was repeated with a 10 mol% catalyst loading. The progress of this reaction has been represented in Figure 5 along with that of the experiment with 5% catalyst loading at the same temperature.

It is interesting to observe that the time required for complete conversion is essentially divided by a factor of **2** when catalyst loading is increased from 5 to 10%. This is clearly indicative that even much shorter contact times could be sufficient for complete conversion at higher catalyst loadings, and tells in favor of **3** as a suitable candidate ligand for enantioselective phenylation in continuous flow systems. As an additional point, it is to be mentioned that the ee of the resulting arylcarbynol **15k** increases in only 1% (from 91 to 92%) while increasing from 5 to 10% catalyst loading. As a result of these observations, a set of optimized practical conditions for the use of **3** in enantioselective phenylation reactions was developed (5 mol% **3**, toluene, 10 °C, 2 h) and tested on a diverse set of aldehydes. The results of this study have been summarized in Table 5.

As inspection of Table 5 reveals, excellent results are obtained for *p*-substituted substrates under this set of experimental conditions. On the other hand, since the studied reaction is in general highly responsive to small variations in experimental conditions (temperature, solvent, catalyst amount), the possibility that higher enantiomeric

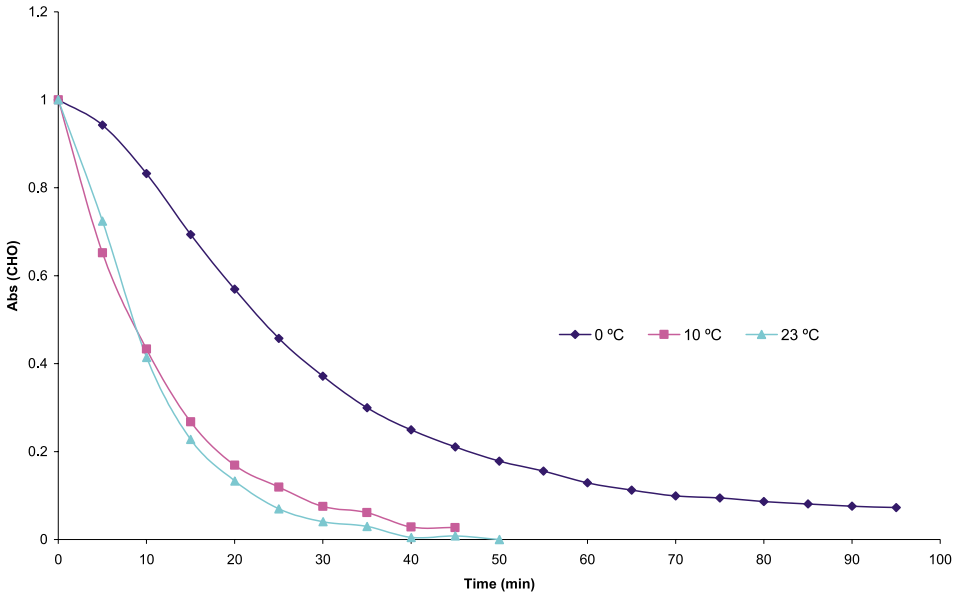


Figure 4. Progress of the phenylation of **13k** mediated by **3** (5 mol%) at different temperatures.

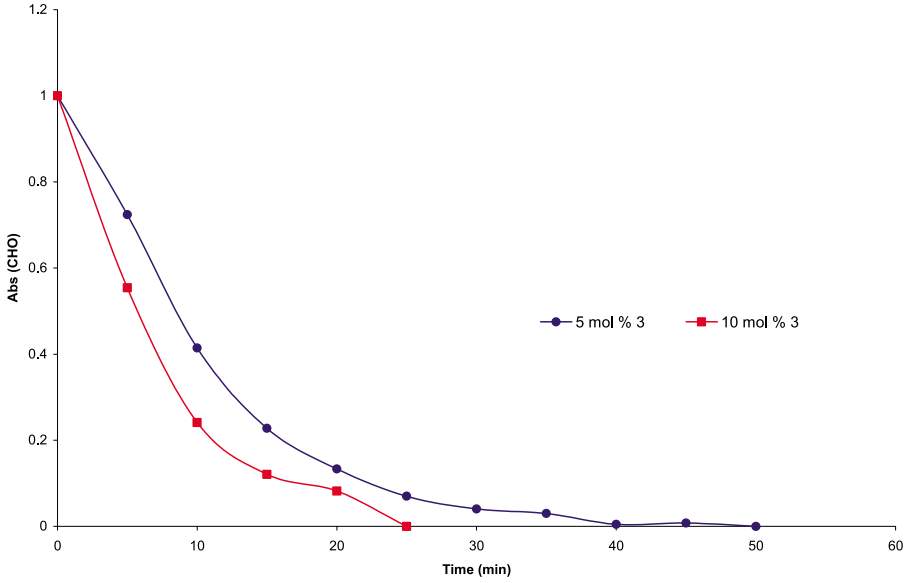


Figure 5. Progress of the phenylation of **13k** mediated by **3** at 23 °C with different catalyst loadings.

excesses can be achieved for some of the substrates under different experimental conditions can not be excluded. In this respect, it is illustrative to compare the results obtained for **13h**, **13m**, and **13o** using either 10 mol% (Table 4) or 5 mol% (Table 5) of resin **3**.

Table 5. Enantioselective phenylation of a selected set of aldehydes mediated by resin **3** (5 mol%) under optimized reaction conditions

Starting aldehyde	Yield (%)	ee (%)
2-Ethylbutanal (**13g**)	83	75
α-Methylcinnamaldehyde (**13h**)	82	79
p-Tolualdehyde (**13k**)	100	94
Pivalaldehyde (**13m**)	97	68
Biphenyl-4-carbaldehyde (**13n**)	69	92
2-Naphthaldehyde (**13o**)	100	85
p-Methoxybenzaldehyde (**13p**)	75	>99
p-Chlorobenzaldehyde (**13q**)	80	82

3. Summary and outlook

In summary, the first polymeric heterogeneous ligands (**2** and **3**) for the highly enantioselective phenyl transfer to aldehydes have been developed. The high catalytic activity depicted by these ligands, probably arising from a design where the handle used for the anchoring of the monomers to the polymer backbone introduces a minimal perturbation on the catalytic center, appears to be key to this behavior. With respect to enantioselectivity, **2** and **3** appear to be complementary in many aspects, and experimental conditions have been found for efficiently controlling the enantioselectivity of the phenylation of aromatic aldehydes (90.5% mean ee, eight examples) by a proper ligand choice. Although fewer examples have been studied, only marginally inferior results are recorded with α-substituted aliphatic

and α,β-unsaturated aldehydes. With respect to catalytic activity, reaction times of only 25 min have been determined by on-line FTIR analysis through the use of 10 mol% amounts of ligand **3**. As an application of this property, the development of flow systems for the continuous enantioselective phenylation of aromatic aldehydes is being actively pursued in our laboratories and will be reported in due course.

4. Experimental

4.1. General

Optical rotations were measured at 23 °C (concentration in g/100 mL). Melting points were determined in open capillary tubes and are uncorrected. IR spectra were recorded as film between NaCl plates or by KBr pellet techniques. ^{1}H and ^{13}C NMR spectra in solution were recorded in $CDCl_3$. Carbon multiplicities have been assigned by distortionless enhancement by polarization transfer (DEPT) experiments. The NMR gel samples were prepared as follows: the appropriate mass of resin was placed in a 5 mm NMR tube, and the mass volume of solvent was added. When the solvent had been absorbed, small additional fractions of solvent were added to obtain a homogeneous gel. The so-prepared samples were allowed to stand for 8–12 h before recording the spectra. ^{13}C NMR gel phase NMR spectra were recorded at 75.4 MHz in $CDCl_3$. Elemental analyses were carried out by the 'Servei d'Anàlisis Elementals del C.S.I.C. de Barcelona'. Tungsten(IV) oxide was used in the resin analyses to ensure total combustion of the samples. DMF, piperidine, and CH_2Cl_2 were distilled from CaH_2 and stored under N_2. Hexane, THF, and Toluene were distilled from Na and stored under N_2. Barlos resins were obtained from commercial sources. Online FTIR analysis were performed with a React IR-4000 instrument fitted with an immersible diamond (DiComp) ATR probe from Mettler Toledo.

4.1.1. (*S*)-4-(2-Azido-1-hydroxy-2,2-diphenylethyl)-benzonitrile (7). Enantiomerically pure (>99.9% ee) (*S*)-**6** (4.8 g; 16.1 mmol), prepared according to a reported procedure, were dissolved in 40 mL anhydrous benzene, and added to a freshly prepared suspension of diisopropoxytitanium diazide (5 g; 19.9 mmol) in anhydrous benzene (40 mL) under reflux. After 320 min, the mixture was cooled down, benzene was removed under vacuum, and the residue was dissolved in diethyl ether (50 mL). Aqueous 5% H_2SO_4 (50 mL) and the mixture was vigorously stirred for 60 min. Phases were then separated, and the aqueous one extracted with diethyl ether (4×50 mL). The combined organic extracts were dried (Na_2SO_4), filtered and evaporated to afford 6.21 g of crude (*S*)-**7**, that was submitted to azide reduction without further purification. $[\alpha]_D^{23}$ −35.8 (*c* 1.01, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.78 (br s, 1H), 5.73 (s, 1H), 7.01–7.44 (m, 14H) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$) δ: 75.8 (C), 78.4 (CH), 111.4 (C), 118.7 (C), 127.3 (CH), 127.8 (CH), 128.1 (CH), 128.4 (CH), 128.5 (CH), 128.7 (CH), 130.9 (CH), 139.3 (C), 140.0 (C), 144.3 (C) ppm. IR (film, NaCl) υ_{max}: 3457, 2228, 2109 cm^{-1}. MS (CI, NH_3) *m/e*: 359 ($[M+19]^+$, 26%), 358 ($[M+18]^+$, 100%).

4.1.2. (*S*)-4-(2-Amino-1-hydroxy-2,2-diphenylethyl)-benzonitrile (8). The crude azide **7** (6.21 g; 18.4 mmol) was dissolved in MeOH (100 mL) and added via canula to a suspension of 10% Pd/C (0.76 g) in MeOH (100 mL) under hydrogen (1 atm). After 15 h stirring at room temperature, the reaction mixture was filtered through a pad of Celite to remove the catalyst, and MeOH was evaporated under vacuum. The residue was purified by column chromatography on Et_3N pre-treated SiO_2 (2.5% v/v) eluting with hexane/ethyl acetate mixtures of increasing polarity to afford (*S*)-**8** (4.40 g) in 85% yield [from (*S*)-**6**] as a white solid. Mp: 166 °C. $[\alpha]_D^{23}$ −249.5 (*c* 1.02, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.2–2.8 (br s, 2H), 5.6 (s, 1H), 6.8–7.7 (m, 14H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$) δ: 65.9 (C), 76.9 (CH), 111.0 (C), 118.8 (C), 126.6 (CH), 127.0 (CH), 127.2 (CH), 127.5 (CH), 128.0 (CH), 128.5 (CH), 130.9 (CH), 144.4 (C), 145.3 (C), 145.4 (C) ppm. IR (film, NaCl) υ_{max}: 3478, 3350, 3290, 3090, 3060, 2228 cm^{-1}. MS (CI, NH_3) *m/e*: 315 ($[M+1]^+$, 100%), 316 ($[M+2]^+$, 23%). Elemental analysis: calcd for $C_{21}H_{18}N_2O$: C, 80.23; H, 5.77; N, 8.91. Found: C, 80.21; H, 5.75; N, 8.92.

4.1.3. (*S*)-4-(1-Hydroxy-2,2-diphenyl-2-(pyrrolidin-1-yl)-ethyl)benzonitrile (9). Amino alcohol (*S*)-**8** (3.49 g, 11.1 mmol) was dissolved in absolute ethanol (21 mL). Anhydrous potassium carbonate (3.10 g; 22.4 mmol) and 1,4-diiodobutane (2.92 mL, 22.2 mmol) were added to the solution, and the resulting mixture was heated under reflux. Over 3 days, additional 1,4-diiodobutane (7.6 mL; 57.4 mmol) was added in portions to the refluxing reaction mixture. Afterwards, the reaction mixture was cooled down and filtered, and ethanol was removed at reduced pressure. The residue was purified by column chomatography on Et_3N pre-treated SiO_2 (2.5% v/v) eluting with hexane/ethyl acetate mixtures of increasing polarity to afford (*S*)-**9** (2.60 g) in 64% yield as a white solid. Mp: 71 °C. $[\alpha]_D^{23}$ +39.6 (*c* 1.00, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.4–1.8 (br s, 4H), 2.2–2.6 (br s, 4H), 5.9 (s, 1H), 6.9–7.5 (m, 14H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$) δ: 22.1 (CH_2), 45.9 (CH_2), 71.8 (CH), 110.3 (C), 119.0 (C), 126.3 (CH), 126.9 (CH), 127.0 (CH), 127.5 (CH), 128.4 (CH), 130.5 (CH), 130.7 (CH), 146.2 (C) ppm. IR (film, NaCl) υ_{max}: 3400, 2228 cm^{-1}. MS (CI, NH_3) *m/e*: 368 (M^+, 100%), 369 ($[M+1]^+$, 28%). Elemental analysis: calcd for $C_{25}H_{24}N_2O$: C, 81.49; H, 6.57; N, 7.60. Found: C, 81.50; H, 6.57; N, 7.62.

4.1.4. (*S*)-4-(1-Hydroxy-2,2-diphenyl-2-(pyrrolidin-1-yl)-ethyl)benzaldehyde (10). A solution of DIBALH (2.7 mL, 2.7 mmol) in hexane was added dropwise to a solution of (*S*)-**9** (0.252 g, 0.70 mmol) in hexane (6.5 mL) and diethyl ether (2 mL) at −78 °C. After 1 h, ethyl acetate (1 mL) was slowly added, and the reaction mass was allowed to heat to room temperature. After 20 min, a saturated solution of NH_4Cl (3 mL) was added, and the resulting mixture was stirred at room temperature for 2 h. The crude was then filtered through a pad of Celite, the two phases were separated, the aqueous phase was extracted with ethyl acetate (3×10 mL), and the combined organic phases were dried (Na_2SO_4) and concentrated under vacuum. The residue was purified by column

chomatography on Et_3N pre-treated SiO_2 (2.5% v/v) eluting with hexane/ethyl acetate mixtures of increasing polarity to afford (*S*)-**10** (0.231 g) in 92% yield as a white solid. Mp: 67 °C. $[\alpha]_D^{23}$ +51.1 (*c* 1.00, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ: 1.5–1.8 (br s, 4H), 2.2–2.8 (br s, 4H), 5.9 (s, 1H), 6.8–7.6 (m, 14H), 9.8 (s, 1H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$) δ: 22.1 (CH_2), 45.9 (CH_2), 72.1 (CH), 74.6 (C), 126.2 (CH), 126.8 (CH), 126.9 (CH), 127.4 (CH), 128.2 (CH), 128.5 (CH), 130.6 (CH), 130.8 (CH), 134.9 (C), 147.8 (C), 192.2 (CH) ppm. IR (film, NaCl) υ_{max}: 3380, 2834, 1697 cm^{-1}. MS (CI, NH_3) *m/e*: 371 (M^+, 100%), 372 ($[M+1]^+$, 27%).

4.1.5. (*S*)-1-(4-(Hydroxymethyl)phenyl)-2,2-diphenyl-2-(pyrrolidin-1-yl)ethanol (11). $NaBH_4$ (71.4 mg, 1.88 mmol) was added to a solution of (*S*)-**10** (176 mg; 0.5 mmol) in absolute ethanol (3.5 mL). After 0.5 h at room temperature, saturated aqueous NH_4Cl solution was added dropwise, and the resulting aqueous phase was extracted with CH_2Cl_2 (3×5 mL). The combined organic phases were washed with water (3×5 mL), dried ($MgSO_4$), filtered and concentrated under vacuum. The residue was purified by column chomatography on Et_3N pre-treated SiO_2 (2.5% v/v) eluting with hexane/ethyl acetate mixtures of increasing polarity to afford (*S*)-**11** (113 mg) in 65% yield as a white solid. Mp: 79 °C. $[\alpha]_D^{23}$ +18.0 (*c* 1.00, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ: 1.5–1.8 (br s, 4H), 2.2–2.7 (br s, 4H), 4.5 (s, 2H), 5.9 (s, 1H), 6.6–6.8 (m, 2H), 6.8–7.5 (m, 12H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$) δ: 22.2 (CH_2), 45.9 (CH_2), 65.0 (CH_2), 72.3 (CH), 74.5 (C), 125.3 (CH), 126.0 (CH), 126.6 (CH), 126.7 (CH), 127.1 (CH), 128.4 (CH), 130.9 (CH), 131.0 (CH), 137.3 (C), 139.4 (C), 139.5 (C) ppm. IR (film, NaCl) υ_{max}: 3397 cm^{-1}. MS (CI, NH_3) *m/e*: 373 (M^+, 100%), 374 ($[M+1]^+$, 29%).

4.1.6. Anchoring of amino alcohol 11 to a Barlos resin: resin 5 (f_{max}: 1.06) from Barlos' resin with an initial substitution level of 1.60 mmol Cl/g. Diisopropyletylamine (0.15 mL, 0.88 mmol) was added to a mixture of aminodiol **11** (171 mg, 0.46 mmol) and the resin (232 mg, 0.38 mmol of active Cl) in CH_2Cl_2 (2.5 mL), under nitrogen, at room temperature. After smoothly stirring for 24 h, the resulting mixture was filtered, washed with DMF (2×10 mL), DMF/water 1:1 (4×10 mL), water (4×10 mL), pH 9 $Na_2CO_3/NaHCO_3$ buffer (4×10 mL), water (8×10 mL), MeOH (4×10 mL), toluene (4×10 mL) and CH_2Cl_2 (4×10 mL), and dried under vacuum to constant weight to afford 0.301 g (100%) of resin **12** (*f*: 0.896). ^{13}C gel-phase NMR (75.4 MHz, $CDCl_3$) δ: 22.2 (CH_2), 40.4 (CH), 45.9 (CH_2), 65.7 (CH_2), 72.3 (CH), 74.5 (C), 86.2 (C). Anal. Calcd for f_{max}: N, 1.43. Found: N, 1.30. Anchoring yield: 85%.

4.1.7. (*S*)-2,2-Diphenyl-2-(pyrrolidin-1-yl)-1-(4-(trityloxymethyl)phenyl)ethanol (12). A solution of (*S*)-**11** (50 mg, 0.13 mmol) and *N*-tritylpyridinium tetrafluoroborate (66 mg, 0.16 mmol) in acetonitrile (0.6 mL) was kept under nitrogen at room temperature for 24 h. Diethyl ether (5 mL) was then added, and the resulting solid material was separated by filtration. Solvents were removed at reduced pressure, and the residue was purified by column chomatography on Et_3N pre-treated SiO_2 (2.5% v/v) eluting with hexane/ethyl acetate mixtures of increasing polarity to afford (*S*)-**12** (68 mg) in 83% yield as a white solid. Mp: 79 °C. $[\alpha]_D^{23}$ +34.0 (*c* 0.55, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ: 1.5–1.8 (br s, 4H), 2.3–2.6 (br s, 4H), 3.9 (s, 2H), 5.9 (s, 1H), 6.6–6.7 (m, 2H), 6.8–7.6 (m, 27H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$) δ: 22.2 (CH_2), 45.9 (CH_2), 65.6 (CH_2), 72.4 (CH), 74.6 (C), 86.8 (C), 125.4 (CH), 126.0 (CH), 126.6 (CH), 126.9 (CH), 127.1 (CH), 127.7(CH), 128.1 (CH), 128.7 (CH), 130.9 (CH), 137.5 (C), 138.9 (C), 144.2 (C) ppm. IR (film, NaCl) υ_{max}: 3385 cm^{-1}. MS (CI, NH_3) *m/e*: 243 (Ph_3C^+, 100%), 615 (M^+, 9%), 616 ($[M+1]^+$, 4%).

4.2. General procedure for the enantioselective addition of $ZnEt_2$ to aldehydes catalyzed by resin 5

Twenty three milligram of resin **5** (8 mol%, *f*: 0.90) were suspended under a nitrogen atmosphere in 125 μL of anhydrous toluene. After swelling for 24 h under slow stirring, 0.5 mL (0.5 mmol) of diethylzinc 1 M in hexanes were added. The mixture was cooled to 0 °C, and 125 μL of a 2 M solution of four aldehydes (0.062 mmol of each one) in hexanes were added dropwise. After 6 h at 0 °C, the reaction was quenched with saturated aqueous NH_4Cl, extracted with dichloromethane (3×15 mL), and the aqueous extracts dried over Na_2SO_4. The resulting solution was analyzed by GC using a chiral β-DEX capillary column and a FID detector. The analysis method was developed using a racemic sample. For the particular analytical conditions for each alcohol, see Ref. 8a.

4.3. Typical procedure for the enantioselective phenyl transfer to aldehydes catalyzed by resins 2, 3, and 5

In first place, a mixture of 293 mg (1.33 mmol) of $ZnPh_2$ and 333 mg (2.7 mmol) of pure $ZnEt_2$ was dissolved in 25 mL of anhydrous toluene. Then, the corresponding weight of resin, according to f and to the desired molar amount, was suspended in 6.4 mL of the $ZnPh_2/ZnEt_2$ solution under argon, and allowed to swell for 1 h. After cooling to 10 °C, 59 μL (0.50 mmol) of *p*-tolualdehyde were added. After 2 h, the reaction was quenched with saturated aqueous NH_4Cl, filtered under vacuum to remove the catalyst, extracted with CH_2Cl_2 (3×15 mL), dried (Na_2SO_4), and solvents removed under vacuum. The diarylcarbynol was obtained in quantitative yield. Enantiomeric excess was determined by HPLC with a Chiralcel OD chiral column. For the particular analytical conditions for each alcohol, see Ref. 15.

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Combining enabling techniques in organic synthesis: solid-phase-assisted catalysis under microwave conditions using a stable Pd(II)-precatalyst

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Abstract—The catalytic activity of a 2-pyridinealdoxime-based Pd(II)-complex covalently anchored via the oxime moiety to a glass/polymer composite material was evaluated in Suzuki–Miyaura cross-coupling reactions of aryl and heteroaryl halides, including arylchlorides, with aryl and heteroaryl boronic acids both under thermal as well as microwave irradiating conditions in water. The stability and reusability of this Pd-precatalyst is part of the present study.

1. Introduction

Organic synthesis seems to have become so very advanced that basically every molecular target, how structurally complex it may be, can be addressed. However, these advances are not fully reflected in the industrial context.[1] Many developments from the research laboratories lack practicability as far as scale-up, easy and rapid workup and product isolation as well as recyclability of catalysts are concerned. New synthetic methods need to be combined with new techniques termed 'enabling technologies for organic synthesis' to achieve rapid incorporation into industrial processes.[2] Typical enabling technologies are microwave assistance,[3] new solvent systems,[4] continuous flow reactors[5] and immobilization of chemically active species such as reagents and homogeneous catalysts[6] which have recently seen widespread applications in research laboratories. Truly new synthetic technology platforms, however, will not be based on the individual use of these new techniques but will require the integration of two or more of these enabling techniques (Fig. 1). Various successful examples of combining two or more of these techniques in order to achieve faster synthesis or improved work-up have recently appeared in the literature, particularly in the field of catalysis.

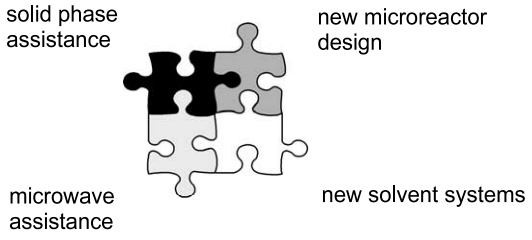

Figure 1.

In this context, we have combined solid-phase assisted synthesis with new continuous flow reactors (PASSflow) leading to an almost workup free procedure for carrying out many different reactions including nucleophilic substitutions, reductive aminations, oxidations, Horner–Wadsworth–Emmons and Pd-catalyzed C–-C coupling reactions in the flow through mode.[7]

Other groups have combined microwave-assisted solid-phase technique was applied in the synthesis of several heterocycles,[8] C–C cross couplings[9] and natural products derivatives.[10] However, publications concerning the use of insoluble Pd-catalyst under microwave irradiating conditions are scarce.[11] The combination of immobilized homogeneous catalysts and microwave assistance is particularly appealing in order to overcome the less favourable kinetics of biphasic systems.

Transition metal-mediated cross-coupling reactions, particularly those based on palladium, have become key

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transformations in organic synthesis. However, traditional palladium catalysts often rely on phosphine ligands which show various disadvantages. These are associated with their high price, their air-sensitivity, and difficulties when the ligands and their degradation by-products have to be removed during workup. Recently, new catalytic candidates have appeared in the literature, namely palladacycles which exert high activity and often they are air stable (selected examples are depicted in Fig. 2).[12] In many cases, these compounds are dimeric chloro-bridged *ortho*-palladated complexes such as the acetophenone oxime-based palladacycle **1** utilized by Nájera et al.[13] a versatile complex which is able to catalyze various carbon–carbon coupling reactions such as Suzuki–Miyaura and Heck cross-couplings. Garcia and co-workers[14] covalently anchored these thermally stable palladacycles via an aryl ether linkage to modified silica support yielding catalyst **2**[14] allowing facile recycling of the catalytic species. This species was tested in Suzuki–Miyaura reactions and was found to be a highly active and recyclable complex when heating the reaction mixture conventionally under nitrogen atmosphere. Related examples of immobilized Pd catalysts were disclosed by Nowotny et al.[15] and Bedford et al.[16] who studied palladium(II) complexes **3** and **4** immobilized on polystyrene and silica, respectively. These complexes were found to be highly active in Heck and Suzuki–Miyaura cross coupling reactions, respectively, but were not well suited for recycling protocols. More precisely, the precatalyst **3** lost its activity after the first run of the Heck reaction between iodobenzene and styrene in NMP whereas catalyst **4** was tested in Suzuki–Miyaura cross coupling of only aryl bromides and with recyclability far from being ideal. Recently, evidence has been collected that complexes described here serve as 'dormant species'[12a] that are not involved in the real catalytic cycle but are a source of a catalytically active species of unknown nature. Thus, solvents like NMP may coordinate and stabilize Pd species that have left the solid phase and therefore, seem not to be well suited as solvents for immobilized Pd species.

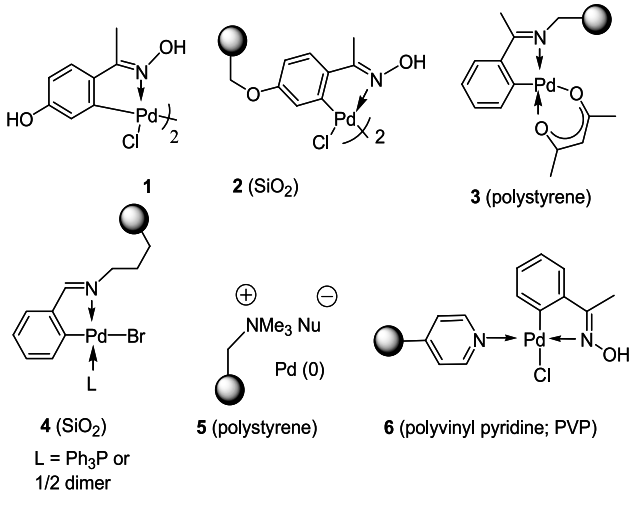


Figure 2.

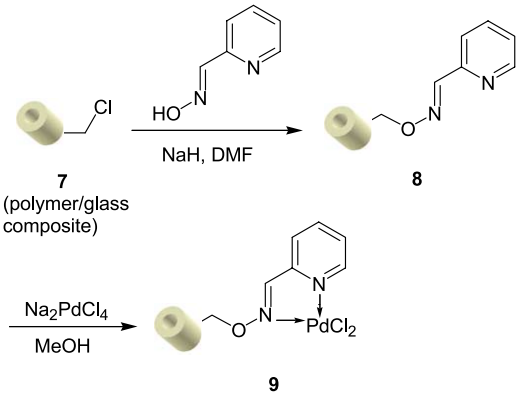
Recently, we initiated a program dedicated to the immobilization of catalytically active Pd species inside a megaporous glass/polymer composite material which we developed for incorporation inside a continuous flow reactor as a monolithic material thereby combining two enabling techniques.[5] For this purpose different strategies of attachment such as physisorption of Pd particles **5**,[17] and immobilization of Najera's catalyst to polyvinyl pyridine by covalent linkage **6**[18] were pursued. The resulting catalysts were tested in a batch set up as well as under continuous flow conditions using the PASSflow system.[7] However, they lack of stability under microwave irradiating conditions and show substantial degree of leaching under continuous flow conditions in PASSflow reactors when polar organic solvents like DMF are required. In order to overcome these drawbacks (a) stability under microwave irradiation and (b) recyclability, search for an alternate Pd(0) catalyst or an appropriate precatalyst were conducted. Here, we report on the development of a new polymer-bound palladium(II) complex **9** which is anchored to the glass/polymer composite material. In order to evaluate its suitability in Suzuki–Miyaura reactions under microwave irradiating conditions we used a composite material shaped as Raschig rings which is a material with relevance in industrial applications (Fig. 3).

Figure 3. Megaporous glass Raschig rings.

2. Results and discussion

2.1. Preparation of Pd-precatalyst

For generating immobilized Pd-precatalyst **9** (Scheme 1), first the monolithic glass/polymer composite phase **7** had to be prepared by precipitation polymerization inside the pores of porous glass which was shaped as Raschig rings according to the protocol that we recently described in detail.[7] 2-Pyridinealdoxime was then coupled to the polymer matrix **7** by heating it at 80 °C in DMF in the presence of sodium hydride. Finally, the heterogeneous precatalyst **9** was obtained by treatment of **8** with a solution



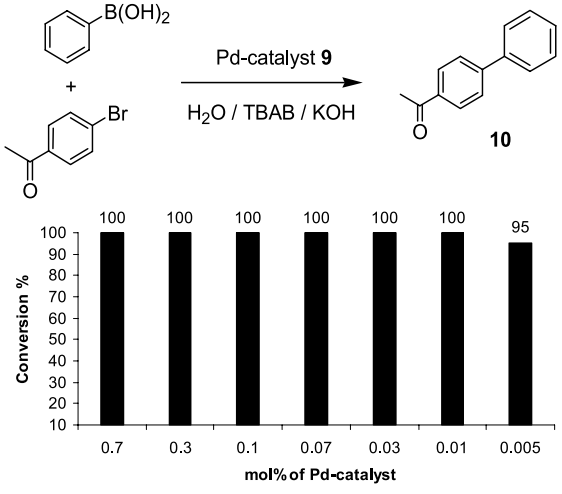
Scheme 1.

of sodium tetrachloropalladate in methanol. The loading of catalyst **9** was estimated to be ca. 0.09 mmol/g Raschig rings according to weight increase.[19]

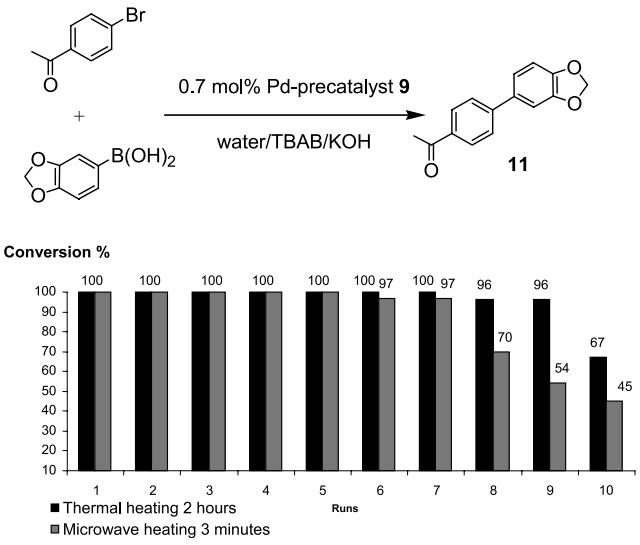
2.2. Optimization of conditions for catalysis

The high price of palladium renders processes based on this metal less attractive unless very active species or catalytic species easy to recycle are available.[20] Therefore, we firstly studied the factors affecting the optimization of the catalytic activity of the Pd-precatalyst **9**. Thus, the effect of concentration of palladium precatalyst **9** on the coupling reaction between phenylboronic acid and *p*-bromoacetophenone under thermal conditions in water at 100 °C was evaluated. At first, the reaction was conducted using 0.7 mol% of precatalyst **9** with a molar ratio of *p*-bromoacetophenone/phenylboronic acid/tetrabutylammonium bromide/potassium hydroxide: 1/1.2/0.6/2, to give 98% isolated yield of 4-acetyl-1,1′-biphenyl (**10**). In the second experiment, we used 0.3 mol% of the catalyst to give full conversion in 97% isolated yield. The reaction was repeated with different catalytic mol% as shown in Scheme 2. Almost full conversion was obtained even in the presence of 0.005 mol% of the catalyst **9** using *p*-bromoacetophenone (40 mmol), phenylboronic acid (48 mmol), tetrabutylammoium bromide (24 mmol), potassium hydroxide (80 mmol) and water (100 mL) to give the 4-acetyl-1,1′-biphenyl (**10**) in 95% (GC-analysis; 92% isolated yield), revealing the good activity of the catalytic system.

Furthermore, we studied the recyclability of Pd-precatalyst **9** in a second model Suzuki–Miyaura cross-coupling reaction using 3,4-methylenedioxyphenylboronic acid (1.2 equiv) and *p*-bromoacetophenone (1 equiv) in the presence of precatalyst **9** (0.7 mol%) in water (3.5 mL) at 100 °C under air, and potassium hydroxide (2 equiv) as base and tetrabutylammonium bromide (TBAB) (0.6 equiv) as phase transfer agent (Scheme 3). Under these conditions, the reaction was completed within 2 h (GC-monitoring). The product of the reaction, 3,4-methylenedioxy-4′-acetyl-1,1′-biphenyl (**11**), was isolated after flash chromatographic



Scheme 2. Effect of concentration of the Pd-precatalyst **9** on the transformation rate. Conditions: Bromide/boronic acid/KOH/TBAB/water (mL): 1/1.2/2/0.6/3.5 mL, reaction time for runs 1–5 was 2 h and for runs 6–7 was 3 h.



Scheme 3. Recyclability of the Pd-precatalyst **9** under thermal and microwave heating. Conditions: bromide/boronic acid/base/TBAB/water (mL): 1/1.2/2/0.6/3.5, 0.7 mol% Pd precatalyst **9**, 100 °C/2 h for thermal heating; 160 °C/250 W/3 min for microwave irradiation.

purification in 95% yield. At this point, the Pd-precatalyst **9** was removed, washed with ethyl acetate and water and subsequently dried.[21] This used catalyst was reemployed in nine successive runs under identical conditions promoted for the first run. Nearly full conversion was achieved within 2 h up to the 9th run as depicted in Scheme 3. Recyclability of the precatalyst **9** under microwave irradiation conditions was next evaluated using the same model reaction described above at 160 °C and 250 watt for ten successive runs as shown in Scheme 3. Under these conditions, the precatalyst **9** was highly active with almost full transformation up to the 7th run and even at the 10th run it was still active (45% transformation). It is noteworthy to mention that the reaction is highly selective as only the cross-coupled product was formed up to the 7th run and from run 8 to 10 the starting *p*-bromoacetophenone was still present along with the product. Homo-coupled products, which are well known by-products in Suzuki–Miyaura reactions were analyzed to be formed in the range of 1–8%. These results indicate the high stability of precatalyst under microwave irradiating conditions which allows to simply reuse it.

Additionally, we optimized the reaction temperature under thermal conditions for the coupling between 3,4-methylenedioxyphenylboronic acid (1.2 equiv) and *p*-bromoacetophenone (1 equiv) in the presence of precatalyst **9** (0.7 mol %) in water (3.5 mL), potassium hydroxide (2 equiv) and

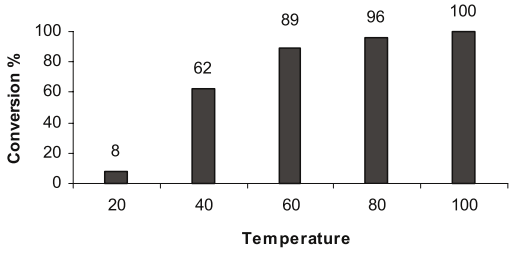
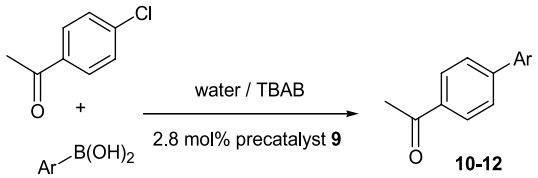
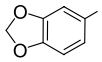


Figure 4. Effect of temperature on the transformation of *p*-bromoacetophenone into **11**. Conditions: Bromide/boronic acid/base/TBAB/water (mL): 1/1.2/2/0.6/3.5, 0.7 mol% Pd-precatalyst **9**, 2 h.

Table 1. Suzuki–Miyaura reactions of aryl chlorides under thermal and microwave heating



	Ar	Base	Product	Thermal heating[a]		μw heating[a]	
				Time (h)	Yield%[b]	Time (min)	Yield%[b]
1		A	**10**	16	65	30	84
2		B	**10**	16	85 (76)	30	98 (92)
3		A	**11**	16	17	15	53
4		B	**11**	16	93 (91)	30	97 (90)
5		A	**12**	16	2	15	11
6		B	**12**	16	22	30	31

[a] Molar ratio of chloride/boronic acid/base/TBAB is 1/1.2/2/0.6, water (3.5 mL), precatalyst **9** (2.8 mol%); thermal heating at 100 °C, microwave heating at 160 °C (250 watt), base A = Cs_2CO_3; B = KOH.
[b] GC-yields; values in parentheses refer to isolated yields of pure products.

TBAB (0.6 equiv). The reaction time was fixed in all cases at two hours. As shown in Figure 4, conversion is best achieved at 100 °C. Interestingly, when the reaction was left shaking at room temperature for an extended time of 20 h, full conversion was also achieved.

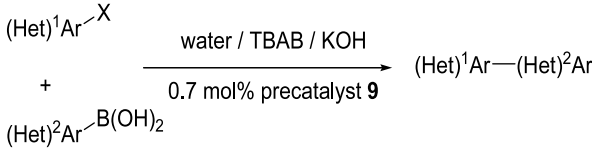
The effect of the absence of tetrabutylammonium bromide (TBAB) and/or palladium catalyst on the above mentioned conversion was also evaluated. Leadbeater and co-workers[22] recently revised there results[23] on a palladium free Suzuki–Miyaura reaction by disclosing that impurities of Pd present in reagents added such as the base K_2CO_3 can result in C–C-coupling of aryl halides and arylboronic acids. In the present case, no product formation was observed without palladium catalyst but in the presence of TBAB and KOH in water both under thermal (2 h) as well as microwave irradiating conditions (3 min). When the reaction was conducted in the presence of palladium precatalyst **9** but without TBAB, the conversion was only 59 and 79% under thermal (2 h) and microwave irradiating conditions (3 min), respectively. These findings show the importance of the palladium source and TBAB in carrying out Suzuki–Miyaura coupling reactions. It is noteworthy to report here, that, when the same reaction was repeated with microwave heating for 3 min in the absence of palladium precatalyst **9** but in glassware that had been used before in Pd-catalysed reactions and that obviously had not been thoroughly cleaned, product **11** was formed in 37% yield.

2.3. Scope and limitations of the precatalyst 9

To test the scope and limitations of precatalyst **9** in Suzuki–Miyaura reactions we first chose aryl chlorides[24] as substrates and applied aqueous conditions which would be beneficial when accelerating the C–C-coupling under microwave irradiating condtions.[25,26]

Thus, we therefore focused on the reaction of *p*-chloroacetophenone with various aryl and heteroarylboronic acids. The results for thermal as well as microwave heating are summarized in Table 1. Treatment of *p*-chloroacetophenone (1 equiv) with phenylboronic acid (1.2 equiv), tetrabutylammonium bromide (0.6 equiv) and potassium hydroxide (2 equiv) in the presence of the precatalyst **9** (2.8 mol%) in water (3.5 mL) at 100 °C under air for 16 h resulted in the formation of 4-acetyl-1,1′-biphenyl (**10**) in 76% isolated yield. When this transformation was repeated under identical conditions except that heating was conducted for 30 min with microwave irradiation (160 °C, 250 watt), the coupling product **10** was isolated in 92% yield. The microwave conditions were optimized with respect to energy and reaction time. Therefore, the degree of conversion under microwave heating (160 °C, 250 watt) for the coupling of phenylboronic acid with *p*-chloroacetophenone was analyzed after 2 min (16%), 4 min (45%), 8 min (63%), 15 min (78%) and 30 min (84%; entry 1, Table 1). When reducing the amount (0.7 mol%) of Pd-precatalyst **9** the product **10** was obtained in 55% after 30 min of microwave irradiation. Suzuki–Miyaura reactions of *p*-chloroacetophenone were also conducted with 3,4-methylenedioxyphenylboronic acid (entry 4, Table 1) and with 3-thienylboronic acid (entry 6, Table 1) both under thermal as well as microwave irradiating conditions using potassium hydroxide as base. For comparison reason also, cesium carbonate was employed which has been found by Glorius et al.[27] and Mino et al.[28] to be an effective base for transformations of aryl chlorides into biaryls in Suzuki cross couplings. However, the former base turned out to be superior to cesium carbonate. Homo-coupled products, which are by-products commonly observed in Suzuki–Miyaura reactions were found to be well below 5% as determined by GC-analysis.

In the following we investigated the general utility of precatalyst **9** in Suzuki–Miyaura cross-coupling reactions (Scheme 4 and Table 2). Aryl and heteroaryl bromides were



Scheme 4. For details refer to Table 2.

Table 2

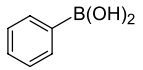
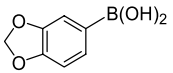
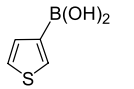
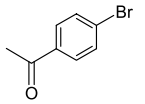
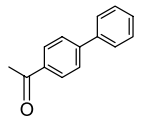
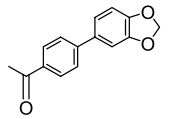
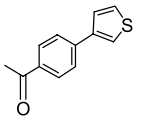
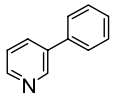
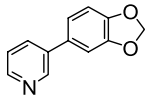
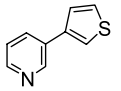
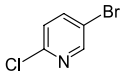
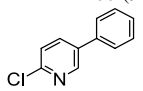
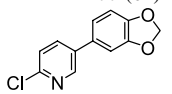
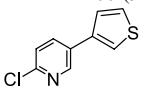
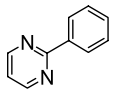
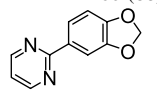
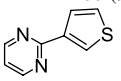
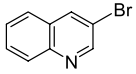
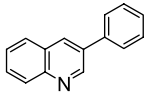
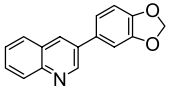
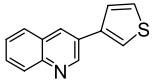
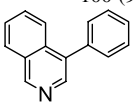
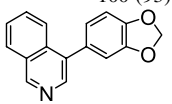
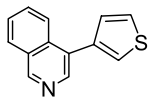
(Het)[1]Ar-X												
	Thermal [a]		Microwave[a]		Thermal [a]		Microwave[a]		Thermal [a]		Microwave[a]	
	Yield%[b]	Time (h)	Yield%[b]	Time (min)	Yield%[b]	Time (h)	Yield%[b]	Time (min)	Yield%[b]	Time (h)	Yield%[b]	Time (min)
			 **10**				 **11**				 **12**	
	100 (97)	2	100 (98)  **13**	2	100 (90)	2	100 (95)  **14**	3	94	7	100 (75)  **15**	3
	100	6	100 (92)  **16**	7	64	7	77 (61)  **17**	10	85	6	100 (91)  **18**	10
	100 (81)	4	100  **19**	5	100 (85)	4	100 (88)  **20**	8	100	2	100 (93)  **21**	4
	11	7	100 (91)  **22**	15	12	7	17  **23**	15	35	4	96 (79)  **24**	15
	100 (97)	4	100 (94)  **25**	8	100 (78)	6	100 (93)  **26**	10	100 (88)	4	94  **27**	11
	64	4	100 (89)	10	100 (96)	7	92	10	92 (84)	8	50	10

Table 2 (*continued*)

(Het)^{1}Ar-X		$B(OH)_2$				$B(OH)_2$				$B(OH)_2$			
		Thermal [a]		Microwave[a]		Thermal [a]		Microwave[a]		Thermal [a]		Microwave[a]	
		Yield%[b]	Time (h)	Yield%[b]	Time (min)	Yield%[b]	Time (h)	Yield%[b]	Time (min)	Yield%[b]	Time (h)	Yield%[b]	Time (min)
		0	6	17	15	0	20	6	15	0	18	18	15
	28												
		100 (89)	6	100 (94)	5	100 (88)	2	100 (98)	3	100 (85)	7	100 (96)	5
	31												
	29												
	32												
	30												
	33												

[a] Conditions: halide (1 mmol), boronic acid (1.2 mmol), KOH (2 mmol), TBAB (0.6 mmol), water (3.5 mL), Pd-precatalyst **9** (0.7 mol%), 100 °C thermal heating; 160 °C (250 watt) microwave heating.
[b] GC-yields; values in parentheses refer to isolated yields of pure products.

coupled with boronic acids both under thermal as well as microwave irradiating conditions. The reaction conditions and molar ratios of the reaction components are cited in the legend of Table 2.

Again heating under microwave conditions led to an acceleration of the C–C-coupling reaction. In some cases, yields dramatically improved when switching from conventional heating to microwave heating as is particularly well demonstrated for the formation of biaryls **19**, **21**, and **25**. Chemoselectivity was encountered in the formation of biaryls **16** to **18**. However, the catalyst derived from precatalyst **9** is even not reactive enough to efficiently couple 2-bromothiazole under Suzuki–Miyaura cross-coupling reactions when microwave irradiating conditions are employed.

Although there had been speculations that palladacycles may operate through a Pd(II)/(IV) cycle,[29] studies by Hartwig et al.[30] strongly suggest that, as expected, Pd(0) species have to be made responsible as active catalysts. Therefore, complexes that are listed in Figure 2 as well as **9** may serve as reservoirs that are not involved in the real catalytic cycle[12a] but are a source of coordinative unsaturated 'PdL_n' species of unknown nature or release a considerable amount of colloidal Pd(0) which also can show catalytic activity at low concentrations. Indeed, De Vries and co-workers noted for Heck reactions that low concentrations of Pd(0) in solution will aggregate and deactivate much more slowly than high concentrations.[31] For related SCS–Pd complexes strong evidence has been collected in Heck reactions that they are actually reservoirs of a catalytically active but ill-defined form of Pd(0).[32] However, the picture is more complex as the choice of solvent is crucial in this context, specifically its complexing properties. Other solvents than water (which we applied in our studies) such as DMF or NMP can give supernatants which unlike in cases of aqueous solvents still show catalytic activity in Heck reactions.[15] However, the pyridine ligand present on our polymeric phase still has the potential to scavenge any catalytic species that may have leached into solution during the catalytic process which would explain the low amount of Pd (1.6×10^{-3}–1.28×10^{-3}%) that we determined by ICP-MS after having cooled the reaction mixture to room temperature. In addition, this process may retard the formation and growth of colloids.

3. Conclusions

In conclusion, we demonstrated that Pd-complex **9** is an efficient and highly active, reusable solid-phase anchored precatalyst with extraordinary potential for Suzuki–Miyaura cross-coupling reactions in aqueous media. Importantly, it not only shows activity under thermal but also under microwave irradiating conditions in water thereby showing sufficient reactivity even for arylchlorides. Having tested this precatalyst on the megaporous monolith glass/polymer composite allows us to utilize this material under continuous flow conditions in PASSflow reactors. These are ongoing studies in our laboratories.

4. Experimental

4.1. Materials and methods

NMR spectra were recorded with a Bruker DPX-400 spectrometer at 400 MHz (^{1}H NMR) and at 100 MHz (^{13}C NMR) using $CDCl_3$ as solvent and internal standard (δ= 7.26 and 77.36 ppm, for ^{1}H NMR and ^{13}C NMR, respectively). Mass spectra (EI) were obtained at 70 eV with a type VG autospec apparatus (Micromass). GC analyses were conducted using an HPGC series 6890 Series Hewlett Packard equipped with an SE-54 capillar column (25 m, Macherey–Nagel) and an FID detector 19231 D/E. Melting points were determined in open glass capillaries with a Gallenkamp apparatus and are uncorrected. Analytical thin-layer chromatography was performed using precoated silica gel 60 F254 plates (Merck, Darmstadt), and the spots were visualised with UV light at 254 nm. Merck silica gel 60 (230–400 mesh) was used for flash column chromatography. Microwave experiments were carried out using a CEM Discover Labmate^{TM} microwave apparatus (300 W with ChemDriver^{TM} Software). Commercially available reagents and dry solvents were used as received.

4.2. Preparation of Pd-precatalyst 9

To a mixture of glass/polymer composite shaped Raschig rings (10 g, 5 mmol) containing 10% chloromethylpolystyrene-divinyl benzene polymer (0.53 mmol polymer/g Raschig rings) **7** and *cis*−2-pyridinealdoxime (3.66 g, 30 mmol) in dimethylformamide (DMF) (50 mL), sodium hydride (0.72 g, 60% in oil, 30 mmol) was added portionwise over a period of 20 min. The mixture was shaken at 80 °C for three days then cooled to room temperature and quenched with water (100 mL). The Raschig rings were filtered and washed successively with DMF, water, ethanol, dichloromethane and again with ethanol (20 mL, each time) and finally well-dried under vacuum. These well-dried Raschig rings to which *cis*-2-pyridinealdoxime was bound **8** (6.92 g) were added to a solution of sodium tetrachloropalladate (1.2 g, 4 mmol) in methanol (80 mL) and the mixture was left to be shaken at room temperature for additional three days. The resulting Raschig rings were dried in vacuo and the loading of catalyst **9** was estimated to be ca. 0.09 mmol/g Raschig rings according to weight increase (the weight increase of each single raschig ring was determined; each ring was loaded with about 2.8 mol% palladium with reference of 1 mmol scaled reactions).

4.3. Effect of concentration of the palladium catalyst 9 on the Suzuki–Miyaura coupling in water with thermal heating

A mixture of *p*-bromoacetophenone (1 mmol), phenylboronic acid (1.2 mmol), TBAB (0.6 mmol), palladium catalyst **9** (0.7 mol%), KOH (2 mmol) and water (3.5 mL) was shaken at 100 °C under air for 2 h (monitored by GC). The same experiment was repeated using 0.3 mol% of palladium precatalyst. The amount (mol%) of the palladium precatalyst **9** was changed with respect to *p*-bromoacetophenone (0.1, 0.07, 0.03 and 0.01 mol% Pd-catalyst with scales of 2, 5, 10 and 20 mmol of *p*-bromoacetophenone, respectively). Finally, the same reaction was repeated using 40 mmol of *p*-bromoacetophenone and only 0.005 mol% palladium-complex **9** and the reaction mixture was heated in this case for 3 h at 100 °C under air. The molar ratio of the reaction components were in all cases as follows; *p*-bromoacetophenone, phenylboronic acid, tetrabutylammonium bromide (TBAB), KOH: 1/1.2/0.6/2 (in 3.5 mL water). The conversion (in %) versus concentration of palladium catalyst is shown in Scheme 2.

4.4. Recycling of the palladium precatalyst 9 with thermal heating in water

A mixture of *p*-bromoacetophenone (1 mmol), 3,4-methylenedioxyphenyl boronic acid (1.2 mmol), TBAB (0.6 mmol), palladium catalyst **9** (0.7 mol%), KOH (2 mmol) and water (3.5 mL) was shaken at 100 °C under air for 2 h (monitored by GC). The solid catalyst was removed by filtration, washed with water followed by EtOAc, dried and then reused in a new reaction mixture with the same molar ratio of components mentioned above. Then the mixture was shaken again at 100 °C under air for 2 h. This experiment was repeated in another nine runs (2 h for each run), as shown in Scheme 3. The product was purified by flash column chromatography on silica gel using EtOAc/petroleum ether (1:10) as eluent.

4.5. Recycling of the palladium precatalyst 9 under microwave irradiating conditions in water

The same reaction mixture used under thermal conditions was mixed in a properly capped process vial and thereafter the mixture was subjected to microwave irradiating conditions at 160 °C and 250 watt for 3 min (monitored by GC). The solid catalyst was removed, washed with water followed by EtOAc, dried and then re-used for the next run with the same molar ratio of components. As shown in Scheme 3, the experiment was repeated in another nine runs, each time irradiating for 3 min.

4.6. General procedure for the Suzuki–Miyaura coupling of *p*-chloroacetophenone in water with thermal heating

A mixture of *p*-chloroacetophenone (1 mmol), aryl(heteroaryl) boronic acid (1.2 mmol), tetrabutylammonium bromide (TBAB) (0.6 mmol), palladium precatalyst **9** (2.8 mol%), KOH or Cs_2CO_3 (2 mmol) and distilled water (3.5 mL) was shaken at 100 °C under air for 16 h. The solid catalyst was removed by filtration, washed with water followed by EtOAc. The combined washings were extracted with EtOAc (3×20 mL). The combined organic extracts were dried over anhydrous $MgSO_4$ then filtered and the solvent was evaporated under reduced pressure. The product was purified as described above.

4.7. General procedure for the Suzuki–Miyaura coupling of *p*-chloroacetophenone in water under microwave heating

A mixture of *p*-chloroacetophenone (1 mmol), aryl(heteroaryl) boronic acid (1.2 mmol), TBAB (0.6 mmol),

palladium catalyst **9** (2.8 mol%), KOH or Cs_2CO_3 as a base (2 mmol) and water (3.5 mL) were mixed in a process vial. The vial was capped properly, and thereafter the mixture was heated under microwave irradiating conditions at 160 °C and 250 watt for the appropriate reaction time as listed in Table 1. After the reaction was completed (monitored by GC), the solid catalyst was removed by filtration and washed. The reaction mixture was extracted with EtOAc (3×10 mL) and combined with the washings. After drying over $MgSO_4$, and concentration in vacuo, the product was isolated by flash column chromatography.

4.8. General procedure for the Suzuki–Miyaura coupling of aryl(heteroaryl) bromides in water with thermal heating

A mixture of aryl(heteroaryl) bromide (1 mmol), aryl(heteroaryl) boronic acid (1.2 mmol), TBAB (0.6 mmol), palladium catalyst **9** (0.7 mol%), KOH (2 mmol) and distilled water (3.5 mL) was shaken at 100 °C under air for the appropriate reaction time listed in Table 2. After the reaction was completed (monitored by GC), the solid catalyst was removed by filtration, washed with water then EtOAc, and the washings were added to the reaction mixture which was then extracted with EtOAc (3×20 mL). The products were purified as described above for the procedure with *p*-bromoacetophenone.

4.9. General procedure for the Suzuki–Miyaura coupling of aryl(heteroaryl) bromides in water under microwave irradiating conditions

A mixture of the appropriate aryl(heteroaryl) bromide (1 mmol), aryl(heteroaryl) boronic acid (1.2 mmol), TBAB (0.6 mmol), palladium catalyst **9** (0.7 mol%), KOH (2 mmol) and water (3.5 mL) were mixed in a process vial. The vial was capped properly, and thereafter the mixture was heated under microwave irradiating conditions at 160 °C and 250 watt for the appropriate reaction time as listed in Table 2. The products were purified according to the procedure described above for *p*-bromoacetophenone.

4.9.1. 4-Acetyl-1,1′-biphenyl (10). Colorless crystals, mp 119–120 °C (Ref.[33] mp 118–120 °C); ^{1}H NMR ($CDCl_3$) δ 2.64 (s, 3H, CH_3CO), 7.36–7.42 (m, 1H), 7.46–7.49 (m, 2H), 7.62–7.65 (m, 2H), 7.69 (d, 2H, J=8.52 Hz), 8.03 (d, 2H, J=8.52 Hz); ^{13}C NMR δ 27.0, 127.5, 127.6, 128.6, 129.2, 129.3, 136.2, 140.2, 146.1, 198.1; MS (*m/e*) 196 (M^+), 181, 152, 127, 102, 91, 76.

4.9.2. 3,4-Methylenedioxy-4′-acetylbiphenyl (11). Colorless crystal, mp 140–141 °C; ^{1}H NMR ($CDCl_3$) δ 2.62 (s, 3H, CH_3CO), 6.01 (s, 2H, –OCH_2O–), 6.89 (d, 1H, J=8.3 Hz), 7.09–7.13 (m, 2H), 7.59 (d, 2H, J=8.4 Hz), 7.99 (d, 2H, J=8.4 Hz); ^{13}C NMR δ 26.9, 101.7, 107.9, 109.1, 121.4, 127.1, 129.2, 134.4, 135.8, 145.7, 148.2, 148.7, 197.9; MS (*m/e*) 240 (M^+), 225, 197, 167, 139, 112, 98, 69. Anal. Calcd for $C_{15}H_{12}O_3$: C, 74.99; H, 5.03. Found: C, 74.96; H, 4.83.

4.9.3. *p*-(3-Thienyl)acetophenone (12).[34] Colorless crystals, mp 149–150 °C (no mp given in Ref.[34]); ^{1}H NMR ($CDCl_3$) δ 2.62 (s, 3H, CH_3CO), 7.42–7.44 (m, 2H), 7.57–7.58 (m, 1H), 7.68 (d, 2H, J=8.52 Hz), 7.98 (d, 2H, J=8.52 Hz); ^{13}C NMR δ 26.9, 122.4, 126.5, 126.7, 127.1, 129.4, 135.9, 140.5, 141.4, 197.9; MS (*m/e*) 202 (M^+), 187, 159, 115, 93, 79.

4.9.4. 3-Phenylpyridine (13).[35] Colorless oil; ^{1}H NMR ($CDCl_3$) δ 7.33–7.61 (m, 6H), 7.84–7.90 (m, 1H), 8.59 (dd, 1H, J=4.86, 1.62 Hz), 8.85 (d, 1H, J=1.76 Hz); MS (*m/e*) 155 (M^+), 127, 102, 87, 77, 64.

4.9.5. 3-(3,4-Methylenedioxyphenyl)pyridine (14). Pale brown crystals, mp 99–100 °C; ^{1}H NMR ($CDCl_3$) δ 5.99 (s, 2H, –OCH_2O–), 6.89 (d, 1H, J=8.5 Hz), 7.01–7.04 (m, 2H), 7.29–7.32 (dd, 1H, J=7.9, 7.9 Hz), 7.76–7.78 (m, 1H), 8.54 (dd, 1H, J=4.8, 1.5 Hz), 8.77 (d, 1H, J=1.9 Hz); ^{13}C NMR δ 101.6, 107.7, 109.1, 121, 123.7, 132.2, 134.2, 136.6, 148, 148.3, 148.3, 148.6; MS (*m/e*) 198 (M^+), 140, 114, 99, 86, 62. Anal. Calcd for $C_{12}H_9NO_2$: C, 72.35; H, 4.55; N, 7.03. Found: C, 72.20; H, 4.32; N, 6.96.

4.9.6. 3-(3-Thienyl)pyridine (15).[36] Colorless crystals, mp 76–77 °C (Ref.[36] mp 73–74 °C); ^{1}H NMR ($CDCl_3$) δ 7.26–7.32 (m, 1H), 7.37–7.44 (m, 2H), 7.50–7.52 (m, 1H), 7.84 (m, 1H), 8.52 (dd, 1H, J=4.8, 1.72 Hz), 8.86 (d, 1H, J=1.72 Hz); ^{13}C NMR δ 121.7, 123.9, 126.2, 127.3, 131.8, 133.8, 139.1, 147.9, 148.5; MS (*m/e*) 161 (M^+), 134, 117, 108, 81, 63, 45.

4.9.7. 2-Chloro-5-phenylpyridine (16).[37] Colorless crystals, mp 54–55 °C (Ref.[37] mp 55–56 °C); ^{1}H NMR ($CDCl_3$) δ 7.37–7.58 (m, 6H), 7.81–7.87 (dd, 1H, J=8.26, 2.52 Hz), 8.61 (d, 1H, J=2 Hz); MS (*m/e*) 189 (M^+), 154, 127, 102, 95, 63, 51.

4.9.8. 2-Chloro-5-(3,4-methylenedioxyphenyl)pyridine (17). Pale yellow powder, mp 150–151 °C; ^{1}H NMR ($CDCl_3$) δ 6.02 (s, 2H, –OCH_2O–), 6.90 (d, 1H, J=8.6 Hz), 6.99–7.02 (m, 2H), 7.35 (d, 1H, J=8.3 Hz), 7.75 (dd, 1H, J=8.3, 2.5 Hz), 8.52 (d, 1H, J=2.4 Hz); ^{13}C NMR δ 101.8, 107.7, 109.3, 121.1, 124.4, 130.9, 135.7, 137.2, 148, 148.4, 148.9, 150.2; MS (*m/e*) 233 (M^+), 140, 113, 99, 85. Anal. Calcd for $C_{12}H_8ClNO_2$: C, 61.69; H, 3.45; N, 5.99. Found: C, 61.62; H, 3.32; N, 5.97.

4.9.9. 2-Chloro-5-(3-thienyl)pyridine (18). Colorless crystals, mp 95–96 °C; ^{1}H NMR ($CDCl_3$) δ 7.33–7.35 (m, 2H), 7.44–7.46 (m, 1H), 7.50–7.51 (m, 1H), 7.81 (dd, 1H, J=8.3, 2.6 Hz), 8.61 (d, 1H, J=2 Hz); ^{13}C NMR δ 122.1, 124.6, 126, 127.6, 130.8, 136.6, 137.7, 147.6, 150.1; MS (*m/e*) 195 (M^+), 160, 133, 116, 89, 63. HRMS, calcd for C_9H_6ClNS: 195.9988. Found: 195.9981. Anal. Calcd for C_9H_6ClNS: C, 55.24; H, 3.09; N, 7.16. Found: C, 55.81; H, 3.19; N, 6.99.

4.9.10. 2-Phenylpyrimidine (19).[38] Pale yellow oil (Ref.[38] mp 36–38 °C); ^{1}H NMR ($CDCl_3$) δ 7.18 (dd, 1H, J=4.88, 4.76 Hz), 7.44–7.51 (m, 3H), 8.42–8.48 (m, 2H), 8.81 (d, 2H, J=4.78 Hz); MS (*m/e*) 156 (M^+), 128, 103, 76, 51.

4.9.11. 2-(3-Thienyl)pyrimidine (21).[39] Pale yellow powder, mp 95–97 °C (Ref.[39] mp 95 °C); ^{1}H NMR ($CDCl_3$) δ 7.12 (dd, 1H, J=4.90, 4.76 Hz), 7.36–7.41 (dd, 1H, J=5.02, 1.12 Hz), 7.28–7.30 (dd, 1H, J=3.02,

1.12 Hz), 8.74 (d, 1H, J=4.90 Hz); MS (*m/e*) 162 (M^+), 135, 109, 81, 45.

4.9.12. 3-Phenylquinoline (22).[40] Pale yellow powder, mp 49–50 °C (Ref.[40] mp 52 °C); ^{1}H NMR ($CDCl_3$) δ 7.36–7.56 (m, 4H), 7.64–7.73 (m, 3H), 7.80 (d, 1H, J=8.4 Hz), 8.15 (d, 1H, J=8.4 Hz), 8.22 (d, 1H, J=1.88 Hz), 9.18 (d, 1H, J=2.28 Hz); MS (*m/e*) 205 (M^+), 176, 151, 126, 102, 88, 76, 63.

4.9.13. 3-(3,4-Methylenedioxyphenyl)quinoline (23). Pale yellow powder, mp 110–111 °C; ^{1}H NMR ($CDCl_3$) δ 6.02 (s, 2H, –OCH_2O–), 6.94 (d, 1H, J=8.5 Hz), 7.13–7.19 (m, 2H), 7.51–7.59 (m, 1H), 7.65–7.73 (m, 1H), 7.81 (d, 1H, J=7.7 Hz), 8.12 (d, 1H, J=8.3 Hz), 8.18 (d, 1H, J=2 Hz), 9.11 (d, 1H, J=2.2 Hz); ^{13}C NMR δ 101.7, 108, 109.3, 121.4, 127.3, 128.2, 128.3, 129.4, 129.5, 132.2, 133, 133.8, 147.3, 148.1, 148.8, 150; MS (*m/e*) 249 (M^+), 190, 163, 124, 110, 96, 81, 62. Anal. Calcd for $C_{16}H_{11}NO_2$: C, 77.10; H, 4.45; N, 5.62. Found: C, 77.00; H, 4.23; N, 5.54.

4.9.14. 3-(3-Thienyl)quinoline (24).[41] Pale yellow powder; mp 88–89 °C (Ref.[41] mp 86–88 °C); ^{1}H NMR ($CDCl_3$) δ 7.45–7.58 (m, 3H), 7.63–7.74 (m, 2H), 7.81–7.86 (dd, 1H, J=8.14, 1.12 Hz), 8.12 (d, 1H, J=8.24 Hz), 8.27 (d, 1H, J=2 Hz), 9.20 (d, 1H, J=2 Hz); ^{13}C NMR δ 121.9, 126.4, 127.4, 128.2, 128.4, 129.1, 129.5, 129.6, 132.4, 139.1, 147.4, 149.7; MS (*m/e*) 211 (M^+), 179, 167, 139, 105, 92, 79.

4.9.15. 4-Phenylisoquinoline (25).[42] Light yellow oil; (Ref[42] mp 76–78 °C); ^{1}H NMR ($CDCl_3$) δ 7.37–7.62 (m, 7H), 7.86–7.99 (m, 2H), 8.48 (s, 1H), 9.23 (s, 1H); MS (*m/e*) 205 (M^+), 176, 151, 102, 88, 76.

4.9.16. 4-(3,4-Methylenedioxyphenyl)isoquinoline (26). Yellow-brownish powder, mp 157–158 °C; ^{1}H NMR ($CDCl_3$) δ 6.04 (s, 2H, –OCH_2O–), 6.95–6.98 (m, 3H), 7.58–7.68 (m, 2H), 7.94 (d, 1H, J=8.5 Hz), 8.01 (d, 1H, J=8.5 Hz), 8.46 (s, 1H), 9.23 (s, 1H); ^{13}C NMR δ 101.5, 108.8, 110.7, 123.9, 125, 127.4, 128.1, 128.7, 130.8, 130.9, 133.2, 134.6, 143, 147.8, 148.1, 152; MS (*m/e*) 249 (M^+), 190, 163, 110, 96, 82, 63. HRMS, calcd for $C_{16}H_{11}NO_2$: 250.0868. Found: 250.0857. Anal. Calcd for $C_{16}H_{11}NO_2$: C, 77.10; H, 4.45; N, 5.62. Found: C, 76.61; H, 4.16; N, 5.51.

4.9.17. 4-(3-Thienyl)isoquinoline (27).[43] Yellow oil (Ref.[43] mp 198–200 °C); ^{1}H NMR ($CDCl_3$) δ 7.31 (dd, 1H, J=4.88, 1.36 Hz), 7.44–7.50 (m, 2H), 7.58–7.69 (m, 2H), 8.01 (dd, 1H, J=7.76, 7.64 Hz), 8.54 (s, 1H), 9.22 (s, 1H); ^{13}C NMR δ 124.6, 124.9, 126.3, 127.5, 128.2, 128.5, 128.7, 129.4, 130.9, 134.5, 137.6, 143.0, 152.2; MS (*m/e*) 211 (M^+), 184, 166, 152, 139, 105, 91, 83.

4.9.18. 2-Phenylthiophene (31).[44] Colorless powder, mp 33–34 °C (Ref.[44] mp 35 °C); ^{1}H NMR ($CDCl_3$) δ 7.08 (dd, 1H, J=5.14, 5.02 Hz), 7.26–7.42 (m, 5H), 7.58–7.64 (m, 2H); MS (*m/e*) 160 (M^+), 134, 115, 102, 89, 63, 45.

4.9.19. 2-(3,4-Methylenedioxyphenyl)thiophene (32). Pale green powder, mp 58–59 °C; ^{1}H NMR ($CDCl_3$) δ 5.94 (s, 2H, –OCH_2O–), 6.79 (d, 1H, J=8.5 Hz), 7.01 (m, 1H), 7.07 (m, 2H), 7.14 (d, 1H, J=3.9 Hz), 7.18 (d, 1H, J=5 Hz); ^{13}C NMR δ 101.5, 106.9, 108.9, 120, 122.8, 124.3, 128.2, 129.1, 144.6, 147.4, 148.4; MS (*m/e*) 204 (M^+), 145, 102, 87, 63. Anal. Calcd for $C_{11}H_8O_2S$: C, 64.69; H, 3.95. Found: C, 64.67; H, 3.84.

4.9.20. 2,3′-Bithienyl (33).[45] Brown crystals, mp 64–66 °C (Ref.[45] mp 62–64 °C); ^{1}H NMR ($CDCl_3$) δ 7.02 (dd, 1H, J=4.38, 4.26 Hz), 7.17 (s, 1H), 7.18–7.20 (m, 1H), 7.29–7.31 (m, 2H), 7.34–7.37 (m, 1H); MS (*m/e*) 166 (M^+), 134, 121, 108, 90, 69, 45.

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Polymer-bound aluminium salen complex as reusable catalysts for CO_2 insertion into epoxides

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Abstract—Two polymeric aluminium salen complexes in where the backbones are either a partially crosslinked polystyrene [(Al(salen)/PS)] or poly(ethylene glycol bismethacrylate) [(Al(salen)/PEA)] have been synthesised and used for the carbon dioxide insertion into epoxides to form cyclic carbonates. The catalytic activity of these polymers is similar to that of the unsupported aluminium salen complexes, and the polymeric catalysts can be easily separated from the reaction mixture and reusable in consecutives runs. The activity and reusability of the polymeric salen complex depends on the nature of the polymer: PEA being a polymer with a high oxygen content in the backbone enhances the initial activity as compared to PS, but Al(salen)/PEA exhibits lower stability as compared to Al(salen)/PS and a Al depletion occurs upon use. The presence of nucleophiles such as *N*-methylimidazole or *N*,*N*-dimethylaminopyridine in excess increases the catalytic activity of the polymeric Al(salen) catalyst. Also polymeric nucleophiles have been found to be suitable reusable co-catalysts for this reaction.

1. Introduction

The increase in the atmospheric concentration of carbon dioxide is playing a negative effect in the climatic change due to the green house effect and there are many international programs aimed at balancing CO_2 emission and absorption.[1–10] The availability of CO_2 and the interest in using it as feedstock has motivated a large effort in developing industrial processes based on the use of CO_2 as C_1 raw material.[11–20] Among the possible processes to use CO_2 as reagent, the synthesis of carbonates and polycarbonates is very appealing, due to the properties of dialkyl carbonates as solvents and also as synthetic intermediates for urethanes, ureas and isocyanates.[20–28] On the other hand, polycarbonates have excellent properties as engineering plastics.[29,30] For this reason the report by Nguyen that chromium salen complex is a suitable catalysts for the CO_2 insertion into epoxides to form cyclic carbonates has constituted a significant breakthrough in this area.[31] The main reason for this is the ease of the synthesis of metal salen catalysts and that their use does not require especial precautions to avoid the presence of moisture and oxygen. Later other reports have also described the catalytic activity of other metal salen complexes and porphyrins.[31–39]

A general trend in catalysis is to transform a successful homogeneous catalytic process into a heterogeneous one.[40,41] Heterogeneous catalysts can be easily separated from the reaction products and reused in successive runs, provided that they do not become deactivated in the reaction. Also, heterogeneous catalysis is more suitable for continuous flow operation that is more appropriated than batchwise processes for large scale industrial synthesis. On the other hand, from the green chemistry point of view the use of a non-recoverable catalyst, particularly considering the toxicity of some transition metals such as chromium, must be avoided. Recently, we have reported the catalytic activity of chromium salen complexes anchored on silicas as solid catalyst for the CO_2 insertion into epoxides.[42] However, given the negative environmental impact of chromium metal, and in order to improve the 'greenness' of the metal Schiff base complex catalysts for the carbon dioxide fixation process, we wanted to replace chromium by aluminium as the Lewis metal atom of the complex. Precedents in the chemical literature have already shown that some aluminium complexes are also active for carbon dioxide insertion.[43–46] As a continuation of this research

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line, herein we describe the synthesis and catalytic activity of aluminium salen complexes covalently attached to two different polymeric backbones. We have found that these polymeric catalysts are also active to effect the CO_2 coupling to epoxides, and that the nature of polymer skeleton plays a remarkable effect in the control of the catalytic activity of the complex.

Suitable polymer-bound catalyst can be recovered and reused for several runs. In addition, to make the process completely clean, we have used recoverable polymeric nucleophile co-catalysts instead of dissolved nucleophilic molecules. Compared to other strategies in where the substrates or reagents are supported on a polymer, the approach of supporting catalyst has several advantages including: (i) the fact that no high loadings on the polymeric support are required; (ii) the amplification effect since few supported catalytic sites can effect the transformation of considerable amounts of substrate; (iii) and the higher added-value of catalysts as compared to substrates that makes advisable their recovery and reuse.

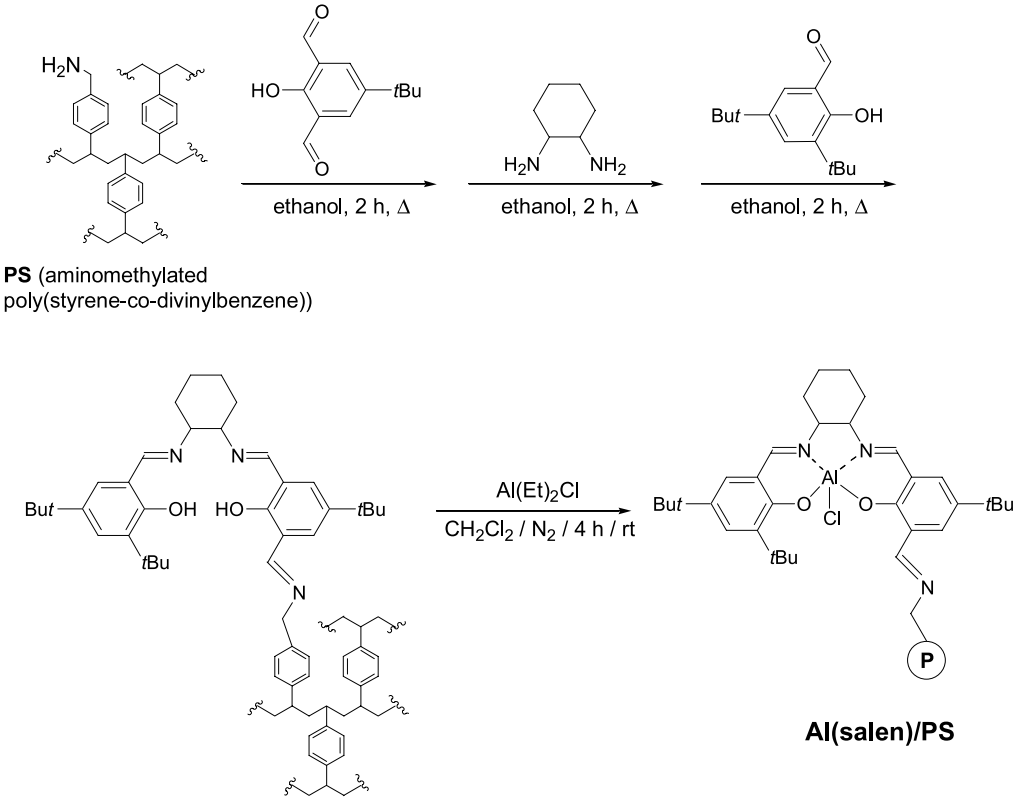
2. Results and discussion

2.1. Polymeric catalyst preparation

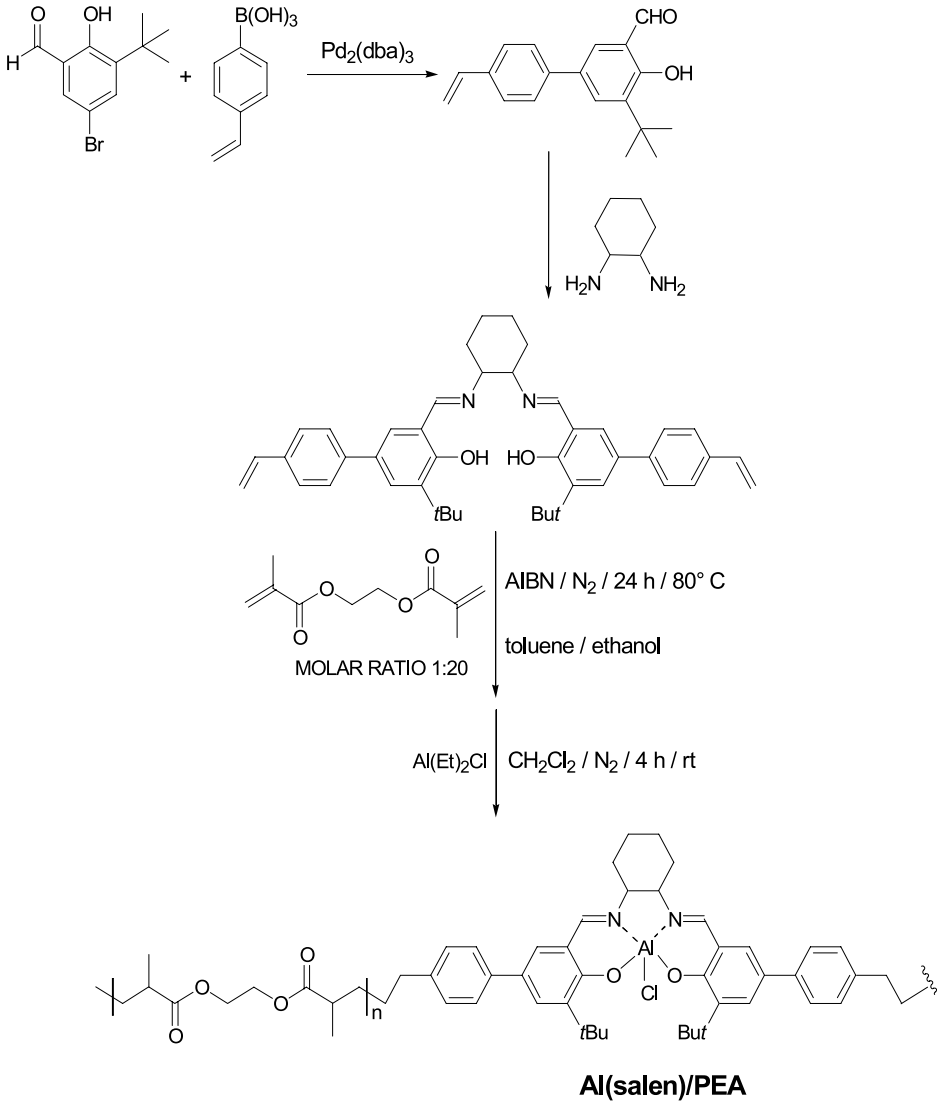
For the present work we have prepared two different polymers containing covalently anchored Al(salen) complex. One of them in where the polymer backbone was a partially crosslinked poly(styrene-*co*-*p*-divinylbenzene) having some pendant amino methyl groups. These lateral groups were used to construct a salen ligand covalently attached to the polystyrene polymer. The polymer-bound ligand was obtained in three steps from 2,6-diformil-4-*tert*-butylphenol. The last step was metal complexation by reacting diethylaluminium chloride with the polymer-bound ligand under inert atmosphere in the absence of humidity. In this way, Al(salen) complex was attached to the polymer backbone through imino groups. Scheme 1 shows the route followed to prepare the 6-methimine substituted Al(salen) complex bonded to polystyrene.

Working with CO_2 one important parameter to favour its reactivity is to use a medium that is able to dissolve a sufficiently high concentration of CO_2. Thus, we anticipated based on previous literature reports that the affinity for CO_2 of polystyrene-derived polymers may be hot as high as desirable, and therefore, the CO_2 insertion reaction should occur mostly on the interface between the solid polymeric catalyst and the fluid phase.[47–50] In this context we wanted to compare the activity of polystyrene anchored Al(salen) complexes with that of an analogous Al(salen) complex anchored on a different backbone that could show different affinity for CO_2. In this regard it is known that polymers containing ethylene dioxy groups can be suitable to dissolve significantly high CO_2 concentrations due to a high oxygen density in the polymer backbone.[51–56]

Aimed at the purpose of having an Al(salen) complex anchored on a polymer with ethylenedioxy units, we designed a synthetic strategy completely different to that shown in Scheme 1. For having a polymer containing ethylendioxy units our approach was not to use a preformed



Scheme 1. Synthetic route for the preparation of Al(salen)/PS.



Scheme 2. Synthetic route for the preparation of Al(salen)/PEA.

polymer, but to perform a copolymerization with a salen ligand containing reactive styryl units. Thus, in this case, the key salen derivative is one containing *p*-styryl units in peripheral positions of the salen ligand. The corresponding compound was obtained from 4-styryl-6-*tert*-butylsalicylaldehyde synthesised through a Pd catalyzed Suzuki cross coupling between *p*-styrylboronic acid and the *para* brominated salen ligand, as it has been reported previously.[57] With the *p*-styryl substituted salen ligand we proceeded to perform a copolymerisation with ethylene bismethacrylate using AIBN as radical initiator and an inert atmosphere. The actual synthetic route is illustrated in Scheme 2. The last step in the synthesis was again the formation of the aluminium complex by reacting in dichloromethane an organometallic diethylaluminium chloride as metal source compound. All the synthetic intermediates required in the synthesis indicated in Scheme 2 were characterized by analytical and spectroscopic methods.

Polymers Al(salen)/PS and Al(salen)/PEA were characterizated by analytical and spectroscopic techniques. The aluminium content of Al(salen)/PS and Al(salen)/PEA were 1.26 and 0.42 mmol$\times$g^{-1}, respectively. IR spectra of the polymers were in agreement with the simultaneous presence of Al(salen) complex and the organic polymer. Figure 1 shows the IR spectra of Al(salen)/PS and Al(salen)/PEA polymers.

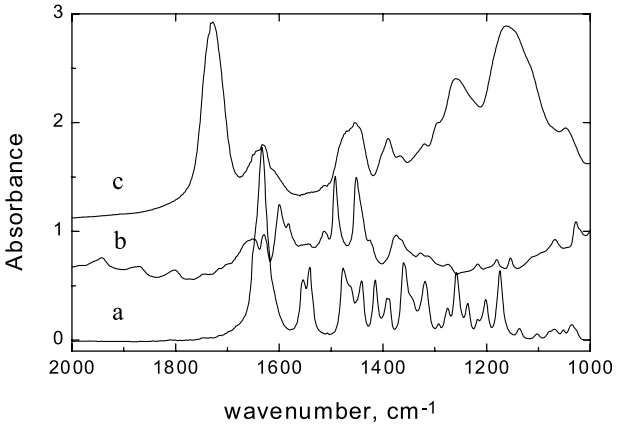
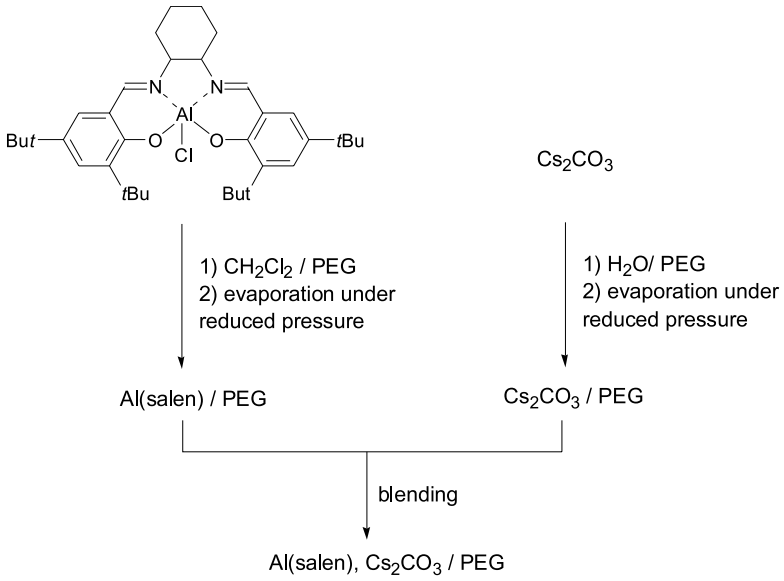


Figure 1. IR spectra of Al(salen) (a); Al(salen)/PS (b); Al(salen)/PEA (c) recorded at room temperature in KBr disks.



Scheme 3. Procedure for the preparation of a PEG solid phase containing Al(salen) and cesium carbonate.

Finally, we included in our study a different recoverable catalytic system consisting in a CO_2-phylic PEG polymer containing dissolved the Al(salen) complex and Cs_2CO_3 as base (Scheme 3). Since PEG (average MW 6000 Da) is a solid at room temperature, but melted at 40 °C, we have taken advantage of it and dissolved the Al(salen) and Cs_2CO_3 on melt PEG. After dissolving in PEG Al(salen) and Cs_2CO_3 remain on the PEG phase during the recovery of the reaction products.

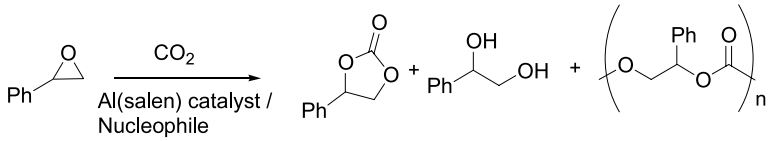
2.2. Catalytic activity

As a model reaction to test the catalytic activity of the two polymeric Al(salen) complexes, we selected the CO_2 insertion into styrene oxide (Scheme 4). The series of reactions were carried out in a mechanically stirred autoclave working in supercritical CO_2 at 80 °C and 100 bar (CO_2 critical point: $T_c=31$ °C; $P_c=74$ bar). Through the series of reactions we varied the amount of nucleophile co-catalyst to determine the optimum Al(salen)/nucleophile molar ratio. It has been demonstrated that the presence of *N*-methylimidazole and other bases in adequate metal-to-base molar ratios can enhance considerably the catalytic activity, the presence of base playing a detrimental effect if a large excess is used.[35,37] For the sake of comparison we have included also in our study a non-polymeric Al(salen) complex. The list of reactions performed and the results obtained are summarized in Table 1.

Some preliminary experiments were carried out using lesser amounts of styrene oxide (400 mg) but these experiments were flawed by the poor recovery of the reaction mixture upon reactor discharge. Working under supercritical conditions in a 125 mL autoclave with 4 g of styrene oxide the mass balances of the reaction were almost complete (see Table 1). In addition, we purposely stopped the reactions at low conversion in order to obtain a valid information of the relative catalytic activity of the different polymer-supported aluminium complexes catalysts. It is obvious that at sufficiently long times for which complete conversions are achieved, the information about the distinctive performance and activity of the catalyst will be lost.

The reaction mixtures were analysed by GC and IR, and the amount of cyclic carbonate quantified by GC using the external standard method. In most of the experiments, the only product observed was the corresponding five member ring cyclic carbonate, but in some cases the corresponding glycol and polycarbonate were also observed (Scheme 4). Phenyl ethylene glycol comes from the hydrolytic epoxide aperture catalyzed by acids.

In the literature it has been shown that epoxides of cycloalkenes give exclusively or predominantly polycarbonates while epoxides of acyclic alkenes lead predominantly cyclic carbonates.[38] Therefore, in our case we expected to obtain mostly the cyclic carbonate. Nevertheless, we assessed in each reaction mixture the presence or absence of polycarbonate by IR spectroscopy. While pentacyclic carbonate exhibits a carbonyl stretching vibration band 1820 cm^{-1}, the corresponding carbonyl in the polymeric carbonate band appears at 1750 cm^{-1}. Figure 2 shows two



Scheme 4. Reaction products observed for the catalytic CO_2 coupling with styrene oxide.

Table 1. Results obtained at 6 h reaction time for the CO_2 insertion into styrene oxide (4 mL) catalyzed by Al(salen) complexes and nucleophile (3.6% mol) at 80 °C and 100 bar in a mechanically stirred (300 rpm) autoclave (125 mL)

Run	Catalyst [catalyst-to-substrate mol %]	Mass balance (%)	Conversion[a] (%)	Yield (%)	TON
1	Al(salen) [0.1]	91	19	17	59
2	Al(salen)[b] [0.1]	100	20	17	59
3	Al(salen)[c][0.1]	98	4	3	10
4	Al(salen)[d] [0.1]	97	4	3	10
5	Al(salen)/PEA (use 1) [0.14]	87	22	19	47
6	Al(salen)/PEA (use 2) [0.14]	95	9	6	15
7	Al(salen)/PEA (use 3) [0.14]	92	9	6	15
8	Al(salen)/PEA[e] [0.14]	98	8	8	20
9	Al(salen)/PEA[f] [2]	95	89	78	39
10	Al(salen)/PS (use 1) [0.44]	100	9	9	7
11	Al(salen)/PS (use 3) [0.44]	97	9	9	7
12	[PEG-Al-$CsCO_3$][g] [0.1]	86[f]	15	11	38

[a] Based on the disappearance of styrene.
[b] Dimethylaminopyridine was used instead of *N*-methylimidazole.
[c] $P=20$ bar.
[d] 2 equiv of *N*-methylimidazole
[e] Dimethylaminopyridine polymer-bound was used as co-catalyst.
[f] Reaction time 15 h.
[g] 1% of polymer it was observed as by-product.

representative IR spectra of the reaction mixture to illustrate how the presence or absence of polycarbonate can be determined by this technique.

Before performing experiments with polymeric salen catalyst, we carried out a preliminary study on the activity of Al(salen) complex not covalently bonded to any support (0.1% mol) varying the excess of *N*-methylimidazole as co-catalyst. The results are contained in Table 1 and it can be seen that the presence of bases in a large excess plays a large beneficial influence on the conversion. When no supercritical conditions were used (Table 1, entry 3) the conversion reached was considerably lower. The positive influence of the supercritical conditions can be interpreted considering that when no supercritical conditions are used, there should be two phases, one of them being liquid styrene oxide saturated in CO_2, but most of the CO_2 being in a separate gas phase. In contrast under supercritical conditions a single phase should be ideally present inside the reactor in where supercritical CO_2 dissolves styrene oxide. The ability of supercritical CO_2 to mix with hydrocarbons is well known and used as a tool to control some properties of supercritical CO_2 phase.[58–60]

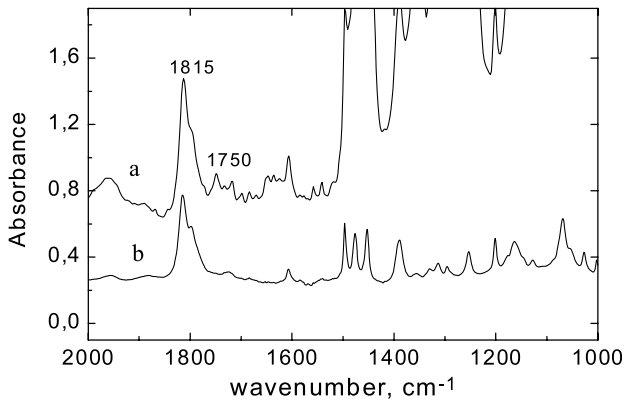


Figure 2. IR spectra of two reaction mixtures obtained after the treatment of styrene epoxide (35 mmol) with CO_2 in autoclave (125 mL) at 80 °C and 100 bar using Al(salen)/PEA (a) or Al(salen)/PS (b) as catalysts. The peaks at 1750 cm^{-1} indicates the presence of polycarbonate, while the peak at 1815 cm^{-1} corresponds to cyclic carbonate.

With the aim of having a reusable and recoverable polymeric catalyst we proceeded to perform the same reaction under supercritical CO_2 conditions using Al(salen)/PS and Al(salen)/PEA solids. The results are also contained in Table 1.

Noteworthy was that the initial activity of fresh Al(salen)/PEA was significantly higher than that of the analogous Al(salen)/PS, although the turnover number for unsupported Al(salen) was still higher than those obtained using polymeric Al(salen)/PEA. These results can be easily interpreted considering that the PEA backbone exhibits a high oxygen density, in contrast to the PS skeleton that is only a hydrocarbon. Also noteworthy was that the higher activity of Al(salen)/PEA results in a somewhat lower selectivity towards the cyclic carbonate since some polycarbonate is formed in this case. The polymeric carbonate becomes deposited on the catalyst. The presence of polycarbonate on Al(salen)/PEA results in a change of the texture of the initially soft and sticky Al(salen)/PEA powder that becomes much harder. The presence of polycarbonate can be spectroscopically determined by observing in the IR spectrum of the used Al(salen)/PEA catalyst the presence of a band 1750 cm^{-1} corresponding to the stretching vibration to the carbonate group to the polymer (see Fig. 2). Also, optical microscopy (Fig. 3) reveals a variation on the Al(salen)/PEA particle morphology with different size and optical properties that those the fresh Al(salen)/PEA catalyst. In contrast to the behaviour of Al(salen)/PEA, Al(salen)/PS does no form detectable amounts of polycarbonate as evidenced by IR spectroscopy (absence of 1750 cm^{-1} peak, see Fig. 2). However, optical microscopy reveals that the initial spherical shape of the PS beads also disappears upon catalyst use (Fig. 4). Although polymer attrition can not be disregarded, the mild mechanical stirring used to perform the reactions makes more probable that changes in the polymer morphology are due to the influence of the reaction and interaction with CO_2.

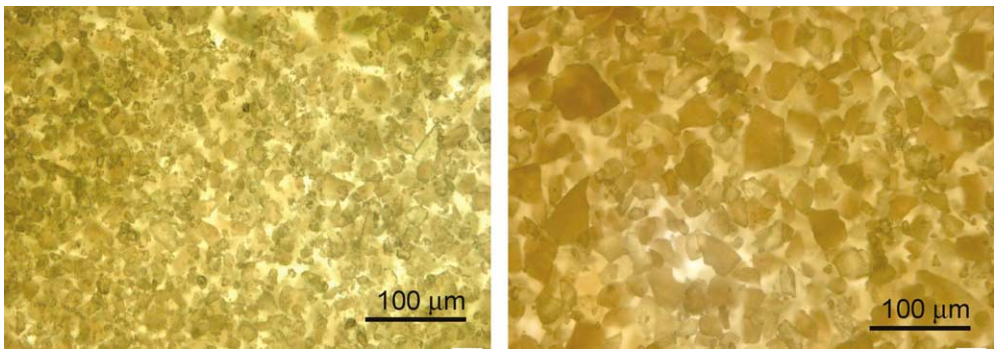


Figure 3. Optical microscopy of Al(salen)/PEA powder before (left) and after(right) being used as catalyst for the CO_2 insertion into styrene oxide. Particle size and texture of Al(salen)/PEA changes upon its use as catalyst.

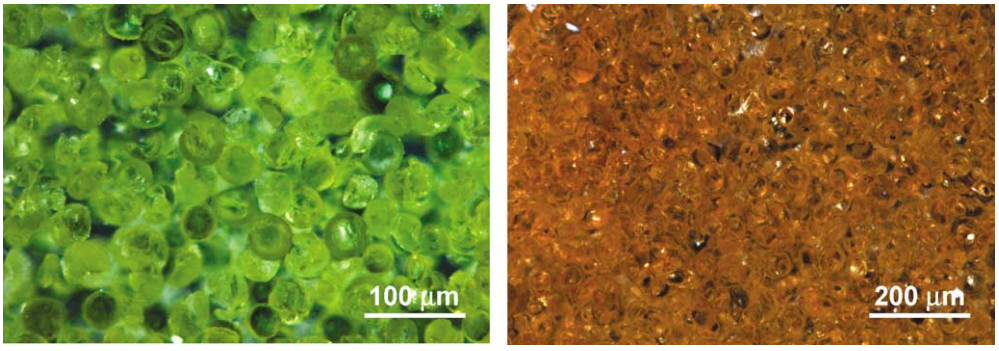
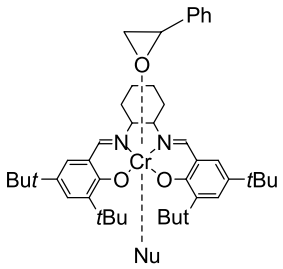


Figure 4. Optical microscopy of Al(salen)/PS powder before (left) and after (right) being used as catalyst for the CO_2 insertion into styrene oxide. The typical spherical shape of the Al(salen)/PS beads disappears upon catalyst use.

Concerning the reaction conversion, when higher amounts of Al(salen)/PEA catalyst is present and the reaction time is longer (Table 1, entry 9), then, obviously the yield of the cyclic carbonate increases, although the turnover number decreases somewhat with respect to those experiments using higher substrate-to catalyst molar ratio.

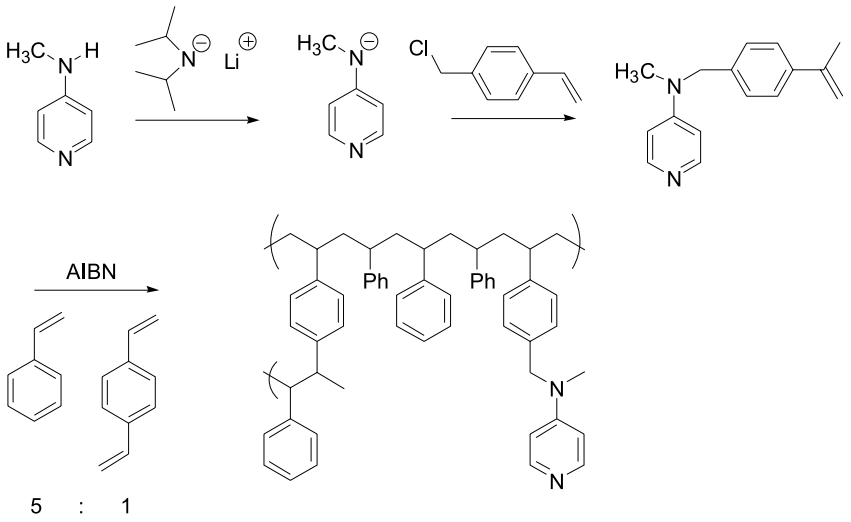
According to the proposed reaction mechanism for the *N*-methylimidazole enhancement of the catalytic activity of Cr(salen) complexes for the CO_2 insertion into epoxides,[35–37,61] the key intermediate consists in a distorted octahedrally coordinated chromium ion interacting at the apical positions with the nucleophile and the epoxide. In other words, the role of *N*-methylimidazole has been proposed to be the softening of the chromium-epoxide interaction by *N*-methylimidazole coordination to the chromium (Scheme 5). If this were so, in our case using polymer-bound Al(salen) complexes, addition of the supported base co-catalyst should inhibit dramatically its co-catalyst role by impeding the interaction between the polymer bound nucleophile and the polymer bound metal salen complex that will be in different solid phases. According to this, the expected yield of the CO_2 coupling using a mixture of polymeric Al(salen) and polymeric nucleophile should be much lower, since the promoting effect the nucleophile will be lost.



Scheme 5. Proposed structure of activated epoxide in where the nucleophile co-catalyst is simultaneously bonded to the epoxide-chromium(salen) intermediate.

However, as it can be seen in Table 1, this was not exactly the case and a mixture of polymeric dimethylaminopyridine and polymeric aluminium salen complex gives also rise to the formation of cyclic carbonate with only half the turnover activity than those obtained using molecular nucleophiles (compare entries 5 and 8). Polymeric dialkylaminopyridine (see structure and preparation procedure in Scheme 6) was prepared as previously reported in the literature.[62] A blank control in where the same experiment using Al(salen)/PEA as catalyst was used in the absence of any nucleophile (either molecular or polymeric) under the same conditions gave essentially no epoxide conversion.

This result using polymeric dialkylaminopyridine seems to indicate that the reaction mechanism should be probably revisited to take in consideration that the formation of a single species between the nucleophile and the metal complex as shown in Scheme 5 may not be absolutely necessary. From the practical point of view, the use of both



Scheme 6. Route for the preparation of the polystyrene containing pendant dialkylaminopyridine units.

polymeric nucleophile and polymeric metal complex has even more advantages in terms complete reusability of the catalytic system and avoidance of waste.

A different reusable system that was also tested for this reaction was a mixture of Al(salen) and Cs_2CO_3 dissolved in polyethyleneglycol (PEG) (Table 1, entry 12). PEG (av. MW 600 Da) becomes liquid at about 40 °C and is a suitable solvent for CO_2 reactions due to the high CO_2 solubility in PEG. After the reaction and upon cooling, the mixture becomes solid and the catalyst and base remains in the solid PEG phase, while the cyclic carbonate can be extracted with diethyl ether or methanol. Cs_2CO_3 is a suitable base in PEG media since large alkali metal ions become solvated through interaction with ethylendioxy oxygens, increasing the solubility and boosting the nucleophilic strength of the base. As it can be seen in the Table 1, also this system based with PEG in where there is no covalent linkage between the polymer acting as solvent and the complex could be of interest for performing the CO_2 insertion into epoxides, while still permitting reusability of the metal complex and nucleophile.

In fact, reusability of polymeric catalyst was performed by simple filtration of the solid from the reaction mixture and washing it with dimethylcarbonate and ethanol. After drying, the solids were used as catalysts for a new batch under the same conditions. The results obtained are also shown in Table 1 (entries 6, 7 and 11). It can be seen there that while the activity of fresh Al(salen)/PS is lower than that of Al(salen)/PEA, upon reuse the activity of Al(salen)/PS remains as in the first use. In contrast, the activity of Al(salen)/PEA undergoes a significant decrease between the first and second runs, although then the activity is maintained going from the second to the third use and is still higher than that of Al(salen)/PS. These results can be interpreted considering that miscibility CO_2 in the polymeric PEA skeleton is high, this leading to partial depletion of the Al(salen) complex, most probably by extracting the aluminium cation producing the leaching of Al from the polymer to the liquid phase. In support of this, IR spectroscopy reveals that the characteristic Al(salen) complex IR bands at 1640 cm^{-1} is significantly dismin-ished after the first use of the polymeric Al(salen)/PEA catalyst.

3. Conclusions

Aluminium salen complex anchored to polymeric backbones is an active catalyst for the CO_2 insertion into epoxide. However, as anticipated, polymeric catalysts exhibit somewhat lower turnover numbers than that of the non-polymeric complex. The activity of fresh polymeric catalyst depends on the composition of the backbone and its affinity for CO_2. PEA is more suitable in this regard than partially crosslinked PS. However, stability and reusability on the catalyst also depends on the nature of the polymer and from this point of view Al(salen) bonded to PS appears as a more stable catalyst than when bonded to PEA, in where a susbtancial diminution in the number of Al(salen) complexes is observed after the first use. The use of PEG as co-solvent and cesium carbonate as a base is also an interesting medium that permits the reusability of the system. Finally also the base can be anchored in a polymeric skeleton without producing a detrimental effect of the catalytic activity of the system. This is in contrast of could have been expected in view of the accepted reaction mechanism and the role of nucleophiles as catalyst promoter. Given the interest of this reaction and the possibility to perform enantioselective CO_2 insertions, current work is aimed at expanding the process using other epoxides as starting materials and to determine the enantiomeric excess achieved for asymmetric epoxides.

4. Experimental

4.1. General

IR spectra of polymer bound Al(salen) were recorded on a Nicolet 710 FT-IR spectophotometer using KBr disks. The polymer (10 mg) was mixed in a mortar with dry KBr (20 mg) and the mixture pressed at 1 ton$\times cm^{-2}$ for 2 min.

Optical microscopy of the polymeric catalysts were obtained with a Leica DFC 300FX microscope placing the powder between slides. Images were saved and manipulated using IMSO program package.

4.2. Preparation of Al(salen)/PS catalyst

2,6-Diformyl-4-*tert*-butylphenol was prepared from 4-*tert*-butylphenol as reported in the literature.[63] Al(salen)/PS was prepared using as support (0.6 g) of commercial aminomethylated poly(styrene-*co*-divinylbenzene) (2% wt of divinylbenzene) that was added to a solution of 2,6-diformyl-4-*tert*-butylphenol (216 mg, 1.05 mmol) in ethanol (10 mL). Polystyrene *co*-DVD (2%) aminomethylated (1.6 mmol N/g) was purchased from Aldrich.

The mixture of polystyrene and dialdehyde was magnetically stirred for 2 h at reflux temperature. The solid was removed by filtration, Soxhlet extracted with dichloromethane for 24 h and dried under vacuum. In the second step, the previous functionalised solid and (*R*,*R*)-1,2-diaminocyclohexane (120 mg, 1.05 mmol) were added to ethanol (10 mL), stirred magnetically while refluxing for 2 h. The solid was filtered, Soxhlet extracted with dichloromethane for 24 h, and dried under vacuum. The solid obtained in the previous step having cyclohexadiamine units was added to a solution of 3,5-*tert*-butylsalicylaldehyde (246 mg, 1.05 mmol) in ethanol (10 mL), and the mixture stirred at reflux temperature. After 2 h, the solid was removed by filtration, Soxhlet extracted with dichloromethane for 24 h and dried under vacuum. The synthesis of Al(salen)/PS was accomplished at room temperature under nitrogen atmosphere, charging in a flamed flask Al(salen)/PS and dry dichloromethane (10 mL). Diethyl aluminium chloride (1 mL, 1.8 mmol, 1.8 M solution in toluene) was added slowly to the stirred solution. After 4 h, the solid was removed by filtration, Soxhlet extracted with dichloromethane for 24 h and dried under vacuum. The content of aluminium was 1.26 mmol Al/g as determined by absorption spectroscopy corresponding to 77% of the maximum polymer loading according to the density of aminomethyl groups in PS.

4.3. Preparation of Al(salen)/PEA catalyst

Divinyl salen ligand was prepared as reported by Seebach and co-workers.[57] A mixture of divinyl salen ligand (0.70 g, 1.10 mmol) and ethylene glycol bis(methacrylate) (2.07 mL, 10.96 mmol) was dissolved in toluene (7 mL) and ethanol (3 mL). The polymerisation mixture was bubbled with nitrogen for 30 min. 2,2′-Azobisisobutyronitrile (25 mg) was added, and the mixture was heated at 80 °C for 24 h in nitrogen atmosphere. The polymer (Alsalen/PEA) was removed by filtration, Soxhlet extracted with dichloromethane for 24 h and dried under vacuum.

A flamed flask was charged with salen/PEA (1.2 g) and dry dichloromethane (12 mL) and the solution purged with nitrogen atmosphere at room temperature for 1 h. Then, 300 μL of diethyl aluminium chloride (1.8 M solution in toluene, 0.52 mmol) was added slowly to the stirred solution. After 4 h, the solid was removed by filtration, Soxhlet extracted with dichloromethane for 24 h and dried under vacuum. The content of aluminium was determined by absorption spectroscopy (0.42 mmol Al/g) corresponding to about 95% of the maximum loading capacity according to the ligand and the N content (0.88 mmol/g).

4.4. Preparation of [PEG-Al-CsO_3]

PEG (250 mg) and Cs_2CO_3 (41 mg) were dissolved in water (2 mL) and stirred for 15 min. After this time, the water is removed under vacuum. Independently, PEG (250 mg) and Al(salen) complex (2.6 mg) were dissolved in dichloromethane (2 mL), and the dichloromethane is removed under vacuum. The two PEG solids, one containing the base and the other Al(salen) complex, were mixed mechanically and melted at 40 °C. The resulting solid was dried under vacuum for 6 h.

4.5. Preparation of DMAP-polymer

4-[*N*-methyl-*N*-(*p*-vinylbenzyl)amino]pyridine was prepared starting from 4-(methylamino)pyridine sodium salt and *p*-(chloromethyl)styrene. This *N*,*N*-dialkylaminopyridine derivative was copolymerised with styrene (1 equiv) and divinylbenzene (0.02 equiv) to give the polymer-bound 4-(*N*-benzyl-*N*-methylamino)pyridine. A more detailed experimental procedure can be found elsewhere.[62]

4.6. Reaction procedure

Styrene oxide (4 mL) and the appropriate amount of Al(salen) catalyst and co-catalyst is placed in a 125 mL stainless steel autoclave that is subsequently charged with liquid CO_2 until an approximate pressure of 75 bars is reached. Then, the temperature is increased at 80 °C while the mixture is mechanically stirred. The approximate pressure is 100 bar. The reaction mixture was maintained under these conditions for 6 h. After this time the system was allowed to cool at ambient temperature and, then, the reactor valve is opened and the reactor pressure smoothly decreased over a period of 12 h. The reaction mixture was extracted with diethyl ether, the polymer washed with ethanol and the product analysed by IR of the mixture (to assess the absence of polycarbonate) and GC or GC/MS. The products were identified by comparison with authentic samples.

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A high-swelling reagent scaffold suitable for use in aqueous and organic solvents

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Abstract—A polymeric scaffold with excellent swelling properties in organic and aqueous environments is highly desirable for the medicinal chemist. Here, we demonstrate that a cross-linked polyacrylamide hydrogel that displays large swelling properties in both organic solvent and water can serve as a scaffold for the photosensitizer hematoporphyrin. Upon exposure to light, the resulting resin efficiently generates singlet oxygen which can then react with appropriate substrates.

1. Introduction

Following the implementation of solid-phase peptide synthesis by Merrifield,[1] the use of polymeric supports in organic synthesis has become commonplace, particularly in the context of combinatorial chemistry. In particular, insoluble polymers such as lightly cross-linked polystyrene have been implemented in a wide range of synthetic methodologies.[2–4] Primarily, the synthetic uses of these polymers have fallen into one of two scenarios: (A) the use of the polymer as a scaffold for chemical synthesis or (B) the use of the polymer as a support for reagents and catalysts to be used during a reaction sequence. Both of these methods allow for rapid product purification and the ability to drive a given reaction to completion through the use of an excess of reagents. However, traditional polystyrene-based polymer supports are restricted in their utility because they have poor swelling properties in most polar solvents such as water and methanol. In an effort to improve the swelling properties of polystyrene-based polymers, a variety of cross-linkers, such as poly(tetrahydrofuran),[5] and appended functionalities, such as poly(ethylene glycol) (PEG), have been employed. For example, TentaGel, a polymer comprised of PEG chains (50–60 ethylene oxide units long) tethered onto a polystyrene support, has some swelling in polar solvents including water and has been reported to possess a more 'solution-like' interior.[6] However, kinetic analyses of reactions performed on this resin relative to reactions performed on cross-linked polystyrene have revealed that there is no predictable kinetic advantage to using TentaGel, presumably because the appended PEG polymer chains themselves act as the 'solvent', thus indicating that the assumption of free-floating PEG chains in solution is invalid.[7]

In our laboratory, we have advanced the concept of providing the synthetic chemist with a 'toolbox' of resins suitable for a range of chemistries.[8] In this context, a key physical property of an 'ideal' resin would be compatibility with both polar and nonpolar solvents. Recently, we have demonstrated that insoluble polyacrylamide hydrogels cross-linked with a triethylene glycol-derived cross-linker (**1**) have excellent swelling in both nonpolar organic solvents (e.g., CH_2Cl_2) and water.[9] In this study, polymer monoliths were readily prepared from inexpensive starting materials under extremely mild conditions for the encapsulation and controlled release of proteins.[10] Based upon the significant swelling properties of these resins, we speculated that they could also have application in organic synthesis as a support for reagents and catalysts. In this context, these polymers would provide a general platform for reagent immobilization, independent of the specific chemical reaction conditions.

As a model reaction, we chose to examine the dye-sensitized photooxidation of unsaturated substrates with singlet

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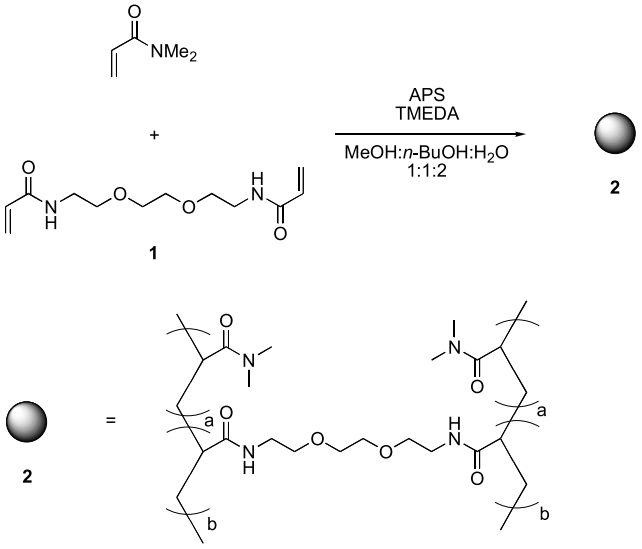
oxygen O_2 ($^1\Delta_g$). This choice was predicated on the ability of many of these reactions to be conducted in both aqueous and organic media. Furthermore, the dyes typically used as photosensitizers are poorly soluble, and can greatly complicate product purification. For example, the sensitizer hematoporphyrin is only moderately soluble in most organic solvents (e.g., ether, chloroform), and nearly insoluble in water. Previous reports have described the conjugation of various sensitizers to polymeric supports such as polystyrene and TentaGel, however the utility of these polymeric reagents is limited by poor swelling properties, particularly in aqueous environments.[11,12] Herein, we disclose the preparation of a sensitizer-functionalized hydrogel and its demonstration as a polymer-supported reagent suitable for use in synthetic schemes requiring organic solvents or water.

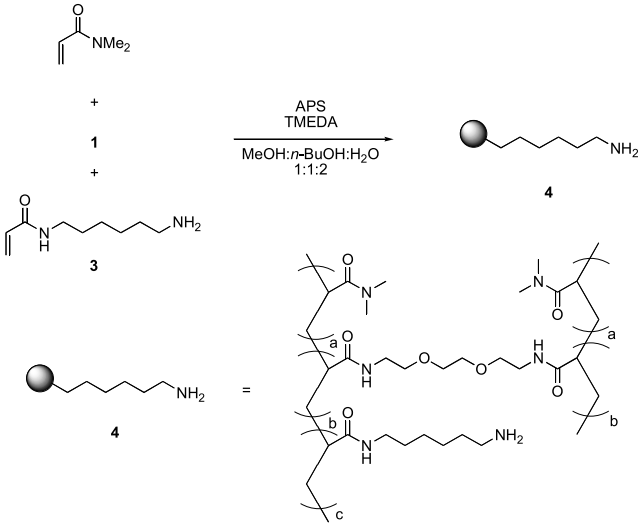
2. Results and discussion

A key advantage of cross-linked polyamide hydrogels over traditional polystyrene-based polymeric supports is the ease of preparation. For example, unfunctionalized hydrogels can be readily prepared from a mixture of *N*,*N*-dimethylacrylamide, cross-linker **1**, and ammonium persulfate (APS) in a mixture of methanol, *n*-butanol, and water. After brief degassing, polymerization is initiated by the addition of TMEDA. Reactions were routinely conducted in a disposable glass test tube and were complete after one hour at room temperature. Polymer **2** was returned as a colorless monolith, which was simply crushed using a mortar and pestle (Scheme 1).



Scheme 1. Synthesis of unfunctionalized hydrogel **2**. $a=96$, $b=4$.

Encouraged by our previous results in which polymerization proceeded smoothly over a range of cross-linker concentrations, in the presence of protein, and with different acrylamide monomers,[9] we attempted to synthesize a functionalized hydrogel suitable for reagent immobilization. An amino-functionalized hydrogel was chosen as a convenient support for hematoporphyrin, which could be linked to the polymer via an amide bond formed between the resin and the carboxylic acid moieties of the sensitizer. Accordingly, a solution of 20 mol% functional monomer **3**, readily prepared from acryloyl chloride and excess hexamethylenediamine, was subjected to the polymerization conditions in the presence of 4 mol% **1**, and *N*,*N*-dimethylacrylamide as the bulk monomer (Scheme 2). As was the case for the preparation of **2**, polymerization proceeded smoothly, affording hydrogel **4** in approximately 1 h. After crushing the resulting colorless monolith, the resin was washed with water, methanol, and CH_2Cl_2 then dried in vacuo prior to further use.

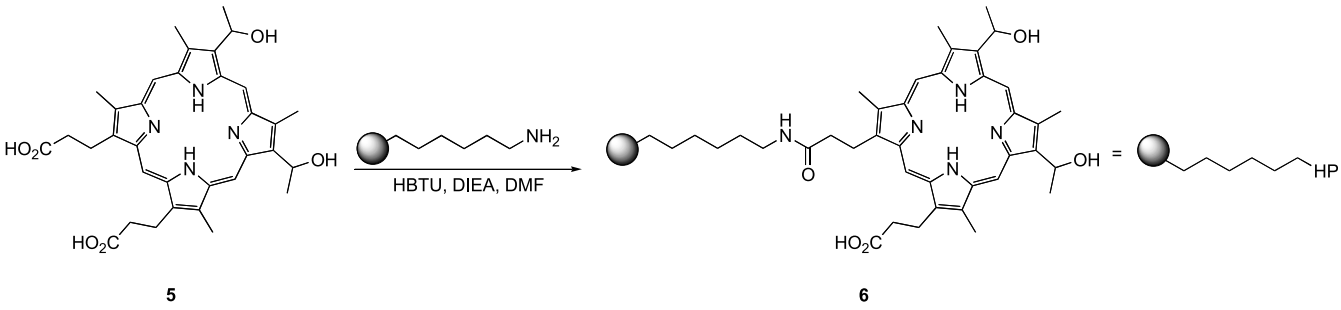


Scheme 2. Synthesis of functionalized hydrogels **4**. $a=76$, $b=4$, $c=20$.

With functionalized hydrogels in hand, the preparation of polymer-bound photosensitizing reagent was performed under standard amide bond formation conditions (HBTU, Hünig's base, DMF). The reaction was complete after shaking overnight at room temperature as determined by IR analysis (Scheme 3). The resulting polymer-bound photosensitizer **6** was isolated as dark red beads after extensive washing with multiple volumes of DMF to remove unreacted **5**. Upon the disappearance of color from the rinse fractions, the resin was washed with CH_2Cl_2 and dried in vacuo.

The ability of a resin to swell in a given solvent has been employed as a method to assess the utility of a support for SPOS; furthermore, studies have demonstrated that increased resin swelling leads to greater site accessibility and more 'solution-like' diffusion.[13] As such, the swelling properties of **6** were measured in a variety of solvents using the syringe method (Table 1).[14,15] Similar to unfunctionalized resin **2**, hydrogel **6** had good swelling properties in water, methanol, CH_2Cl_2, and DMF, and poor swelling properties in acetonitrile. Critically, even though hydrogel **6** has a relatively large loading of photosensitizer (20 mol%), there are no adverse effects on the swelling properties of the support in both aqueous and organic environments.

With polymer-immobilized hematoporphyrin in hand, the rate at which the resin-bound sensitizer generated O_2 ($^1\Delta_g$) was measured using the fluorescent probe Singlet Oxygen



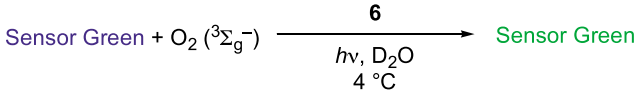
Scheme 3. Preparation of hydrogel-bound hematoporphyrin **6**.

Table 1. Swelling parameters for hydrogel resins

Solvent	Hydrogel **2**[a]	Hydrogel **6**
H_2O	9.6	8.6
MeOH	10.0	8.3
CH_2Cl_2	9.8	7.1
DMF	7.8	7.2
MeCN	6.8	5.4

Swelling was measured by the syringe method according to Ref. 14, and expressed in mL/g of dry resin.
[a] Values from Ref. 9.

Sensor Green (Scheme 4).[16] This sensitive probe is selective for O_2 ($^1\Delta_g$), as opposed to other reactive oxygen species such as the superoxide anion ($O_2^{\cdot -}$) or hydroxyl radical ($^{\cdot}OH$). Upon reacting with O_2 ($^1\Delta_g$), the weak blue fluorescence ($\lambda_{ex}=372$ nm, $\lambda_{em}=395$ nm) is lost, returning a product with strong green fluorescence ($\lambda_{ex}=504$ nm, $\lambda_{em}=525$ nm). The rate of the reaction was measured by adding a solution of 100 μg of dye to 15 mg of **6** swollen in D_2O. Deuterium oxide was chosen as the solvent due to its ability to stabilize O_2 ($^1\Delta_g$), relative to water.[17] The solution was saturated with O_2 and the reaction was initiated upon exposure to light. Aliquots were removed from the solution at regular time points and the fluorescence of both the product and starting material measured. Oxidation of the probe was rapid ($t_{1/2}=18$ min), suggesting that **6** efficiently generated O_2 ($^1\Delta_g$) even under the extremely mild conditions of the study (white light transilluminator, 3.4 mW/cm^2).



Scheme 4. Photooxidation of Sensor Green probe in the presence of singlet oxygen.

Encouraged by the rapid rate in which hydrogel **6** generated singlet oxygen in D_2O, we next examined the ability of this sensitizer resin to produce $^1O_2$ and thus catalyze reactions in organic solvent. Here, the resin was employed in the photooxidation of anthracene in methylene chloride. Anthracene was dissolved in CH_2Cl_2 and added to 0.15 equiv of preswollen **6**. The solution was saturated with oxygen and exposed to light for 4 h at 4 °C. Isolation of the resulting endoperoxide **7** was achieved simply by filtration of the resin followed by removal of the solvent. The conversion proceeded smoothly and cleanly to give the product in 66% yield. Spectral characterization of the resulting endoperoxide product was consistent with literature values.[18] Upon completion of this reaction, no color was observed leaching from the resin, indicating that the resin-bound photosensitizer is stable to the reaction conditions and suggesting that it can be easily reused for further reactions. This finding is consistent with previous studies examining the ability of solid-supported porphyrins as singlet oxygen sources (Figure 1, Scheme 5).[12]

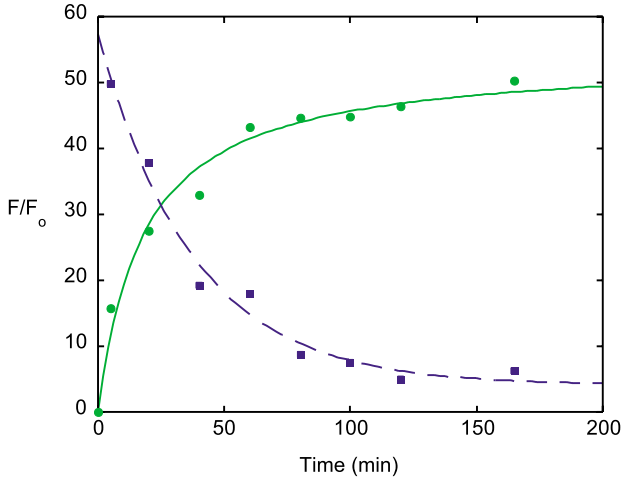
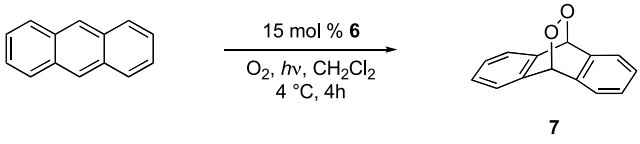


Figure 1. Rate of oxidation of Singlet Oxygen Sensor Green. Formation of the product of the oxidation of the fluorescent probe ($\lambda_{ex}=504$ nm, $\lambda_{em}=525$ nm) was represented in green. Loss of the unoxidized probe ($\lambda_{ex}=372$ nm, $\lambda_{em}=395$ nm) represented in blue.



Scheme 5. Photooxidation of anthracene by hydrogel **6**.

3. Conclusion

Polymer-supported reagents have become an indispensable tool for the modern organic chemist. The development of resin scaffolds with applicability to polar and apolar solvents would greatly simplify the current decision process that must accompany any synthetic route employing cross-linked polymeric systems. In total, our results demonstrate that a cross-linked polyacrylamide hydrogel can serve as an excellent scaffold for hematoporphyrin catalyzed photo-oxidation in both aqueous and organic media. Furthermore, we envision that this scaffold will also prove useful in

multistep synthetic schemes where the use of both aqueous and organic solvents is desirable.

4. Experimental

4.1. General methods

FT-IR spectra were recorded using a Thermo Nicolet AVATA 360 spectrometer equipped with a Golden Gate single reflection diamond ATR accessory. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AMX-400 at 400 and 100 MHz, respectively. NMR spectra were referenced with respect to the residual solvent peak. Fluorescence spectroscopy was performed on a Spectra Max Gemini plate reader. Methylene chloride and triethylamine were distilled from CaH_2 prior to use. All other solvents and chemicals were used without further purification. Flash chromatography was carried out using Merck silica gel 60 (230–400 mesh).

4.1.1. *N*-(6-Aminohexyl)acrylamide 3. Acryloyl chloride (0.8 mL, 10 mmol) was slowly added to a solution of hexamethylenediamine (5.8 g, 50 mmol) and triethylamine (1.8 mL, 13 mmol) in CH_2Cl_2 at 0 °C. The resulting mixture was allowed to slowly warm to room temperature. After stirring 12 h, the reaction was quenched by the addition of saturated aqueous $NaHCO_3$. After washing the mixture with CH_2Cl_2, the combined organic fractions were washed with water and brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was purified on silica gel chromatography (2.5% MeOH/CH_2Cl_2+0.1%Et_3N) to return the pure product (91%): ^{1}H NMR (400 MHz, d_6-DMSO) δ 8.17 (t, J=6.5 Hz, 1H), 6.23 (dd, J=10, 17 Hz, 1H), 6.04 (dd, J=2, 17 Hz, 1H), 5.54 (dd, J=2, 10 Hz, 1H), 5.36 (br s, 2H), 3.09 (q, J=6.5 Hz, 2H), 1.45–1.39 (m, 10H). ^{13}C NMR (100 MHz, d_6-DMSO) δ 164.4, 132.0, 124.7, 30.1, 29.0. ESI-TOF calcd $C_9H_{18}N_2O$ [M+H^+] 171.1419, found 171.1419.

4.1.2. Synthesis of 4 mol% cross-linked hydrogel 4. A catalytic amount of ammonium persulfate (3 mg, 0.013 mmol) was added to a solution of *N*,*N*-dimethylacrylamide (0.93 mL, 9.04 mmol), cross-linker 1 (96.4 mg, 0.376 mmol) and functional monomer 3 (mg, mmol) in a mixture of H_2O/MeOH/^{n}BuOH (2 mL, 2:1:1) in a 10×75 test tube. After the solution was degassed for 10 min, TMEDA (10 μL, 0.066 mmol) was added, and the test tube capped and placed in a water bath at room temperature. After 1 h, polymerization was complete. The test tube was cracked and the polymer monolith was crushed into beads with a mortar and pestle. The beads were thoroughly washed with water, MeOH, and CH_2Cl_2 and dried under vacuum.

4.1.3. Synthesis of hydrogel 6. A suspension of hematoporphyrin (3.2 g, 5.3 mmol), HBTU (1.0 g, 2.7 mmol), Hünig's base (0.47 mL, 2.7 mmol), and preswollen **4** (0.96 g, 0.67 mmol) in DMF was shaken in the dark. After 12 h, the mixture was filtered and washed with DMF. Once the rinse fractions were clear, the beads were washed with CH_2Cl_2 and dried in vacuo to return dark red beads (93%).

4.1.4. Synthesis of endoperoxide 7. A solution of anthrecene (20 mg, 0.112 mmol) in CH_2Cl_2 (2 mL) was added to preswollen **6** (24 mg, 0.017 mmol) and protected from light. The solution was saturated with oxygen and irradiated with white light at 4 °C. After 4 h, the solution was filtered and the filtrate evaporated. The residue was redissolved in $CDCl_3$ and analyzed by NMR: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44–7.40 (m, 4H), 7.32–7.28 (m, 4H), 6.04 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.0, 127.9, 123.6, 104.3, 79.3. ESI-TOF calcd $C_{14}H_{10}O_2$ [M+Na^+] 233.0573, found 233.0578.

4.1.5. Hydrogel swelling studies. Crushed dry polymer (20–30 mg) was placed in a 1 mL syringe equipped with a sintered frit. The desired solvent was added (0.8 mL) and the syringe vortexed briefly and gently agitated. After 1 h, the resin was allowed to settle for 30 min and the volume of swollen resin was measured. This value was divided by the mass of dry polymer to return the value for swelling expressed in mL/g.

4.1.6. Rate of Sensor Green oxidation by singlet oxygen. A suspension of **6** (15 mg, 0.011 mmol) in D_2O (967 μL), protected from light, was saturated with oxygen. Singlet Oxygen Sensor Green (100 μg) was added as a solution in methanol (33 μL) for a total concentration of 165 μM, and the solution was exposed to white light. At various time points, a 30 μL aliquot was removed from the solution. Triplicate solutions of 10 μL of this aliquot diluted to 100 μL by water were prepared in a black-walled 96-well plate. The fluorescence of both oxidized and unoxidized sensor were measured using a SPECTRAmax GEMINI (Molecular Devices) plate reader.

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Copper (I) 1,3-R_2-3,4,5,6-tetrahydropyrimidin-2-ylidenes (R = mesityl, 2-propyl): synthesis, X-ray structures, immobilization and catalytic activity

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Abstract—The synthesis of novel copper (I) N-heterocyclic carbene complexes is described. Thus, reaction of CuX with 1,3-di(2-propyl)-3,4,5,6-tetrahydropyrimidin-2-ylidene yields CuX(1,3-di(2-propyl)-3,4,5,6-tetrahydropyrimidin-2-ylidene) (X = Cl, (**1a**), Br (**1b**)); however, reaction of CuCl with 1,3-dimesityl-3,4,5,6-tetrahydropyrimidin-2-ylidene yields the bis-N-heterocylcic carbene complex Cu(1,3-dimesityl-3,4,5,6-tetrahydropyrimidin-2-ylidene)$_2^+$CuBr$_2^-$ (**2**). A supported version of **1**, i.e. PS-DVB–CH_2–OCO–CF_2–CF_2–CF_2–COOCu(1,3-di(2-propyl)-3,4,5,6-tetrahydropyrimidin-2-ylidene) (**3**) was prepared from **1** and PS-DVB–CH_2–OCO–CF_2–CF_2–CF_2–COOAg. A copper loading of 4.15 μmol/g was realized. The new compounds were used as catalysts in carbonyl hydrosilylation and cyanosilylation reactions. Excellent reactivity was observed, giving raise to turn-over numbers (TONs) of up to 100,000. Compounds **1a**, **1b**, and **2** have also been used as catalysts for the atom transfer radical polymerization (ATRP) of methyl methacrylate (MMA). A linear conversion of monomer with time was observed, however, no control over molecular weight of PMMA was observed.

1. Introduction

N-heterocyclic carbenes (NHCs)[1–6] are currently among the most intensively investigated compounds since the corresponding transition metal complexes were found to possess good stabilities and high activities in various catalytic processes.[7–14] Recently, our group reported on novel NHC complexes of Ag (I), Pd (II), Rh (I), Ir (I), and Ru (II) based on 1,3-R_2-3,4,5,6-tetrahydropyrimidin-2-ylidenes (R = mesityl, 2-propyl).[15–22] In this context, novel NHC-complexes of the general formula MX(1,3-R_2-3,4,5,6-tetrahydropyrimidin-2-ylidene)(COD) (M = Rh, Ir; X = Cl, Br; R = 2-Pr, mesityl; COD = η^4 − 1,5-cyclooctadiene) have been used for carbonyl arylation and hydrosilylation reactions and were found to possess excellent activity.[19–21] The same applies to the palladium complex $PdCl_2$(1,3-(2-Pr)$_2$-3,4,5,6-tetrahydropyrimidin-2-ylidene) and ruthenium complexes $RuCl_2$(1,3-dimesityl-3,4,5,6-tetrahydropyrimidin-2-ylidene(=CHR)). Encouraged by the high reactivity of these complexes, we were interested in the synthesis and catalytic behaviour of the corresponding Cu (I) NHC compounds. So far, only few reports exist on Cu (I) complexes of N-heterocyclic carbenes.[23–25] In the following, their synthesis, characterization, X-ray structures and catalytic activities are reported.

2. Results and discussion

2.1. Synthesis and X-ray structure of compounds 1a and 1b

Compound **1a** was prepared in 77% isolated yield from CuCl and 1,3-di(2-propyl)-3,4,5,6-tetrahydropyrimidin-2-ylidene in THF (Scheme 1). The latter was generated from 1,3-di(2-propyl)-3,4,5,6-tetrahydropyrimidinium tetrafluoroborate and sodium *tert*-butoxide as described in the lit.[17] Compound **1a** (Fig. 1) was characterized by X-ray crystallography. A summary of the data is given in Tables 1 and 2.

Compound **1a** crystallizes in the orthorhombic space group

Keywords: N-heterocyclic carbenes; Tetrahydropyrimidin-2-ylidenes; Copper; Atom-transfer radical polymerization; Hydrosilylation; Cyanosilylation; Homogeneous catalysis; Heterogeneous catalysis.
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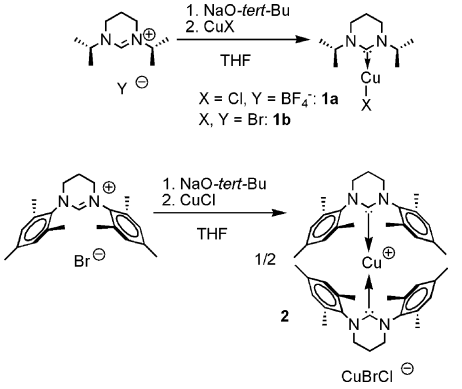
Table 1. Crystal data and structure refinement for **1a** and **2**

	1a	**2**
Molecular formula	$C_{10}H_{20}ClCuN_2$	$C_{44}H_{56}Br_{1.74}Cl_{0.26}Cu2N_4$
Fw	267.27	916.27
Cryst syst	Orthorhombic	Monoclinic
Space group	Pnnm (No. 58)	*C*2/*c* (No. 15)
a (pm)	1220.30(6)	1540.04(3)
b (pm)	986.16(3)	1450.36(2)
c (pm)	1045.55(5)	1916.18(5)
α (deg)	90	90
β (deg)	90	95.088(2)
γ (deg)	90	90
Vol (nm^3)	1.25823(9)	4.26452(15)
Z	4	4
Temperature (K)	233(2)	233(2)
Density (calcd) (Mg/m^3)	1.411	1.427
Abs coeff (mm^{-1})	1.915	2.678
Color, habit	Colorless prism	Colorless prism
No. of rflns with $I>2\sigma(I)$	1276	3156
Goodness-of-fit on F^2	1.057	1.047
R indices $I>2\sigma(I)$	$R_1=0.0208$	$R_1=0.0347$
	$\omega R^2=0.0543$	$\omega R^2=0.0846$



Scheme 1. Synthesis of Cu–NHC complexes **1a**, **1b** and **2**.

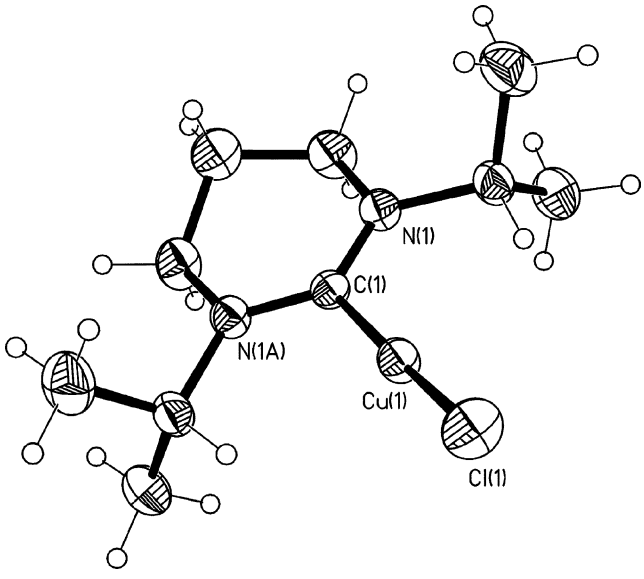


Figure. 1. X-ray structure of compound **1a**.

Pnnm with $a=1220.30(6)$ pm, $b=986.16(3)$ pm and $c=1045.55(5)$ pm, $\alpha=\beta=\gamma=90°$, $Z=4$. The distance Cu(1)–C(1) is 191.50(19) pm, which is significantly shorter than the one reported for CuCl 1,3-(2,6-(2-Pr)$_2$-C_6H_3)(imidazol-2-ylidene) (195.3 pm).[23] This finding underlines the fact that N-heterocyclic carbenes based on tetrahydropyrimidin-2-ylidenes are among the most basic ones. In due consequence, a pronounced trans-effect on the halogen ligand had to be expected and was in fact found. Thus, the distance Cu(1)–Cl(1) in **1a** (211.06(6) pm) is longer than the one observed in CuCl 1,3-(2,6-(2-Pr)$_2$-C_6H_3) (imidazol-2-ylidene) (208.90 pm).

Table 2. Bond lengths (pm) and angles (°) for **1a**

Cu(1)–C(1)	191.50(19)
Cu(1)–Cl(1)	211.06(6)

In a similar way, **1b** was prepared in 75% yield from CuBr and 1,3-di(2-propyl)-3,4,5,6-tetrahydropyrimidin-2-ylidene in THF (Scheme 1). Due to structural similarity, no further discussion appears necessary.

2.2. Synthesis and X-ray structure of compound 2

Compound **2** was prepared in 88% isolated yield from CuCl and 1,3-dimesityl-3,4,5,6-tetrahydropyrimidin-2-ylidene in THF (Scheme 1). The latter was generated from 1,3-dimesityl-3,4,5,6-tetrahydropyrimidinium bromide and sodium *tert*-butoxide as described in the literature.[17] The complex that forms is remarkable. Thus, a cationic Cu (I) bis-(NHC) compound with a $CuBr_2$ anion forms instead of the expected neutral CuBr(NHC) complex. So far, we have no conclusive explanation for this finding, the more, as the sterically demanding ligand should favor a Cu-mono-NHC-complex. Compound **2** (Fig. 2) was characterized by X-ray crystallography. A summary of the data is given in Tables 1 and 3.

Table 3. Bond lengths (pm) and angles (°) for **2**

Cu(1)–C(1)	193.4(2)
Cu(1)–C(1)#1	193.4(2)
C(1)–Cu(1)–C(1)#1	178.73(13)
Cl(1)#2–Cu(2)–Br(1)	179.29(4)
Br(1)#2–Cu(2)–Br(1)	179.29(4)

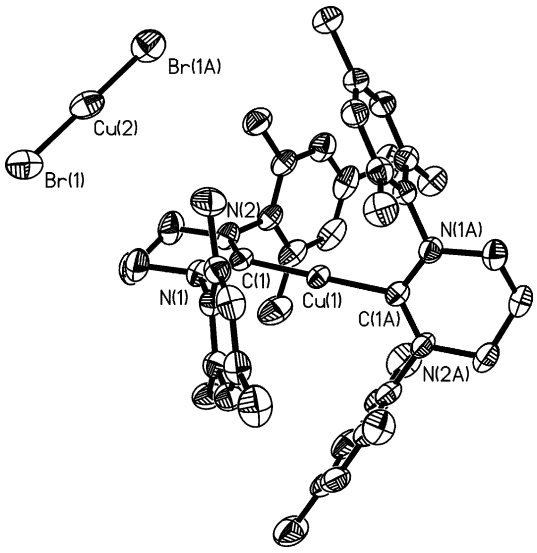


Figure. 2. X-ray structure of compound **2**.

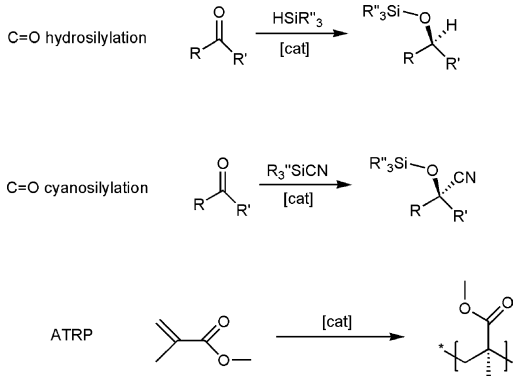
Compound **2** crystallizes in the monoclinic space group *C*2/*c* with $a=1540.04(3)$ pm, $b=1450.36(2)$ pm and $c=1916.18(5)$ pm, $\alpha=\gamma=90°$, $\beta=95.088(2)$, $Z=4$. As expected, the distances Cu(1)–C(1) and Cu(1)–C(1)# are identical (193.42(2) pm). This distance is only slightly longer than in the one found in **1a** indicating only minor, if any, steric repulsion of the two NHC ligands. The angle C(1)–Cu(1)–C(1)# is 178.73(13)°, illustrating an almost perfect alignment of the two NHC ligands. As expected, the $CuBr_2$ anion is almost perfectly linear with an angle Brl(1)–Cu(1)–Br(1)# of 179.29(4)°. It should be emphasized that the anion is in fact best described by the formula $CuBr_{1.74}Cl_{0.26}$. This irregularity may also account for the slight (calculated) deviation in the linearity of this anion.

2.3. Synthesis of an immobilized version of 1a/1b

In view of the high demand on supported catalysts,[26] we synthesized a supported version of **1a** respectively **1b** by reaction with a perfluoroglutaric acid-derivatized PS-DVB-based support according to an established procedure (Scheme 2).[27,28] A catalyst loading of 4.15 μmol/g was accomplished. With this set of catalysts in hand, a series of catalytic reactions as outlined below were investigated.

2.4. Catalytic activity of compounds 1a, 1b and 2 in C═O cyanosilylation reactions

Compounds **1a**, **1b** and **2** were used in the cyanosilylation of various carbonyl compounds including aromatic aldehydes and ketones (Scheme 3). A summary of the results is given in Table 4, entries 1–8.

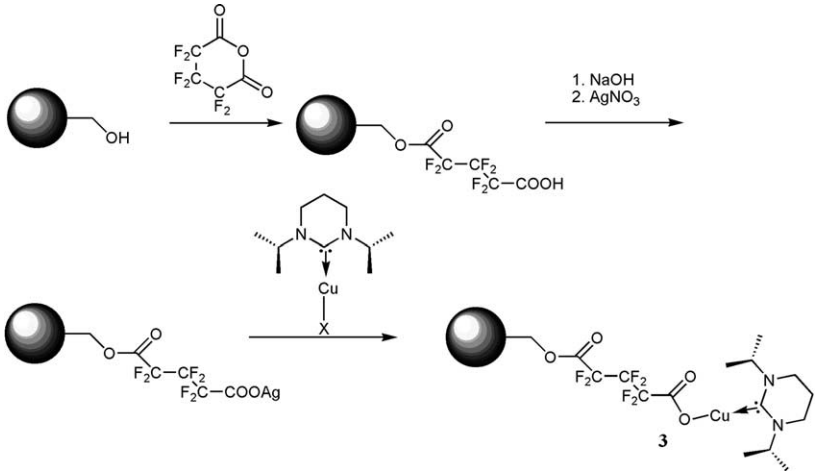


Scheme 3. C═O hydrosilylation, C═O cyanosilylation reactions and attempted ATRP of MMA.

As can be seen, catalyst **1b** showed excellent reactivity in this type of reaction. Yields were in the 22–100% range, TONs up to 50,000 were obtained. The more stable complex **2** resulted in even improved yields (80–100%), TONs reached 100,000. The supported version **3** gave significantly, however, still acceptable yields approaching 100% in selected cases. As a consequence of both the low copper loadings (12–71 μmol%) and the immobilization, products obtained with **3** were basically free of any copper residues (<1 ppm).

2.5. Catalytic activity of compounds 1a, 1b and 2 in C═O hydrosilylation reactions

Copper (I) catalyzed C═O hydrosilylation reactions (Scheme 3) were first described by Nolan and coworkers



Scheme 2. Immobilization of **1a** on a PS-DVB-based support.

Table 4. Cyanosilylation of carbonyl compounds using trimethylsilylcyanide

#	Educt/product	Time (h)	**1b**[a]/yield (%)[b]	TON	Time (h)	**2**[c]/Yield (%)[b]	TON	μmol (%) 3	Yield (%)[b]	TON
1	4-Chlorobenzaldehyde/2-(4-Cl-phenyl)-2-trimethylsilyloxyacetonitrile	1	100	50,000	0.75	100	100,000	12	100	8600
2	4-Fluorobenzaldehyde/2-(3-F-phenyl)-2-trimethylsilyloxyacetonitrile	1	100	50,000	1	100	50,000	2.2	93	42,300
3	3-Hydroxybenzaldehyde/2-(3-trimethylsilyl-oxyphenyl)-2-trimethylsilyloxyacetonitrile	1	80	40,000	1	98	98,000	20	100	4900
4	Benzoin/1,2-diphenyl-1,2-bis(trimethylsilyl-oxy)propionitrile	6	22	11,000	6	80	80,000	71	4	60
5	Benzoylacetone/1-trimethylsilyloxy-1-methyl-3-benzoylpropionitrile	1	80	40,000	1	80	80,000	54	81	1500
6	4-Bromoacetophenone/2-(4-Br-phenyl)-2-tri-methylsilyloxypropionitrile	24	0	0	48	80	80,000	66	0	0
7	Benzaldehyde/1-phenyl-trimethylsilyloxy-acetonitrile	1.5	90	45,000	1	99	99,000	18	80	4500
8	Diphenyldiketone/2,3-diphenyl-2,3-bis(trimethyl-silyloxy)butanedinitrile	1.5	99	49,500	1	100	100,000	70	93	1300

[a] 0.002 mol% of **1b**.
[b] Determined by GC–MS. Reactions were run in dichloroethane at 75 °C.
[c] 0.001 mol% of **2**.

for Cu-imidazol-2-ylidenes.[23,24] With their systems, excellent yields approaching 100% were achieved using 3 mol% of the corresponding catalyst, translating into maximum turn-over numbers (TON_{max}) of 33.

As can be deduced from Table 5, entries 1–9, catalyst **1b**, if used on a 0.002 mol% scale, allowed for TONs up to 50,000. Yields were in the 80–100% range. Even better, catalyst **2**, used on a 0.001 mol% scale, allowed for TONs up to 100,000, yields for all substrates investigated were in the 70–100% range. The supported version **3** showed again reduced, however, still acceptable activity, allowing for TONs up to 42,500 and yields up to 100%.

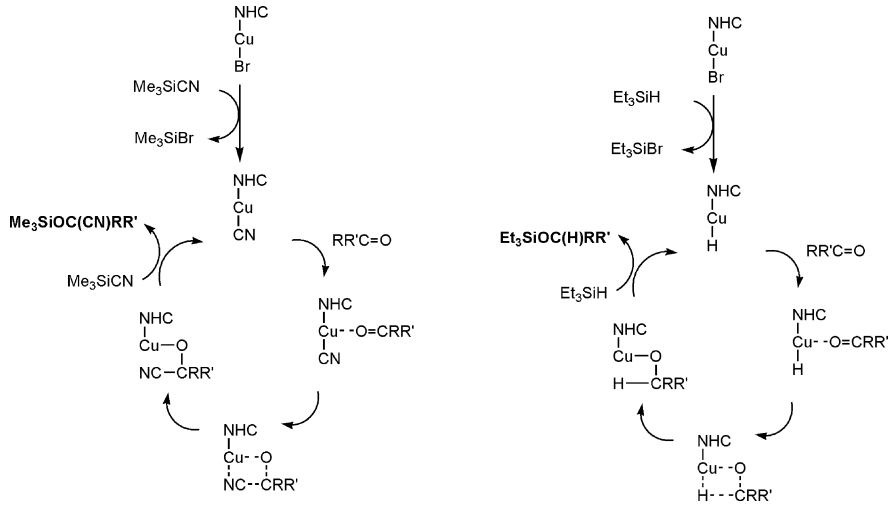
2.6. Differences in catalyst structure accounting for differences in reactivity

From the set of data presented above, three important conclusions may be drawn. Firstly, ALL catalysts presented here are by far the most reactive Cu (I)–N-heterocyclic carbene complexes that have been prepared for the above-mentioned reactions. Secondly, no change in selectivity is observed upon immobilization of **1a**, respectively **1b** on a Merrifield type support. However, presumably due to diffusion issues, reactivity is reduced, however, still exceeds any system reported so far. Thirdly, complex **2** is by far the more reactive one. This is believed to be a direct

Table 5. Hydrosilylation of carbonyl compounds using triethylsilane

#	Educt/product	Time (h)	**1b**[a]/Yield (%)[b]	TON	Time (h)	**2**[c]/Yield (%)[b]	TON	μmol% of 3	Yield (%)[b]	TON
1	4-Chlorobenzaldehyde/4-Cl-phenyl-1-triethoxysilylmethane	1 h	100	50,000	45 min	100	100,000	29	100	38,800
2	4-Fluorobenzaldehyde/4-F-phenyl-triethoxysilylmethane	45 min	100	50,000	0.5	100	100,000	1.1	23	21,000
3	4-Bromoacetophenone/2-(4-Br-phenyl)-1-triethoxysilylethane	24 h	0	0	1	100	100,000	33	0	0
4	Benzophenone/diphenyltriethoxy-methane	1.5 h	90	45,000	1.5	98	98,000	30	20	660
5	4-*N*,*N*-Dimethylaminobenzaldehyde/4-*N*,*N*-dimethylaminophenyl-triethoxy-silylmethane	2 h	90	45,000	1	98	98,000	12	40	3200
6	4-Chloroacetophenone/2-(4-Cl-phenyl)-1-triethoxysilylethane	24 h	0	0	5[c]	98	98,000	26	0	0
7	Benzaldehyde/4-Cl-phenyl-triethoxy-silylmethane	1 h	98	49,000	1	100	100,000	24	100	42,500
8	Norborn-5-ene-2-carbaldehyde/norborn-5-ene-2-yltriethoxysilyl-methane	1 h	80	40,000	1	80	80,000	102	54	5300
9	Benzoin/1,2-diphenyl-2-triethoxysilyl-ethanol	1.5 h	0	0	1.5	70	70,000	35	0	0

Room temperature.
[a] 0.002 mol%.
[b] Determined by GC–MS. Reactions were run in THF at 65 °C using 0.15 mmol% of NaO-*tert*-Bu.
[c] 0.001 mol%.



Scheme 4. Proposed mechanism for the cyanosilylation (left) and C=O hydrosilylation (right). Bromide may (in part) be replaced by *tert*-butoxide.

consequence of the structure of **2**. As a matter of fact, it consists of a cationic Cu (I) species, well protected by the two N-heterocyclic carbenes, and a 'naked' dibromocuprate. However, according to the mechanism proposed by Nolan et al. (Scheme 4), the formation of CuBr(1,3-dimesityl-3,4,5,6-tetrahydropyrimidin-2-ylidene) and Cu(*tert*-butoxy)(1,3-dimesityl-3,4,5,6-tetrahydropyrimidin-2-ylidene), respectively, in course of the reaction is proposed. Here the copper center is well-protected by the large N-heterocyclic carbene ligand and the mesityl moieties, respectively, leaving still enough space for the substrates to coordinate. Unfortunately, we were not able to retrieve unambiguous experimental evidence for this assumption so far.

2.7. Attempted ATRP of MMA using compounds 1b and 2

Atom transfer radical polymerization (ATRP) is a well-developed polymerization technique for the synthesis of narrow disperse polymers.[29] The polymerization mechanism involves a metal complex, where the metal changes reversibly its oxidation state. In addition, some additional free metal has been identified to play a positive role. In due consequence, the new copper (I) complexes and in particular complex **2** were expected to be suitable. However, **2** failed to provide an ATRP system capable of controlling the molecular weight. Instead, PMMA with similar molecular weights in the range of 70,000–90,000 g/mol was produced. The reason for this behavior apparently lies in the insolubility of **2** in the polymerization medium. Thus, once polymerization commences, the back reaction, forming the 'dormant species' is hindered, resulting in the rapid production of polymer. Once the deactivation step is successfully accomplished, reactivation of the polymer chain does not occur. Instead, the initiator forms new growing polymer chains facing the same fate.

Therefore, **1b** was used. This complex is more soluble and in fact allowed for a more controlled polymerization of MMA. Graphs of monomer conversion versus time as well as a graph showing M_n versus the number of monomer equivalents added (N) are shown in Figs. 3 and 4, respectively. Polymerization results are summarized in Table 6.

As can be seen, monomer consumption proceeded linearly over time. Similarly, molecular weights developed linearly up to a monomer:catalyst ratio of 300 and then remained unchanged. However, molecular weights, as determined by light scattering, were about twice as high as calculated. This clearly indicates an initiation efficiency of roughly 0.5. In view of this finding and the comparably high polydispersity

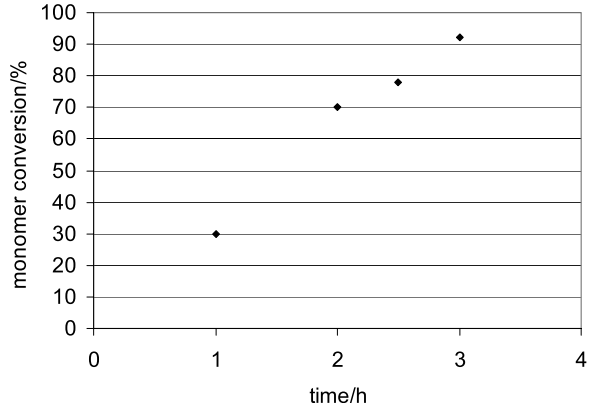


Figure. 3. Graph showing monomer conversion versus time for the polymerization of MMA by **1b**.

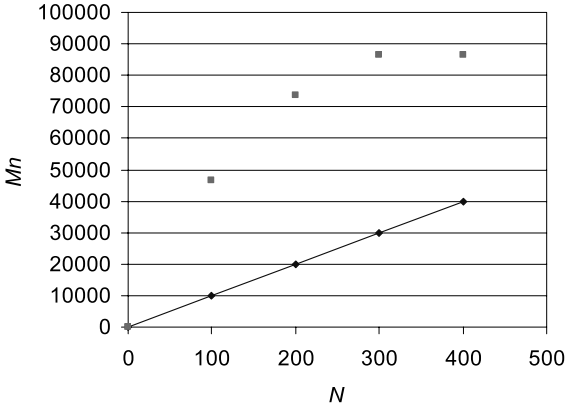


Figure. 4. Graph of number of monomer equivalents added (N) versus M_n. The line shows the theoretical values for M_n.

Table 6. Summary of polymerization results for MMA using **1b**

Entry	*N*	M_n (calcd)	M_n (found)	PDI
1	100	10,000	4700	1.39
2	200	20,000	7400	1.53
3	300	30,000	8600	1.55
4	400	40,000	8708	1.82

N, number of monomer equivalents added. Polymerizations were carried out at 90 °C in diphenyl ether.

indices (1.4–1.8, Table 6), the polymerization certainly does not fulfil the stringent criteria of a true, controlled ATRP. However, it should be emphasized, that this is the first report on the use of an N-heterocyclic carbene–Cu system for these purposes.

3. Experimental

3.1. General

All manipulations were performed under a nitrogen atmosphere in a glove box (MBraun LabMaster 130) or by standard Schlenk techniques. Purchased starting materials were used without any further purification. Pentane, diethyl ether, toluene, methylene chloride and tetrahydrofurane (THF) were dried using a solvent dry system (SDS, MBraun). Chloroform-d_1 was distilled from calcium hydride. Styrene and methyl methacrylate (MMA) were dried over CaH_2 overnight, distilled under vacuum and stored under argon at −15 °C. The initiator ethyl-2-bromo isobutyrate (EBIB) was distilled under reduced pressure prior to use. Diphenyl ether was dried over molecular sieves (3 Å) and distilled prior to use.

NMR data were obtained at 300.13 MHz for proton and 75.74 MHz for carbon in the indicated solvent at 25 °C on a Bruker Spectrospin 300 and are listed in parts per million downfield from tetramethylsilane for proton and carbon. Coupling constants are listed in Hz. IR spectra were recorded on a Bruker Vector 2000 using ATR technology. Elemental analyses were carried out at the Mikroanalytisches Labor, Anorganisch-Chemisches Institut, TU München, Germany. Molecular weights and polydispersity indices (PDIs) of the polymers were determined by GPC at 30 °C on Polymer Laboratories columns (PLgel 10 μm MIXED-B, 7.5×300 mm) in THF at 25 °C using a Waters Autosampler, a Waters 484 UV detector (254 nm), a light scattering detector (Wyatt) and an Optilab Rex refractive index detector (685 nm, Wyatt). The flow rate was 0.7 mL/min. A *dn/dc* of 0.086 was used for the determination of M_w by light scattering.

3.1.1. Synthesis of CuCl(1,3-di(2-Pr)-3,4,5,6-tetrahydropyrimidin-2-ylidene) (1a). In a 100 mL Schlenk flask were added copper (I) chloride (0.28 g, 2.82 mmol), 1,3-bis(2-propyl)-3,4,5,6-tetrahydropyrimidinium tetrafluoroborate (0.70 g, 2.73 mmol) and sodium *tert*-butoxide (0.27 g, 2.82 mmol). Dry THF was added (25 mL) under argon and the mixture was stirred for 24 h at room temperature. The reaction mixture was filtered through celite and the solvent was evaporated in vacuo. A light green colored solid was obtained, which was recrystallized from dichloromethane/pentane to yield 0.56 g (77%) of the desired compound. FTIR (ATR): 2965 (m), 2929 (m), 2868 (m), 1677 (m), 1518 (s), 1311 (s), 1169 (m). ^{1}H NMR ($CDCl_3$) δ 1.19 (d, 12H, CH_3), 1.86 (q, 2H, CH_2), 3.0 (t, 4H, NCH_2), 4.59 (m, 2H, NCH). ^{13}C NMR ($CDCl_3$)δ 194.7 (C:–N), 60.3 (N–H), 37.1 (N–H_2), 20.5 (CH_2), 20.4 (CH_3).

3.1.2. Synthesis of CuBr(1,3-di(2-Pr)-3,4,5,6-tetrahydropyrimidin-2-ylidene) (1b). In a 100 mL Schlenk flask were added copper (I) chloride (120 mg, 1.21 mmol), 1,3-bis(2-propyl)-3,4,5,6-tetrahydropyrimidinium bromide (300 mg, 1.20 mmol) and sodium *tert*-butoxide (118 mg, 1.23 mmol). Dry THF was added (25 mL) under argon and the mixture was stirred for 24 h at room temperature. The reaction mixture was filtered through celite and the solvent was removed in vacuo, leaving a brown coloured precipitate behind. Recrystallization from dichloromethane/pentane yielded 285 mg (75%) of **1b**. FTIR (ATR): 2968 (m), 2932 (m), 2869 (m), 1517 (s), 1311 (s), 1169 (s). ^{1}H NMR ($CDCl_3$) δ 1.19 (d, 12H, CH_3),1.84 (q, 2H, CH_2), 3.0 (t, 4H, NCH_2), 4.6 (m, 2H, NCH); ^{13}C NMR ($CDCl_3$) δ 195.1 (C:–N), 60.7 (N–H), 38.4 (N–H_2), 20.5 (CH_3), 20.7 (CH_2); elemental analysis calcd for $C_{10}H_{20}BrCuN$: C, 38.41; H, 6.77; N, 8.96; found, C, 38.81; H, 6.12; N, 9.04.

3.1.3. [Cu(1,3-dimesityl-3,4,5,6-tetrahydropyrimidin-2-ylidene)$_2^+$ CuBr$_2^-$] (2). In a 100 mL Schlenk flask were added copper (I) chloride (0.370 g, 3.74 mmol), 1,3-dimesityl-3,4,5,6-tetrahydropyrimidinium bromide (1.50 g, 3.74 mmol) and sodium *tert*-butoxide (0.36 g, 3.75 mmol). Dry THF was added (40 mL) under an inert atmosphere and the mixture was magnetically stirred for 24 h at room temperature. The reaction mixture was filtered through a plug of celite and the solvent was evaporated in vacuo, leaving a light pink colored precipitate behind. Recrystallization from dichloromethane/pentane yielded 2.3 g (88%) of the desired compound. FTIR (ATR mode): 3275 (br), 2944 (br), 2912 (br), 1608 (br), 1509 (s), 1481 (br), 1443 (br), 1302 (s), 1205 (s), 1034 (br), 993 (br), 856 (s), 722 (br), 649 (br), 611 (br) cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.74 (24H, O–H_3 of mesityl), 2.10 (m, 4H of CH_2), 2.27 (s, p–CH_3 of mesityl), 3.10 (t, 8H, N–H_2), 6.89 (s, 8H, aromatic); ^{13}C NMR ($CDCl_3$): δ 18.2 (o–CH_3 of mesityl), 21.2 (p-CH_3 of mesityl), 20.0 (CH_2), 44.3 (N–H_2), 130.1, 135.1, 138,7, 141.9 (aromatic C), 198.9 (C:–N); elemental analysis calcd for $C_{44}H_{56}Br_2Cu_2N_4$: C, 56.96; H, 6.08; N, 6.04. Found: C, 57.63; H, 6.14; N, 6.05.

3.1.4. PS-DVB–CH_2–OCO–$CF_2NCF_2NCF_2$–COOCu(1,3-di(2-propyl)-3,4,5,6-tetrahydropyrimidin-2-ylidene) (3). PS-DVB-CH_2-OH (1.00 g, 1.1 mmol OH/g) was suspended in dry THF (20 mL). Perfluoroglutaric anhydride (1.00 mol equiv, 246 mg, 1.10 mmol) was added. Stirring was continued for 2 h, then the product was filtered off and washed three times with THF. It was dried in vacuo resulting in a white solid (1.35 g). FT-IR (ATR-mode): 3024 (br), 2 920(br), 1773 (s), 1600 (br), 1492 (s), 1451(s), 1306 (br), 1240 (br), 1174 (br), 1141 (br), 1046 (br), 1028 (br), 942 (br,) 871 (br), 823 (w), 747 (s), 696 (s) cm^{-1}. The solid was re-suspended in THF (10 mL) and 1.0 equiv of NaOH (46 mg) dissolved in 25 mL of water was added. The mixture was stirred for 2 h, then the solid was filtered off, washed three times with water and re-suspended in 20 mL of water. $AgNO_3$ (1.30 mol equiv, 230 mg,

1.43 mmol), dissolved in 10 mL of water, was added and stirring was continued for a further 4 h. The product was filtered and washed three times each with water, diethyl ether and pentane. Drying in vacuo gave a white solid (1.52 g). FT-IR (ATR-mode): 3058 (br), 3024 (br), 2918 (br), 2848 (br), 1772 (br), 1654 (br), 1600 (br), 1510(s), 1492 (s), 1450 (s), 1372 (w), 1177 (w), 1153 (w), 1027 (w), 906 (br), 841 (w), 820, (w), 749 (m), 696 (s). The solid was re-suspended in THF (25 mL) and **2** (65 mg, 0.20 mmol) was added. Stirring was continued for a further 4 h. The product was filtered off, washed with THF, dichloromethane and pentane and dried in vacuo to yield a brown colored powder (1 g). FT-IR (ATR-mode): 3057 (br), 3023 (br), 2918 (br), 2848 (br), 1657 (br), 1600 (br), 1491 (s), 1450 (br), 1370 (br), 1285 (br), 1155 (w), 1055 (w), 1027 (w), 947 (br), 835 (br), 749 (m), 696 (s) cm^{-1}. Cu content as determined by ICP-OES after dissolving a 20.0 mg sample in aqua regia: 4.15 μmol/g.

3.2. Typical procedure for hydrosilylation reactions

In a 50 mL Schlenk tube the catalyst (1.0 mmol%) was dissolved in 1 mL of THF, sodium *tert*-butoxide (5.5 mg, 15 mmol%) and 4 mol equiv of triethylsilane (166 mg, 1.42 mmol) were added and the solution was stirred for 5 min. Then, the carbonyl compound (0.20–0.40 mmol), dissolved in 2 mL of THF, was added to the reaction mixture. The solution was heated to 65 °C. Product conversion was monitored by GC–MS at defined time intervals. Compounds were identified by GC–MS. Quantification was accomplished using an internal standard (*tert*-butylbenzene).

3.3. Typical procedure for cyanosilylation reactions

In a 50 mL Schlenk tube the catalyst (1.0 mmol%) was dissolved in 1 mL of dichloroethane, then 2 mol equiv of trimethylsilylcyanide (71 mg, 0.71 mmol), dissolved in 2 mL of dichloroethane, as well as the carbonyl compound (0.20–0.40 mmol) were added. The solution was heated to 75 °C. Product conversion was monitored by GC–MS at defined time intervals. Compounds were identified by GC–MS. Quantification was accomplished using an internal standard (*tert*-butylbenzene).

3.4. Typical procedure for the ATRP of MMA

A 50 mL Schlenk flask was charged with 5 mL of diphenyl ether and the corresponding catalyst (0.5 mmol%), MMA (3.0 mL 28.3 mmol), EBIB (1.0 mmol%) and 0.500 mol equiv of *tert*-butylbenzene (internal standard for monitoring of monomer conversion) were added. 0.200 mL of the reaction solution was withdrawn, mixed with acetone, and used as reference solution. Then the reaction mixture was heated to 90 °C. At appropriate timed intervals, 0.500 mL aliquots of the solution were withdrawn and 3.0 μl thereof were dissolved in acetone. Acetone solutions were analysed by GC–MS, percent conversions were calculated relative to the reference solution. The rest of the 0.500 mL samples were mixed with methanol, the polymer that precipitated was filtered off, washed with methanol and re-dissolved in THF, passed through 0.2 μm Teflon filters and analysed by GPC.

3.5. X-ray measurement and structure determination of 1a and 2

Data collection was performed on a Nonius Kappa CCD equipped with graphite-monochromatized Mo-K_α-radiation ($\lambda=0.71073$ Å) and a nominal crystal to area detector distance of 36 mm. Intensities were integrated using DENZO and scaled with SCALEPACK.[30] Several scans in ϕ and ω direction were made to increase the number of redundant reflections, which were averaged in the refinement cycles. This procedure replaces in a good approximation an empirical absorption correction. The structures were solved with direct methods SHELXS86 and refined against F^2 SHELX97.[31] The function minimized was $\Sigma[w(F_o^2-F_c^2)^2]$ with the weight defined as $w^{-1}=[\sigma^2(F_o^2)+(xP)^2+yP]$ and $P=(F_o^2+2F_c^2)/3$. All non-hydrogen atoms were refined with anisotropic displacement parameters. Positions of hydrogen atoms were calculated and refined isotropically.

3.6. Supporting information available

The crystallographic data for **1** and **2** have been deposited with the CCDC-No. xxx and xxy, and at the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK. (fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk or www:http://www.ccdc.cam.ac.uk).

4. Summary

In summary we have developed new copper (I)-1,3-R_2-3,4,5,6-tetrahydropyrimidin-2-ylidene-based catalysts. Immobilization was accomplished at a Merrifield type support. All catalysts showed unprecedented high activity in the cyanosilylation and C=O hydrosilylation reactions resulting in TONs up to 100,000. Unfortunately, all catalysts failed to provide suitable ATRP systems capable of polymerizing methyl methacrylate (MMA) in a perfectly controlled way.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2005.07.116

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Synthesis and utilization of functionalized polystyrene resins

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Abstract—Co-polymerised 4-bromopolystyrene has been converted to a range of polymer-supported reagents and scavengers by bromine–magnesium exchange using Oshima's trialkylmagnesate complex followed by quenching with a variety of electrophiles. Mitsunobu, halogenation and Wittig reactions, were explored to assess the utility of the resins for target oriented and diversity oriented synthesis.

1. Introduction

The use of solid-supported reagents and scavengers have become increasingly popular in organic chemistry as their use bypasses the purification difficulties associated with traditional solution-phase reactions whilst retaining the beneficial aspects, such as ease of reaction monitoring (TLC, LC–S, NMR, etc.). Solid-supported reagents also enable the use of excess reagents to drive the reaction to completion, without complicating the work up procedure. Simple filtration, washing and solvent removal is all that is required to work up the reactions, which is particularly beneficial to high throughput synthesis.[1] Attaching toxic or hazardous compounds to a solid support reduces the risks associated with the reagent. Simple filtration of solid-supported catalysts also means that the catalyst can be recovered, regenerated and reused, reducing the cost associated with these reagents. The simple work up techniques associated with polymer-supported reagents and scavengers also make the use of automation a real possibility. Robots can carry out all the manipulations required and large libraries can be generated quickly and efficiently.

Perhaps the most important insoluble support for organic synthesis is cross-linked polystyrene. Derivatized polystyrene can be made either by *co*-polymerisation of styrene, divinylbenzene[2] and functionalized styrene, or in a more divergent fashion by functionalizing a polystyrene starting material. The functionalization of polystyrene has been achieved by two methods with relatively small diameter (<75 μm) polystyrene beads: (1) by direct lithiation of the polystyrene[3] and (2) by halogen–metal exchange.[4] These procedures are not applicable nor optimized for relatively large diameter (>150 μm) cross-linked polystyrene functionalization.

Beads with diameters greater than 150 μm possess optimal handling properties. Larger diameter resins (>150 μm) are free flowing, greatly reducing the problem of static often associated with smaller diameter resins, which makes these smaller resins more difficult to manipulate. The rate of filtration of the larger diameter beads is faster, with none of the polymer support passing through the filter. This is often a problem with the smaller diameter beads requiring the reaction mixture to be re-filtered. Although smaller diameter beads often have increased chemical reaction rates, this needs to be balanced by the improved handling and increased functionality per bead associated with larger beads.

In this paper we report on the development of a cost effective method of derivatizing 4-bromopolystyrene, in one step, to generate a range of functionalized resins. Moreover, this methodology can be used on small and large diameter (up to at least 600 μm) beads of polystyrene. These reagents can be used as polymer-supported reagents, scavengers or supports for target oriented and diversity oriented synthesis.

Triphenylphosphine polystyrene (**1**) is one of the most successful polymer-supported reagents developed, as it avoids the need for troublesome purification to remove triphenylphosphine oxide. Triphenylphosphine is used in a wide range of reactions, including Mitsunobu,[5] halogenation[6] and Wittig[7,8] reactions. Furthermore, it is commonly

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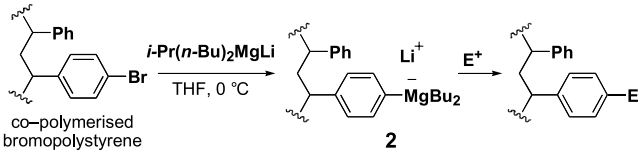
used as a ligand for metal catalysed reactions, such as the Suzuki reaction.[9] Polymer-supported triphenylphosphine, on cross-linked polystyrene, is usually synthesised by bromination followed by lithiation of the polystyrene. The lack of complete selectivity in this process results in less chemically defined resin (**1b**). Higher quality polymer-supported triphenylphosphine has been synthesised by many different methods such as ring opening methathesis polymerization of norbornadiene structures,[10–12] and radical *co*-polymerisation[2] of diphenyl-(4-vinylphenyl)phosphane, styrene and cross-linkers; however, these resins are either expensive or not commercially available.

2. Results and discussion

2.1. Functionalisation of bromopolystyrene

Previously we have reported a reproducible method of derivatising bromopolystyrene using Oshima's trialkylmagnesate complex[13] *i*-Pr(*n*-Bu)$_2$MgLi to form a Grignard-like polymer (**2**) quantitatively, which was then intercepted with a variety of electrophiles to form the derivatised polymer beads (Scheme 1).[14]



Scheme 1. Functionalization of 4-bromopolystyrene resin.

Polymer-supported triphenylphosphine **1a** was prepared using this methodology with chlorodiphenylphosphine as the electrophile (Table 1). Combustion analysis revealed that the commercially available co-polymerised bromopolystyrene starting material contained 16% bromine. When isopropylmagnesium chloride or butyllithium was used to metalate the polymer a significant percentage of bromine in the polymer still remained after the reaction. While this was expected for isopropylmagnesium, 4-bromobenzene reacts completely using butyllithium at −78 °C to form phenyllithium. This indicated that diffusion of butyllithium throughout the resin is a problem. In contrast, the magnesium–ate complex reacts with all the aryl bromides throughout the beads.

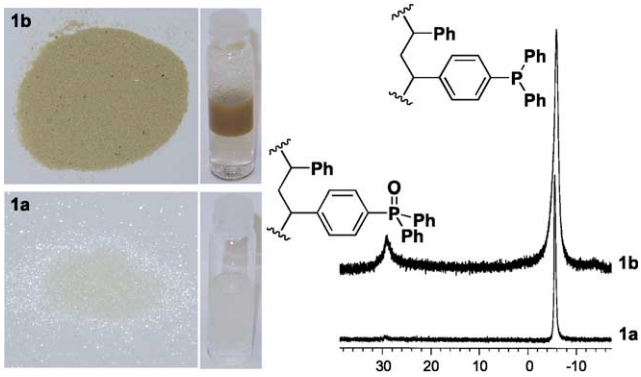


Figure 1. ^{31}P NMR and photographs of triphenylphosphine polystyrene resin **1a** (synthesized using methodology described in this paper) and **1b** (commercially available). Each polymer is photographed dry and suspended in solvent (200 mg beads in 2 ml CH_2Cl_2).

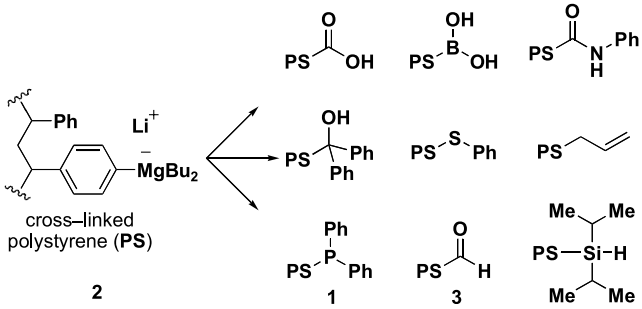
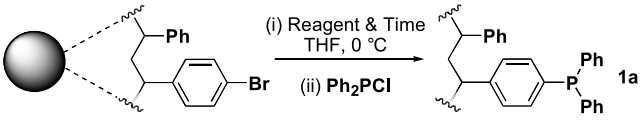


Figure 2.

Longer reaction times were required for larger diameter beads, with 12 h being necessary to ensure complete functionalization. This method of functionalizing polystyrene gave high purity products, with only trace amounts of phosphine oxide being detected by gel-phase ^{31}P NMR. A higher proportion of phosphine oxide was present in commercially available resin **1b** (Fig. 1).

This methodology can be used with a wide range of electrophiles, including CO_2, trimethylborate, DMF, diisopropylchlorosilane[14] and allyl bromide, to generate a variety of resins (Fig. 2), which could be used as polymer-supported reagents and scavengers, and as supports for solid phase synthesis.

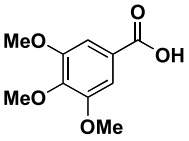
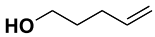
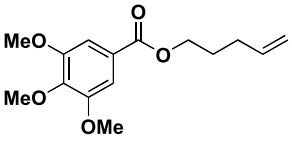
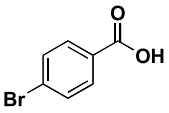
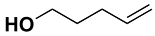
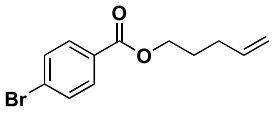
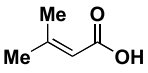
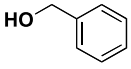
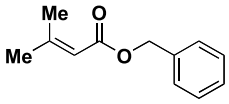
Table 1. Synthesis of triphenylphosphine resin (**1a**)



Bead size (μm)	Reagent	Time (h)	% Br[a]	% P[a]	mequiv/g
150–300	*i*-PrMgCl	5	10.6	0.45	0.15
150–300	*n*-BuLi	5	6.7	2.80	0.90
150–300	*i*-Pr(*n*-Bu)$_2$MgLi	5	0.0	4.20	1.36
400–500	*i*-Pr(*n*-Bu)$_2$MgLi	12	0.0	4.60	1.49
500–600	*i*-Pr(*n*-Bu)$_2$MgLi	12	0.0	4.15	1.34

[a] Starting bromopolystyrene = 16.0% Br: 0% P. The theoretical maximum phosphorous content in product polymer = 5.1%.

Table 2. Mitsunobu reactions[a] comparing triphenylphosphine polystyrene resins **1a** and **1b**

Acid	Alcohol	Product	Polymer reagent	Time (h)	Yield (%)
			**1a**	12	78
			1b	12	68
		4			
			**1a**	12	91
			1b	12	61
		5			
			**1a**	12	87
			1b	12	45
		6			

[a] **1** (1.5 equiv), di-*tert*-butyl azodicarboxylate (1.5 equiv), THF.

2.2. Mitsunobu reaction

Initial work using Mitsunobu reactions showed an increased yield when using resin **1a** compared to the commercial resin **1b**. Di-*tert*-butyl azodicarboxylate (DBAD) was added to the acid, alcohol and triphenylphosphine polystyrene in THF at 0 °C under nitrogen and the reactions were stirred overnight. At the end of the reaction any excess DBAD was scavenged out of the reaction using more triphenylphosphine resin.

Higher yields of **4**, **5** and **6** were obtained for each reaction when using resin **1a** compared to **1b**. One of the major disadvantages of the commercial resin **1b** was encountered during the filtering step. As the resin was so finely powdered occasionally it came through the filter so that re-filtering of the reaction was required. Also, drying the **1b** was problematic. The small diameter beads tended to stick together to form a gum, which was then difficult to dry; no such problems were encountered with resin **1a**. Table 2 shows a summary of the results obtained.

The increased yields obtained using resin **1a**, compared to the **1b** in Mitsunobu reactions led to investigation of other reactions using polymer-supported triphenylphosphine.

2.3. Amide bond formation reactions

The importance of methodology for the efficient formation of amide bonds cannot be overstated. Solid-supported reagents and scavengers can be used to eliminate the necessity for product purification, which can be problematic using standard coupling reagents. A two step strategy was adopted via acid bromide intermediates to synthesize the amides. Cycloheptanecarbonyl bromide was prepared from the corresponding acid using carbon tetrachloride, and polymer-bound triphenylphosphine **1** in dichloromethane. The acid bromide was subsequently used in amide coupling reactions under Schotten–Baumann conditions to give **7** to **10**. The yields for these amide syntheses were comparable when side by side reactions were carried out with **1a** and the commercially available equivalent **1b**. Non-volatile amines, such as cyclohexylamine, required the use of a polymer-bound aldehyde **3** to scavenge out excess amine. This aldehyde resin can be used also as a scavenger to remove excess amines,[7] 1,3-diols and hydride reducing agents.[1] Using cyclohexylamine under standard coupling conditions resulted in a 46% yield of **7**; however, the addition of scavenger resin **3** gave significantly higher yields (>95% purity by ^{1}H NMR). Importantly, the only purification necessary in these reactions was filtration and removal of solvent. The results are summarised in Table 3.

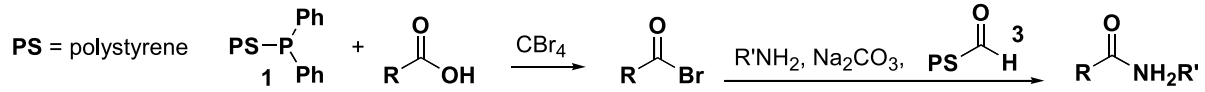
The stability of the resins should also be mentioned. The activity of both the polymer-supported triphenylphosphine **1a** and aldehyde **3** remained the same whether using freshly prepared resin or resin that had been prepared up to a year earlier.

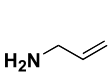
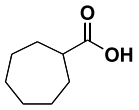
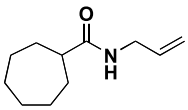
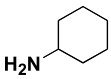
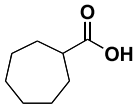
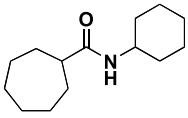
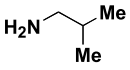
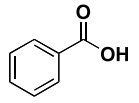
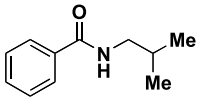
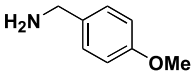
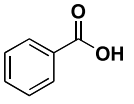
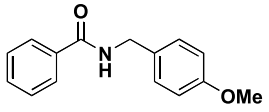
2.4. Wittig reaction

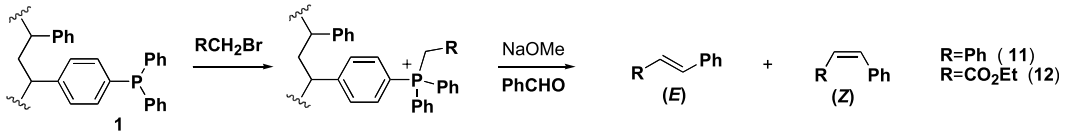
The Wittig reaction is an important reaction in the synthesis of alkenes and one of the most commonly employed reactions using triphenylphosphine. The solution-phase synthesis of stilbene (**11**) via the Wittig reaction results in a 7:3 *E*/*Z* product mixture.[15] In contrast, using solid-supported triphenylphosphine **1b** in the same reaction gives **9** as a 1:1 *E*/*Z* product mixture.[16] Resin **1a** was investigated in this reaction to determine its *E*/*Z* selectivity.

Treatment of the polymer-supported triphenylphosphine **1a** with benzyl bromide generated the phosphonium salt, which was reacted with a stoichiometric quantity of base (NaOMe), followed by 1 equiv of aldehyde (Scheme 2). Filtration of the reaction through a pad of silica generated stilbene **11** in a 48% yield. ^{1}H NMR showed **11** was synthesised in a 51:49 *E*/*Z* product mixture. This result indicates that the selectivity difference between supported

Table 3. Amide bond formation reactions comparing triphenylphosphine polystyrene resins **1a** and **1b**



Amine	Acid	Product		Reagent (**1**)	Scavenger (**3**)	Yield (%)
			**7**	**1a**	No	55
			7	**1b**	No	52
			**8**	**1a**	No	46
			8	**1a**	Yes	79
			**9**	**1a**	Yes	68
			**10**	**1a**	Yes	80



Scheme 2. Witting reaction using solid-supported triphenylphosphine (**1b**).

and unsupported triphenylphosphine (**1a** and **1b** versus Ph_3P) is a general observation and not dependent on the polymer used. A difference between supported and unsupported triphenylphosphine is not observed in the synthesis of **12**, which gives only the *E*-isomer in both cases.

3. Conclusion

We have developed an operationally simple, reliable and cost effective method of metallating throughout small and large diameter co-polymerised 4-bromopolystyrene using Oshima's trialklymagnesiate complex. These polymeric Grignard-like reagents can be quenched with a variety of electrophiles to synthesis a wide range of easy to handle, high purity and stable polymer-supported reagents and scavengers that can be used in target oriented and diversity oriented synthesis.

4. Experimental

4.1. Experimental techniques and apparatus

Experimental techniques and apparatus are standard except as otherwise indicated, reactions were carried out under nitrogen with dry, freshly distilled solvents. Dichloromethane was distilled from calcium hydride. *n*-BuLi in hexane (Aldrich) was titrated with benzyl-biphenyl-4-ylmethylene-amine[17] and anhydrous menthol before use. All other reagents were purified in accordance with the instructions in 'Purification of Laboratory Chemicals'[18] or used as obtained from commercial sources. Yields refer to spectroscopically pure compounds. All reactions were monitored by thin layer chromatography (TLC) using glass plates precoated with Merck silica gel 60 F_{254} or aluminium oxide 60 F_{254}. Visualization was by the quenching of UV fluorescence ($\lambda_{max}=254$ nm) or by staining with ceric ammonium molybdate, potassium permanganate or Dragendorff's reagent (0.08% w/v bismuth subnitrate and 2% w/v KI in 3 M aq. AcOH). Retention factors (R_f) are quoted to 0.01. Melting points were obtained using a Reichert hot plate microscope with a digital thermometer attachment and are uncorrected. Infrared spectra were recorded neat on a Perkin–Elmer Spectrum One spectrometer with internal referencing. Absorption maxima (ν_{max}) are reported in wavenumbers (cm^{-1}) and the following abbreviations are used: w, weak; m, medium; s, strong; br, broad. Proton magnetic resonance spectra were recorded on Bruker Ultrashield 400 or 500. Proton assignments are supported by ^1H–^1H spectra where necessary. Chemical shifts (δ_H) are quoted in ppm and are referenced to the residual non-deuterated solvent peak. Coupling constants (*J*) are reported in Hertz to the nearest 0.5 Hz. Data are reported as follows: chemical shift, integration, multiplicity [br, broad; s, singlet; d, doublet; t, triplet; q, quartet; qui, quintet; sept, septet; m, multiplet; or as a combination of these (e.g. dd, dt, etc.)], coupling constant(s) and assignment. Diastereotopic protons are assigned as X and X′, where the ′ indicates the higher field proton. Carbon magnetic resonance spectra were recorded on Bruker Ultrashield 500 spectrometers. Carbon spectra assignments are supported by DEPT editing and where necessary ^{13}C–^1H (HMQC) correlations. Chemical

shifts (δ_C) are quoted in ppm to the nearest 0.01 ppm, and are referenced to the deuterated solvent. Phosphorous magnetic resonance spectra (^{31}P) were recorded on a DPX 400 MHz spectrometer. Chemical shifts (δ_P) are quoted in ppm to the nearest 0.01 ppm and are referenced to H_3PO_4 (external). LCMS spectra were recorded on an HP/Agilent MSD LC–S APCI 120-1000 full gradient ACq $T=1$ min 1 μl. High resolution mass measurements were made by the EPSRC mass spectrometry service (Swansea) and reported mass values are within the error limits of ± 5 ppm mass units. Microanalyses were performed by the University of Cambridge Microanalytical Laboratory in the Department of Chemistry, and are quoted to the nearest 0.1% for all elements except for hydrogen, which is quoted to the nearest 0.05%. Reported atomic percentages are within the error limits of $\pm 0.4\%$.

4.2. General procedure for functionalizing resins

i-Pr(*n*-Bu)$_2$MgLi was prepared by stirring *i*-PrMgCl (2 equiv, 2.0 M in THF) in anhydrous THF (quantity to result in a 0.2 M solution of *i*-Pr(*n*-Bu)$_2$MgLi) at 0 °C under a nitrogen atmosphere and adding *n*-BuLi (4 equiv, 2.5 M solution in hexanes). The resulting solution was stirred for a further 30 min to leave a clear yellow solution. Dry, white *co*-polymerized (74% styrene; 1% divinylbenzene; 25% 4-bromostyrene) 4-bromopolystyrene beads (1 equiv, 2.0 mmol/g, 150–300 μm) were swollen in anhydrous THF (10–30 ml of THF per gram of beads) for 15 min at 0 °C under a nitrogen atmosphere and then the preformed *i*-Pr(*n*-Bu)$_2$MgLi was added and the resultant mixture stirred slowly. After 5 h (the beads were a golden yellow colour) the electrophile (6 equiv, freshly purified) was added and the mixture was agitated and allowed to warm to room temperature (22 °C) over 2 h. The beads were then filtered and washed with THF (3×5 min), CH_2Cl_2:MeOH 1:1 (3×5 min), CH_2Cl_2 (5×5 min), and dried under reduced pressure to give free-flowing, white beads. Larger beads (400–500 or 500–600 μm) require 12 h to metallate completely throughout the beads

Electrophile	IR absorbance	Elemental analysis
i-Pr$_2$SiHCl	2099 Si–H	Si 4.62%
Ph$_2$PCl	1433 P–C	P 4.60%
4-Iodophenyl isocyanate	1654 (Amide)	N 1.17%

Electrophile	IR absorbance
Carbon dioxide	3372 O–H 1687 C=O
Benzophenone	3414 O–H 1497–1450 C=C
DMF	1700 C=O
Allyl bromide	3026, 1638, 993, 911 RCH=CH$_2$
Trimethyl borate	3358 O–H 1340 B–O
S_8	3300 S–H
PhSSPh	2857 C–S

4.3. General Mitsunobu reaction procedure

To a mixture of carboxylic acid (1 equiv), alcohol (1.5 equiv) and polymer-bound triphenylphosphine (0.9 mmol/g, 1.5 equiv) in THF (ca. 0.1 M) under nitrogen at 0 °C was added di-*tert*-butyl azodicarboxylate (1.5 equiv) in THF (1 ml). The reaction was warmed to room temperature and stirred overnight. The reaction was filtered and the resins washed with CH_2Cl_2. The organic filtrate was washed with 3 M HCl (×2), brine (×2) dried ($MgSO_4$), filtered through a pad of silica and concentrated in vacuo to yield a colourless oil.

4.3.1. 3,4,5-Trimethoxy-benzoic acid pent-4-enyl ester (4). Yield 78%; R_f 0.29 (SiO_2; CH_2Cl_2); ν_{max} (neat)/cm^{-1} 1712s (C=O), 1124s (C–H); δ_H (500 MHz; $CDCl_3$) 7.32 (2H, s, aryl C*H*), 5.86 (1H, ddt, $J=16.0$, 15.0, 10.0 Hz, C*H*CH$_2$), 5.09 (1H, d, $J=16.0$ Hz, CH=C*H*′H), 5.03 (1H, d, $J=10.0$ Hz, CH=CH′*H*), 4.35 (2H, t, $J=6.5$ Hz, OC*H*$_2$CH$_2$), 3.92 (9H s, OC*H*$_3$), 2.22 (2H, dt, $J=15.0$, 6.5 Hz, OCH$_2$CH$_2$C*H*$_2$CH), 1.88 (2H, tt, $J=6.5$, 6.0 Hz, OCH$_2$C*H*$_2$); δ_C (125 MHz; $CDCl_3$) 166.21 (C), 152.95 (C), 142.24 (C), 137.47 (CH), 125.45 (C), 115.35 (CH$_2$), 106.85 (CH), 64.56 (CH$_2$), 60.91 (CH$_3$), 56.25 (CH$_3$), 30.18 (CH$_2$), 27.96 (CH$_2$); LCMS (MeCN) 281 (MH$^+$); HRMS (EI) found 281.1385 $C_{15}H_{21}O_5$ (MH$^+$) required 281.1384.

4.3.2. 4-Bromo-benzoic acid pent-4-enyl ester (5). Yield 91%; R_f 0.81 (SiO_2; CH_2Cl_2); υ_{max} (neat)/cm^{-1} 1717s (C=O); δ_H (500 MHz; $CDCl_3$) 7.89 (2H, d, $J=8.5$ Hz, aryl CH), 7.58 (2H, d, $J=8.5$ Hz, aryl C*H*), 5.88–5.78 (1H, m, C*H*=CH$_2$), 5.10–5.03 (1H, br dt, $J=17.0$ Hz, CH=C*H*′H), 5.02–5.00 (1H, br dt, $J=10.0$ Hz, CH=CH′*H*), 4.32 (2H, t, $J=6.5$ Hz, OC*H*$_2$), 2.21 (2H, dt, $J=14.0$, 6.5 Hz, OCH$_2$CH$_2$C*H*$_2$), 1.87 (2H, tt, $J=7.0$, 6.5 Hz, OCH$_2$C*H*$_2$); δ_C (125 MHz; $CDCl_3$) 165.86 (C), 137.35 (CH), 131.70 (CH), 131.09 (CH), 129.35 (C), 127.96 (C), 110.00 (CH$_2$), 64.65 (CH$_2$), 30.13 (CH$_2$), 27.88 (CH$_2$); LCMS (MeCN) 271 (MH$^+$); HRMS (ES) found 291.0001 $C_{12}H_{13}BrNaO_2$ (MNa$^+$) required 290.9997.

4.3.3. 3-Methyl-but-2-enoic acid benzyl ester (6). Yield 87%; R_f 0.88 (SiO_2; CH_2Cl_2); υ_{max} (neat)/cm^{-1} 1715s (C=O), 1648m (C=C); δ_H (500 MHz; $CDCl_3$) 7.53–7.22 (5H, m, aryl C*H*), 5.75 (1H, s, C*H*CO$_2$Bn), 5.12 (2H, s, C*H*$_2$), 2.18 (3H, s, C*H*$_3$), 1.88 (3H, s, C*H*$_3$); δ_C (125 MHz; $CDCl_3$) 166.41 (C), 157.23 (C), 136.51 (C), 128.51 (CH), 128.11 (C), 128.01 (CH), 115.82 (CH), 65.36 (CH$_2$) 27.42 (CH$_3$), 20.28 (CH$_3$); LCMS (MeCN) 191 (MH$^+$); HRMS (ES) found 213.0890 $C_{12}H_{14}NaO_2$ (MNa$^+$) required 213.0891.

4.4. Amide formation

4.4.1. Cycloheptanecarboxyl allylamide (7). A mixture of cycloheptane carboxylic acid (0.14 ml, 1.03 mmol), polymer-bound triphenylphosphine (2.2 mmol) and carbon tetrabromide (365 mg, 1.1 mmol) in dry CH_2Cl_2 (8 ml) was stirred under nitrogen at room temperature for 3 h. The beads were filtered and the solvent removed in vacuo. To a solution of allylamine (0.11 ml, 0.11 mmol) in sodium carbonate solution (2 M, 8 ml) was added the bromide in dry CH_2Cl_2 (8 ml). The mixture was stirred over night at room temperature. The organic layer was separated and washed with sodium bicarbonate solution (×2), brine (×2), dried ($MgSO_4$), filtered through a pad of silica and concentrated in vacuo to give the title compound as a white solid (95 mg, 55%). R_f: 0.29 (SiO_2; Hexane/Ethyl acetate; 10:4); ν_{max} (neat)cm^{-1} 3299 (N–H), 2922 (C–H), 1637 (C=O); δ_H

(500 MHz, $CDCl_3$) 5.85–5.76 (1H, m, C*H*=CH_2), 5.65 (1H, s, N*H*), 5.14 (1H, dd, J=17.0, 1.5 Hz, CH=CH*H'*), 5.09 (1H, dd, J=10.0, 1.0 Hz, CH=C*H*H'), 3.83 (2H, t, J=5.5 Hz, HNCH_2), 2.26–2.23 (1H, m, C*H*CO), 1.90–1.83 (2H, m, cycloheptane ring) 1.80–1.46 (10H, m, cycloheptane ring); δ_C (125 MHz, $CDCl_3$) 176.09 (C), 133.57 (CH), 115.06 (CH_2), 46.52 (CH), 40.70 (CH_2), 30.75 (CH_2), 27.12 (CH_2), 25.62 (CH_2); LCMS (MeCN): 182.1 (MH^+); mp 44–46 °C; HRMS (ES) found 204.1428 $C_{11}H_{19}NONa$ (MNa^+) required 204.1436.

4.4.2. Cycloheptanecarboxyl cyclohexylamide (8).[19] A mixture of cycloheptane carboxylic acid (0.03 ml, 0.26 mmol), polymer-bound triphenylphosphine (644 mg, 0.58 mmol) and carbon tetrabromide (96 mg, 0.29 mmol) in dry CH_2Cl_2 (5 ml) was stirred under nitrogen at room temperature for 3 h. The beads were removed by filtration and the solvent removed in vacuo. To a solution of cyclohexylamine (0.045 ml, 0.39 mmol) in sodium carbonate solution (2 M, 5 ml) was added the bromide in dry CH_2Cl_2 (5 ml). The mixture was stirred over night at room temperature. The polymer-bound aldehyde (**3**) was added and the reaction stirred overnight. The beads were removed by filtration and the organic layer was separated and washed with sodium bicarbonate solution (×2), brine (×2), dried ($MgSO_4$) and the solvent was removed in vacuo to yield the title compound as a light yellow solid (46 mg, 79%). R_f: 0.23 (SiO_2; Hexane/Ethyl acetate; 10:4); ν_{max} (neat) cm^{-1} 3296 (N–H), 2923 (C–H), 1635 (C=O); δ_H (400 MHz, $CDCl_3$) 5.32–5.01 (1H, br s, N*H*), 3.79–3.70 (1H, m, HNC*H*), 2.16–2.15 (1H, m, C*H*CO), 1.89–1.84 (4H, m), 1.79–1.35 (15H, m), 1.12–1.11 (3H, m); δ_C (125 MHz, $CDCl_3$) 175.29 (C), 47.75 (CH), 47.71 (CH), 32.27 (CH_2), 30.81 (CH_2), 27.12 (CH_2), 25.69 (CH_2), 24.61 (CH_2), 23.89 (CH_2); mp 153–157 °C; HRMS (ES) found 246.1848 $C_{14}H_{25}NONa$ (MNa^+) required 246.1858.

4.4.3. *N*-Isobutyl-benzamide (9).[20] A mixture of benzoic acid (30 mg, 0.25 mmol), polymer-bound triphenylphosphine (0.5 mmol) and carbon tetrabromide (97 mg, 0.29 mmol) in dry CH_2Cl_2 (3 ml) was stirred under nitrogen at room temperature for 3 h. The beads were filtered and the solvent removed in vacuo. To a solution of isobutylamine (0.04 ml, 0.39 mmol) in sodium carbonate solution (2 M, 3 ml) was added the bromide in dry CH_2Cl_2 (3 ml). The polymer-bound aldehyde (**3**) was added and the reaction stirred overnight. The beads were removed by filtration and the organic layer was separated and washed with sodium bicarbonate solution (×2), brine (×2), dried ($MgSO_4$) and the solvent was removed in vacuo to yield the title compound as a white solid (30 mg, 68%). R_f: 0.28 (SiO_2; Hexane/Ethyl acetate; 2:1); ν_{max} (neat) cm^{-1} 3321 (N–H), 2960 (C–H), 1639 (C=O), 1541 (C=C); δ_H (500 MHz, $CDCl_3$) 7.77 (2H, d, J=7.0 Hz, ArH), 7.53–7.50 (1H, m, ArH), 7.43 (2H, t, J=7.5 Hz, ArH), 6.18 (1H, br s, N*H*), 3.31 (2H, t, J=6.5 Hz, NHCH_2), 1.92 (1H, sept, J=6.5 Hz, $NHCH_2CH$), 1.00 (6H, d, J=6.5 Hz, CH_3); δ_C (125 MHz, $CDCl_3$) 167.62 (C), 134.97 (C), 131.32 (CH), 128.58 (CH), 126.81 (CH), 47.36 (CH_2), 28.65 (CH), 20.18 (CH_3); LCMS (MeCN): 178 (MH^+); mp 52–54 °C, lit. 55 °C.[20]

4.4.4. *N*-(4-Methoxy-benzyl)-benzamide (10).[20,21] A mixture of benzoic acid (30 mg, 0.25 mmol), polymer-bound triphenylphosphine (0.5 mmol) and carbon tetrabromide (97 mg, 0.29 mmol) in dry CH_2Cl_2 (3 ml) was stirred under nitrogen at room temperature for 3 h. The beads were filtered and the solvent removed in vacuo. To a solution of 4-methoxy-benzylamine (0.05 ml, 0.39 mmol) in sodium carbonate solution (2 M, 3 ml) was added the bromide in dry CH_2Cl_2 (3 ml). The polymer-bound aldehyde (**3**) was added and the reaction stirred overnight. The beads were removed by filtration and the organic layer was separated and washed with sodium bicarbonate solution (×2), brine (×2), dried ($MgSO_4$) and the solvent was removed in vacuo to yield the title compound as a pale yellow solid (48 mg, 80%). R_f: 0.26 (SiO_2; Hexane/Ethyl acetate; 2:1); ν_{max} (neat) cm^{-1} 3315 (N–H), 2934 (C–H), 1636 (C=O), 1509 (C=C), 1244 (C–H); δ_H (500 MHz, $CDCl_3$) 7.79 (2H, dd, J=7.5, 1.0 Hz, ArH), 7.52–7.50 (1H, m, ArH), 7.44 (2H, t, J=7.5 Hz, ArH), 7.28 (2H, d, J=8.0 Hz, ArH), 6.90 (2H, d, J=8.0 Hz, ArH), 6.52 (1H, br s, N*H*), 4.57 (2H, d, J=5.5 Hz, NHCH_2), 3.81 (3H, s, OCH_3); δ_C (125 MHz, $CDCl_3$) 167.28 (C), 159.13 (C), 134.49 (C), 131.48 (CH), 130.33 (C), 129.30 (CH), 128.55 (CH), 126.97 (CH), 114.17 (CH), 55.32 (CH_3), 43.63 (CH_2); LCMS (MeCN): 241 (MH^+); mp 91–94 °C, lit. 87–88 °C.[20,21]

4.5. Wittig reaction[22]

4.5.1. Stilbene (11). Benzyl bromide (0.22 ml, 1.8 mmol) was added dropwise with stirring to a suspension of a polymer-bound triphenylphosphine (1.0 g, 0.9 mmol) in *N*,*N*-dimethylformamide (15 ml). The mixture was stirred over 48 h at 70 °C, cooled, filtered, washed with toluene (×10), CH_2Cl_2 (×10), diethyl ether (×10) and dried to yield the phosphonium salt as white solid (954 mg).

To a suspension of polymer-bound phosphonium salt (533 mg, 0.375 mmol) in THF at −10 °C was added a suspension of sodium methoxide (54 mg, 1.02 mmol) in methanol dropwise. After 3 h of stirring at room temperature the reaction was cooled down to 10 °C, and benzaldehyde (0.11 ml, 1.03 mmol) was added dropwise. The mixture was stirred over night at room temperature, refluxed for 3 h, filtered and washed with THF (×10), CH_2Cl_2 (×10) and diethyl ether (×10). The combined organic layers were dried ($MgSO_4$), filtered through a pad of silica and concentrated in vacuo to give the title compound as a 49:51 ratio of *E*/*Z* isomers (32 mg, 48%).

4.5.2. (*Z*)-stilbene (*Z*)-11. Colourless oil; R_f: 0.28 (SiO_2; Hexane); δ_H (400 MHz, $CDCl_3$) 7.27–7.19 (10H, m, C*H* aryl), 6.61 (2H, s, C*H*Ph).

4.5.3. (*E*)-stilbene (*E*)-11. White solid; R_f: 0.23 (SiO_2; Hexane); δ_H (400 MHz, $CDCl_3$): 7.53 (4H, d, J=8.0 Hz, C*H* aryl), 7.37 (4H, t, J=8.0 Hz, C*H* aryl), 7.27 (2H, t, J=7.25 Hz, C*H* aryl), 7.12 (2H, s, C*H*Ph); mp 102–104 °C.[22]

4.5.4. (*E*)-2-Methyl-3-phenyl-acrylic acid ethyl ester (12).[23] Ethyl-2-bromo-propioate (0.23 ml, 1.8 mmol) was added dropwise with stirring to a suspension of a polymer-bound triphenylphosphine (1.0 g, 0.9 mmol) in *N*,*N*-dimethylformamide (15 ml). The mixture was stirred over 48 h at 70 °C, cooled, filtered, washed with toluene (×10),

CH_2Cl_2 (×10), diethyl ether (×10) and dried to yield the phosphonium salt as white solid (983 mg).

To a suspension of polymer-bound phosphonium salt (400 mg, 0.3 mmol) in THF at −10 °C was added a suspension of sodium methoxide (16.4 mg, 0.31 mmol) in methanol dropwise. After 3 h of stirring at room temperature the reaction was cooled down to −10 °C, and benzaldehyde (0.03 ml, 0.30 mmol) was added dropwise. The mixture was stirred over night at room temperature, refluxed for 3 h, filtered and washed with THF (×10), CH_2Cl_2 (×10) and diethyl ether (×10). The combined organic layers were dried ($MgSO_4$), filtered through a pad of silica and concentrated in vacuo to give the title compound as a colourless oil (42 mg, 61%). ν_{max} (neat) cm^{-1} 2983 (C–), 1706 (C=O), 1253 (C–), 1111; δ_H (500 MHz, $CDCl_3$) 7.71 (1H, br s, C*H*=CCH$_3$), 7.44–7.32 (5H, m, Ar*H*), 4.30 (2H, q, J=7.25 Hz, CH_3CH_2O), 2.14 (3H, d, J=1.5 Hz, CC*H*$_3$), 1.38 (3H, t, J=7.25 Hz, C*H*$_3$CH$_2$O); δ_C (125 MHz, $CDCl_3$) 168.70 (C), 138.63 (CH), 136.01 (C), 129.62 (CH), 128.68 (C), 128.34 (CH), 128.26 (CH), 60.86 (CH_2), 14.33 (CH_3), 14.04 (CH_3); LCMS (MeCN): 191 (MH^+).

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Synthesis and application of polytetrahydrofuran-grafted polystyrene (PS–PTHF) resin supports for organic synthesis

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Abstract—Cross-linked polystyrene (PS) with polytetrahydrofuran (PTHF) chains were prepared for use in solid phase organic synthesis (SPOS). The resins were prepared from styrene, styrene–PTHF macromonomers and cross-linkers 1,4-bis[4-vinylphenoxy]butane or divinylbenzene by suspension polymerization. The styrene–PTHF macromonomers were prepared by cationic polymerization of 4-vinylbenzyl bromide and 4-(4-vinylphenoxy)butyl iodide activated by silver hexafluoroantimonate and 4-(5-hydroxypentyl)styrene activated by triflic anhydride. Alternatively, polytetrahydrofuran–grafted polystyrene (PS–PTHF) resins could also be directly prepared from 5-hydroxypentyl *J*anda*J*el by cationic polymerization using triflic anhydride as the initiator. These PS–PTHF resins exhibited good swelling characteristics across a wide spectrum of polar and non-polar solvents. These resins were used in the synthesis of 3-methyl-1-phenyl-2-pyrazolin-5-one, which requires β-ketoester formation at low temperature (−78 °C), resulting in good yield and product purity; whereas the same synthesis carried out on PEG–grafted PS (PS–PEG) resin resulted in incomplete synthesis.

1. Introduction

Solid-phase organic synthesis (SPOS) continues to be important in the development of libraries of new molecules.[1] As more complex syntheses are investigated, specialized solid-phase supports are needed to allow facile library development. In essence, the research chemist needs to have a 'menu' of resins to choose from so as to adapt solution-phase synthesis with little or no modification to the solid-phase. The physical and chemical properties of the solid support play an important role in successful implementation of a SPOS strategy. Commercially available Merrifield and *J*anda*J*el resins have proven to be robust supports and allow access to reactive sites because of their good swelling characteristics. These resins are lightly cross-linked styrene-based polymers. *J*anda*J*els (JJ) have improved swelling when evaluated against Merrifield Resins (MF) by virtue of the more flexible cross linker 1,4-bis[4-vinylphenoxy] butane (**7**) compared to the divinylbenzene cross-linker for Merrifield resin.[2] These resins swell well in low polarity solvents such as benzene, toluene, THF, and chlorinated hydrocarbons, as well as DMF. Because of the excellent swelling of *J*anda*J*el resins (e.g., 8–10 ml/g in THF depending on resin functionalization), the environment of the resins becomes more 'solution-like' and thus provides easy access to the reactive sites, and therefore solution phase synthesis conditions can readily be adapted to SPOS.[3] However, polar protic solvents such as alcohols and water do not swell these resins and therefore limits their application, especially in terms of on-bead screening.

Complex multi-step synthesis requires a solid support that can function in both polar and non-polar solvents. Any new solid support needs to provide access to reactive sites in polar as well as non-polar solvents and be robust in severe chemical environments. PEG–grafted polyacrylamide[4] (PAM–PEG; e.g., PEGA) polymer beads as well as PEG–grafted polystyrene[5] (PS–PEG; e.g., TentaGel (TG), ArgoGel) resins have been designed to have utility in polar solvents and have limited swelling in non-polar solvents. However, PEG–grafted polyacrylamide resins have intrinsic limitations since these are not compatible with some common reagents because of the vulnerable amide bond. The grafted PEG chains provide a hydrophilic component to the hydrophobic polystyrene backbone, and exhibit more uniform swelling in both polar and non-polar

Keywords: Organic synthesis; Cross-linked polystyrene; Macromonomers.
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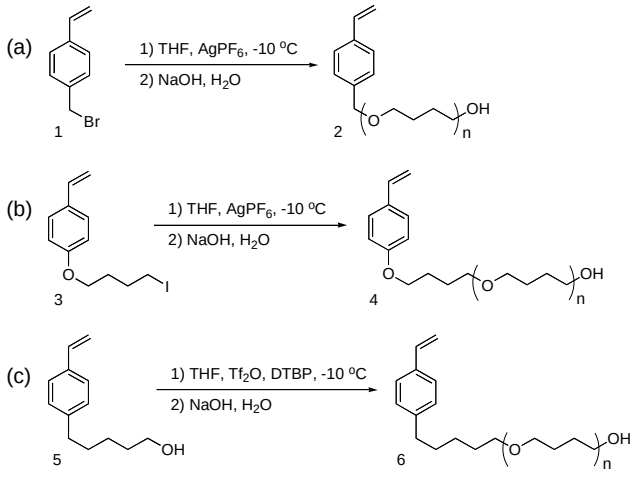
solvents, but the swelling is low compared to the Merrifield and *J*anda*J*el resins, especially in non-polar solvents. PS–PEG resins have superior performance in reactions involving salts and in peptide synthesis. However, studies conducted by Li et al. indicate that the PS resins have superior or equivalent kinetics in many chemical reactions compared to PS–PEG resins.[6] Furthermore, these PS–PEG resins generally have low loading capacity, tend to aggregate and have poor stability in some chemical environments, for example, in acidic media.

In considering new resins that could be adapted to SPOS, we chose to focus on tetrahydrofuran-based resins since tetrahydrofuran is a good organic solvent and is partially miscible with water. Therefore, we speculated that styrene-based resins containing PTHF chains could therefore provide resins with good swelling in a broad spectrum of solvents and increased chemical resistance compared to the PS–PEG resins. Polymerization of THF has been studied over the last 50 years and an extensive body of literature is available on polymeric techniques for preparing THF-based polymers. Based on the literature, two approaches to preparing PS–PTHF resins can be formulated: (1) preparation of macromonomers of styrene–PTHF, followed by suspension polymerization, and (2) grafting of PTHF chains to pre-formed resins similar to the preparation of PS–PEG resins. Evidence for the implementation of the second approach is the reported successful partial graft polymerization of PTHF on polyvinyl chloride (PVC), brominated poly-butadiene and random polymers of styrene and methacryloyl chloride.[7] Styrene–PTHF macromonomers of varying chain length also have been prepared, and successfully used in suspension polymerizations.[8–11] These macromonomers are prepared by cationic ring opening polymerization using initiators prepared from styrene derivatives or end capping of the living polymerization of THF with a styrene compound. For example, vinyl phenoxide PTHF macromonomers have been prepared with low polydispersity by the living polymerization of THF initiated by triethyloxonium tetrafluoroborate and then terminated by end capping with sodium vinyl phenoxide.[8] In another example, macromonomers were prepared by polymerizing THF from vinyl benzyl halides activated by reacting with silver (I) hexafluoroantimonate. PTHF macromonomers have also been prepared from triflic esters of butyl or allyl alcohols.[12]

Herein, we report the preparation of macromonomers 4-vinylbenzyloxy–PTHF **2**, 4-(4-vinylphenoxy)butyl–PTHF **4**, 5-(4-vinylphenyl)pentanoxy–PTHF **6** and suspension polymerization with styrene and styrene-based cross-linkers to produce PS–PTHF resins. We also report the preparation of PS–PTHF resins by a grafting protocol. The synthesis of 3-methyl-1-phenyl-2-pyrazolin-5-one **18** using these resins was used as a test case to evaluate these resins as a support for organic synthesis, particularly to examine the stability of these resins in acidic medium and metallation chemistry at low temperatures (−78 °C).

2. Results and discussion

Macromonomers of 4-vinylbenzyloxy PTHF **2** were prepared from 4-vinylbenzyl bromide **1** activated with silver (I) hexafluoroantimonate (Scheme 1a).[13] The cationic polymerization of THF was carried out in THF at −10 °C, and then terminated by quenching with dilute sodium hydroxide solution, resulting in macromonomers with hydroxyl end groups in quantitative yield.[14]



Scheme 1. Preparation of macromonomers.

The number of PTHF chains, n, was found to be directly proportional to the reaction time and macromonomers of specific chain length were obtained by controlling the reaction times. Two macromonomers of average chain lengths of $n=7.1$ and 13.6 were obtained. The average number of PTHF chains in the macromonomers was calculated by analysis of ^{1}H NMR spectra (Fig. 1), through comparison of the peak ratio of benzyl protons (a: 4.48 ppm) and methylene protons (c: 1.62 ppm). Although the NMR measurement gives an average chain length, these macromonomers contain a statistical distribution of macromonomers with varying chain length (verified by a GPC analysis) and a polydispersity of 1.1 for $n=7.1$ was calculated from the measured distribution.

Since the benzylic carbon of **2** might be susceptible to attack under acidic conditions, two other macromonomers were also prepared, 4-(4-vinylphenoxy)butyl–PTHF **4** and 5-(4-vinylphenyl)pentanoxy–PTHF **6**. Using $AgPF_6$ or $AgBF_4$ activation, 4-(4-vinylphenoxy)butyl iodide was readily converted to the corresponding macromonomers (Scheme 1b). Macromonomers containing $n=17.0$ and 34.0 were prepared using this procedure. However, we were unsuccessful in preparing macromonomer **6** by silver (I) activation from either 4-(5-bromopentyl)styrene or 4-(5-iodopentyl)styrene as precursors, presumably due to lower activity of these aliphatic type halides. We succeeded in making macromonomer **6** from 4-(5-hydroxypentyl) styrene **5** activated with triflic anhydride (Scheme 1c). A macro monomer of number-average molecular weight (M_n) of 689, weight-average molecular weight of (M_w) 747, and polymerization dispersity (M_w/M_n) of 1.1 was prepared (obtained by ESI-TOF, previously calibrated with polyethylene glycol (PEG)) by controlling the reaction time, resulting in a macromonomer with an average chain length of $n=6.9$. All the macromonomers were generally unstable even at low temperature having a shelf life of a few

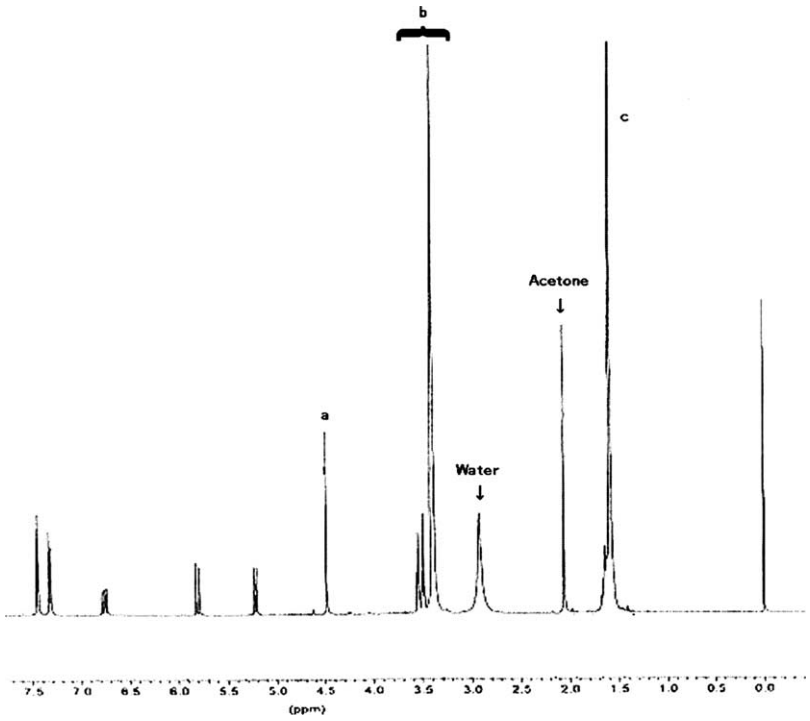
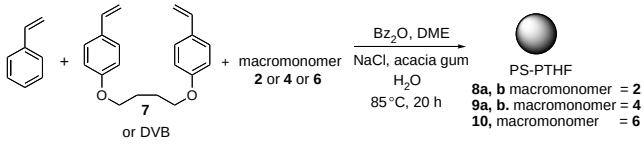


Figure 1. [1]H NMR Spectrum of macromonomer **2**.



Scheme 2. Preparation of macromonomers.

days, however, macromonomer **6** was found to be more unstable and had to be used immediately in resin preparation.

Having the three macromonomers in hand, we prepared PS–PTHF resins **8a**,**b**, **9a**,**b** and **10** (Scheme 2) by suspension polymerization of styrene, PTHF macromonomers **2**, **4** and **6**, and cross linkers divinylbenzene (DVB) and **7**.

The polymers were filtered and washed to obtain the resins in 69, 70, 48, 57 and 40% yield, respectively. In order to avoid problems with emulsions, a 10% higher concentration of NaCl was used with DVB as the cross-linker in the production of the resin **10**. The presence of PS and PTHF in resin **8a** was confirmed by ^{13}C NMR. The NMR spectrum of **8a** (Fig. 2) shows the presence of the methylene protons neighboring the hydroxyl group, the protons labeled as **e** and **f** can be attributed to the peaks at 62.6 and 30.3 ppm, respectively, confirming the presence of both PS and PTHF in the resin.[15] Similarly, magic angle spinning (MAS) [1]H NMR of resin **10** showed very defined peaks at 3.4 and 1.6 ppm, corresponding to the PTHF backbone, confirming the formation of PS–PTHF resins. The loading of the resins **8a**,**b**, **9a**,**b** and **10** was determined to be 0.55, 0.35, 0.29, 0.17 and 0.34 mmol/g, respectively, by Fmoc-glycine loading and quantitation of dibenzofulvene release. Resins **9a**,**b** obtained from 4-(4-vinylphenoxy)butyl PTHF were found to be sticky, presumably because of the long chain lengths ($n=17.0$, 34.0) of the macromonomer **4**; alternatively, resins **8** and **10** were isolated as free flowing powders.

Even though we succeeded in producing resin **10** from 5-(4-vinylphenyl)pentoxy PTHF **6**, precautions were necessary in the preparation of the resin due to the instability of macromonomer **6**. Therefore, we searched for an alternative procedure for making this resin. Since we were successful in activating 4-(5-hydroxypentyl)styrene **6** using triflic anhydride, we hypothesize that this approach could be applied to

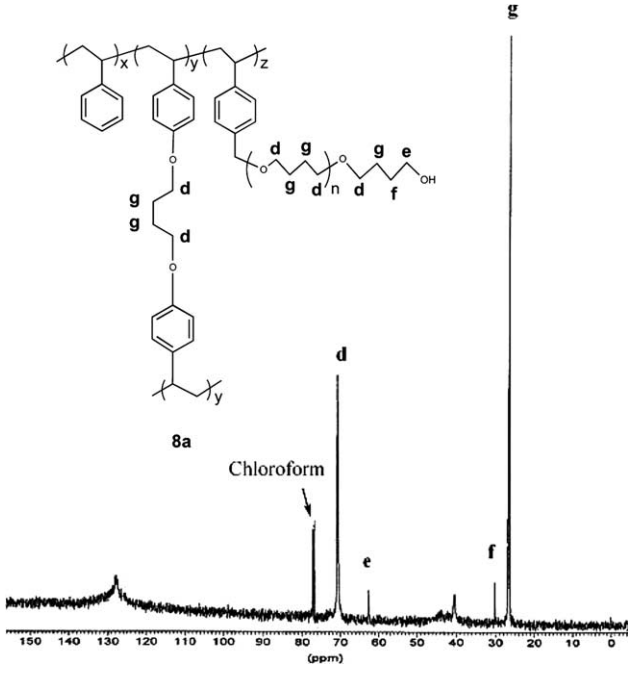
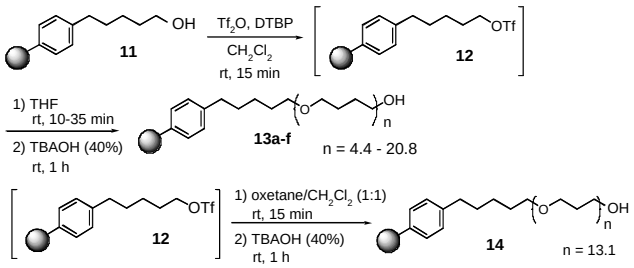


Figure 2. ^{13}C NMR of PS–PTHF resin **8a**.

graft PTHF macromer to 5-hydroxypentyl *J*anda*J*el resin (5-HPJJ resin), a resin previously prepared in our laboratory.[16] Gratifyingly, we were successful in activating this resin with triflic anhydride, and this method proved to be reproducible, reliable and easy to use (Scheme 3).



Scheme 3. Preparation of PTHF–grafted polystyrene from 5-hydroxypentyl *J*anda*J*el.

The procedure for the preparation of the PTHF–grafted polystyrene (PS–PTHF) required activation of 5-hydroxypentyl *J*anda*J*el (**11**) with triflic anhydride and in the presence of 2,6-di-*tert*-butylpyridine (DTBP) to give triflate resin **12**. The terminal triflate acts as an active intermediate for living polymerization of THF. The activated 5-HPJJ complex **12** was isolated and the grafting of PTHF macromer was achieved by adding anhydrous THF to the isolated complex. A series of PTHF–grafted polystyrene resins **13a–f** with varying number of PTHF chain length were prepared by adjusting the reaction time from 10 to 35 min (Table 1). However, when the same procedure was applied to hydroxymethyl polystyrene resins, grafting of PTHF did not take place and PS–PTHF resins were not obtained.

The chain lengths of **13a–f** were calculated from the weight increase, and verified by measuring the hydroxyl loading by 4,4′-dimethoxytrtyl chloride (DMT) titration.[17] The number of grafted PTHF units were found to have a linear correlation with reaction time (Fig. 3), resulting in zero order kinetics, suggesting that the number of PTHF units did not have an effect on the reactivity of the activated triflate end unit. IR spectra of the grafted resin showed two new peaks (C–O bond stretching) at 1028 and 1103 cm^{-1} and one enhanced peak (aliphatic C–H bond stretching) at 2852 cm^{-1} in comparison to 5-HPJJ. We also prepared resin **14** from oxetane, with $n=13.1$ and an –OH loading of 0.57 mmol/g, to determine if these resins may have properties similar to PS–PEG resins. Unlike TentaGel where several ethylene oxide units (more than 30) can be grafted onto the polystyrene polymer, PTHF and oxetane grafted resins with $n>13$ were found to be sticky in consistency. The morphology of PTHF derived resins is

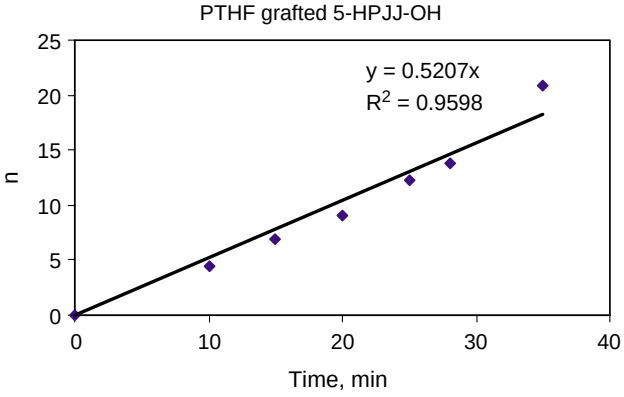


Figure 3. Kinetics for the preparation of PTHF–grafted 5-HPJJ resins.

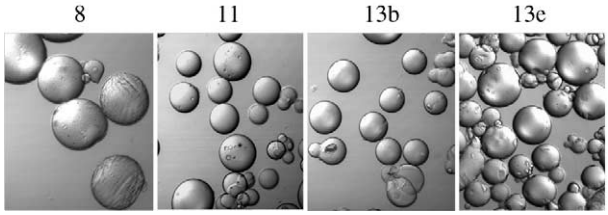


Figure 4. Microscopic images of resins.

shown in optical microscopic images (Fig. 4), demonstrating that the resins were spherical and free-flowing.

The stability of the PS–PTHF resins was examined under severe acidic and basic conditions, and the stability of these resins compared with commercially available hydroxymethyl Merrifield (MF), hydroxymethyl *J*anda*J*el (JJ) and hydroxyl-TentaGel (TG) resins. All resins were stable under strong basic conditions as measured by weight loss (Table 2). However, PEG or PTHF grafted resins were not stable under acidic conditions. Merrifield resin was shown to be inert under all conditions. Among the PTHF derived resins, the pentyl resins **13b**,**e** were found to be more stable than the benzyl resin **8** in TFA (condition C). The IR spectrum of the treated resins confirmed the findings based on weight loss.

The swelling property of resin supports is an essential feature for site accessibility in solid-phase organic synthesis. We measured swelling of these resins in several common solvents used in organic synthesis (Table 3). Unfortunately, none of the PTHF-derived resins showed any swelling in water, whereas TentaGel swells in water. When swelling of resins **13a–f** was examined, it was generally found to mirror the swelling obtained in 5-HPJJ. The best swelling results were obtained in resins **13b** and **13e** ($n=$ 6.9, 13.8, respectively). In methanol and diethyl ether resins

Table 1. Loading and chain lengths of grafted 5-HPJJ resins

Resin		**11**	**13a**	**13b**	**13c**	**13d**	**13e**	**13f**
Time (min)		0	10	15	20	25	28	35
n		—	4.4	6.9	9.1	12.2	13.8	20.8
Weight increase (%)		—	31.8	50.1	65.5	88.3	99.5	150.3
PTHF (wt%)		—	24.1	33.4	39.6	46.9	49.9	60.0
–OH loading (mmol/g)	Calculated	—	0.76	0.67	0.60	0.53	0.50	0.40
	Measured[a]	1.00		0.67			0.44	

[a] Measured by a DMT protocol.

Table 2. Stability test (weight change (%))

Conditions		MF	TG	JJ	PTHF–grafted JJ			
					8a	**11**	**13b**	**13e**
A	10% TBAOH (40%)/THF, 60 °C, 3.5 h	—	—	—	—	—	—	—
B	3% NaH/THF, room temperature, 3.5 h	—	—	—	—	—	—	—
C[a]	50% TFA/toluene, room temperature, 5 h	+10	+4	+10	−24[b]	−10	+6	+6
D	1 M BBr_3/CH_2Cl_2, room temperature, 3 h	—	−25[c]	x[d]	x[d]	x[d]	x[d]	x[d]
E	1 M $SnCl_4/CH_2Cl_2$, room temperature, 3 h	—	−10[e]	—	−30[b]	—	−30[b]	−36[b]

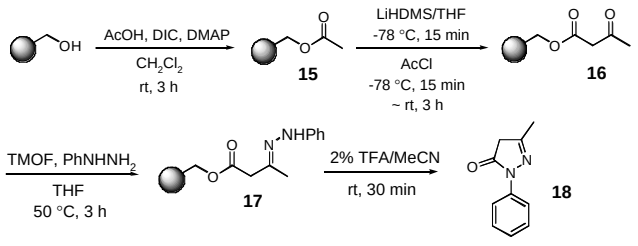
[a] Hydroxyl groups were protected with trifluoroacetyl group.
[b] All PTHF units were cleaved.
[c] All PEG units were cleaved.
[d] Resin dissolved.
[e] Partial cleavage of PEG units.

Table 3. Swollen volume (mL/g) of various resins

		CH_2Cl_2	THF	Dioxane	Toluene	DMF	MeOH	Acetone	Et_2O	*n*-Hexane	H_2O
5-HPJJ	**11**	8.9	8.7	8.3	7.6	6.8	2.4	4.3	4.6	2.4	—
	8a	8.9	8.7	7.8	8.3	5.2	2.4	4.1	4.7	2.6	—
	13a	6.3	6.1	5.6	7.0	4.1	2.6	3.5	3.7	2.5	—
	13b	9.1	8.6	7.9	7.9	5.3	3.0	4.1	4.9	3.0	—
	13c	6.8	6.1	5.3	6.0	3.5	2.6	3.3	3.7	2.6	—
PS–PTHF	**13d**	5.1	4.5	4.1	4.4	2.8	2.2	2.8	2.2	2.5	—
	13e	9.4	8.8	7.3	8.0	4.4	2.8	3.8	5.1	3.2	—
	13f	7.4	6.8	5.9	6.6	3.4	2.5	3.3	4.1	3.2	—
	14	7.7	7.1	6.2	4.8	4.2	2.3	4.0	4.6	3.1	—
	MF	5.9	6.7	6.5	4.5	5.7	2.7	3.7	3.2	2.1	—
	TG	6.9	5.1	5.5	4.6	5.1	3.7	4.0	2.0	—	3.0
	JJ	8.2	8.1	8.0	7.1	6.3	2.2	4.1	3.9	—	—

13b and **13e** exhibited slightly higher swelling compared to 5-HPJJ and JJ. Resin **14** prepared from oxetane showed similar behavior as the PTHF derived resins. We also measured swelling of resins **13b**, **13e** and TG at −78 °C in THF. Compared to swelling at room temperature, a significant reduction in swelling volume (~40%) was found for TG at −78 °C, whereas the PTHF derived resins retained the same degree of swelling obtained at room temperature. Resin **10** exhibited swelling behaviour equivalent to resin **13b**, whereas, resins **9a** and **9b** swelling could not be determined precisely because of the stickiness of the resins. Even though PS–PTHF resins exhibited only a marginal improvement in swelling especially in polar solvents, nevertheless, we decided to test these new resins in a synthetic application.

We chose the synthesis of a β-ketoester to demonstrate the application of these new resins in SPOS and compare their performance to the PEG based resin. The synthesis involves the use of LiHMDS at −78 °C and these conditions have been shown to be problematic for SPOS. Scheme 4 shows the synthesis using TentaGel and PS–PTHF resins **8b**, **13b** and **13e**. The resins were reacted with acetic acid by using 1,3-diisopropylcarbodiimide (DIC) as a condensation reagent to afford **15**, which was reacted with LiHMDS at −78 °C and treated with acetyl chloride to afford β-ketoester **16**.[18] Treatment of **16** with phenylhydrazine afforded **17**, which was cleaved with TFA in acetonitrile at room temperature to obtain **18**. No reaction was obtained with TentaGel, however, with all three PS–PTHF resins **18** was obtained in 42–48% yield with a purity ranging between 91 and 96% (Table 4). PEG-based resins proved ineffective under these conditions, probably due to low solubility of PEG in organic solvents,[19] and as discussed previously, TentaGel was shown to have much lower swelling at low temperature, presumably resulting in inaccessibility of reactive sites for this reaction. The fact that successful synthesis of **18** was achieved suggests that PS–PTHF resins are capable of generating carbanions at low temperatures.



Scheme 4. Preparation of 3-methyl-1-phenyl-2-pyrazolin-5-one **18**.

3. Conclusion

In summary, styrene-based PTHF macromonomers were prepared from the cationic polymerization of THF from styrene-based precursors activated with either silver (I) or

Table 4. Yields and purity of 3-methyl-1-phenyl-2-pyrazolin-5-one **18**

		TG	PS–PTHF		
			8b	**13b**	**13e**
OH loading (mmol/g)	Theoretical[a]	0.44		0.67	0.50
	Measured[b]	0.32	0.35	0.67	0.44
Purity (%)		—	94	96	91
Yield (%)		1	48	47	42

[a] Loading for TG based on reported value from manufacturer and for **13b** and **13e** by weight increase.
[b] Measured by a DMT protocol.

triflic anhydride. PS resins with PTHF graft chains were synthesized by suspension polymerization of styrene, macromonomer and cross-linkers. Alternatively a reproducible procedure was developed for production of resins by grafting PTHF chains to pre-formed 5-hydroxypentyl *J*anda*J*el. These resins were used successfully for the synthesis of 3-methyl-1-phenyl-2-pyrazolin-5-one **18** in good yield and purity, whereas Tentagel was shown to be ineffective in this synthesis. These resins had good chemical stability and swelling characteristics, and compared to commercially available resins should provide equal or better solid supports in SPOS.

4. Experimental

4.1. General methods

Unless otherwise noted, materials were obtained from Aldrich and were used without further purification. TG and MF resins were purchased from Novabiochem. *J*anda*J*el-OH (JJ) was purchased from Aldrich. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker DRX-600, DRX-500, AMX-400 or a Varian Unity-300 spectrometer using tetramethylsilane (TMS) as an internal standard. FT-IR spectra were obtained with a Nicolet Avatar 360 FT-IR spectrometer equipped with a Nicolet Smart Gate (ZnSe). Gel permeation chromatographic analyses (GPC) were carried out on a Shimadzu LC-6A preparative liquid chromatograph with a Shimadzu CR-501A integrator and a Shimadzu SPD-10AV UV–vis detector (254 nm) (Styragel® HR2, HR3, and HR4, THF as eluent) using polystyrene standards. GC–MS analyses were carried out on a Shimadzu QP-5000 equipped with GC-17A gas chromatography instrument using DB-1 (J&W scientific 30 m×0.25 mm×0.25 μm) column. Gas chromatography (GC) analyses were carried out on Shimadzu GC-17A instrument using Ultra Alloy-7 (15 m×0.25 mm×0.25 μm) column. UV analyses were carried out on a Shimadzu UV mini 1240 UV–vis spectrophotometer. Microscope pictures were obtained using a BioRad Rainbow Radiance 2100 Confocal Laser Scanning Microscope (CLSM) attached to a Nikon TE2000U Eclipsed Inverted Fluorescence Microscope equipped with Differential Interference Contrast Optics (20× Plan Apo 0.75 na). Electron spray ionization–time-of-flight determinations were obtained using an Agilent ESI-TOF mass spectrometer. MAS data was collected on a Varian Inova spectrometer at 400 MHz using Varian's nanoprobe. The polymer was suspended in solution and sample spinner was set at 2000 RPM.

4.1.1. Synthesis of 4-vinylbenzyl alcohol. 4-Vinylbenzyl alcohol was prepared by slight modification of the reported method.[20] A mixture of 4-vinylbenzyl chloride (100 ml, 0.71 mmol) and potassium acetate (80 g, 0.84 mmol) in DMSO (300 ml) was stirred at 40 °C for 48 h. The reaction mixture was poured into water (300 ml) and extracted three times with ethyl acetate (300 ml). The collected ethyl acetate layer was dried with $MgSO_4$. The ethyl acetate was evaporated to afford 4-vinylbenzyl acetate and used without further purification. Sodium hydroxide (50 g, 1.25 mol) was added to the crude 4-vinylbenzyl acetate in EtOH (300 ml)/water (50 ml) and refluxed for 1.5 h. The reaction mixture was poured into water and extracted with ethyl acetate, dried with $MgSO_4$. The ethyl acetate layer was evaporated and distilled under vacuum to obtain 4-vinylbenzyl alcohol (92.3 g, 97% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.66 (s, 2H), 5.24 (d, 1H, J=10.5 Hz), 5.75 (d, 1H, J=17.7 Hz), 6.71 (dd, 1H, J=17.4, 10.8 Hz), 7.31 (d, 2H, J=7.8 Hz), 7.40 (d, 2H, J=7.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 65.0, 113.8, 126.3, 127.1, 136.4, 136.9, 140.4.

4.1.2. Synthesis of 4-vinylbenzyl bromide 1. 4-Vinylbenzyl bromide **1** was prepared by slight modification of the procedure for preparation of 4-styrylbenzyl bromide from 4-styrylbenzyl alcohol.[21] Phosphorous tribromide PBr_3 (18.4 g, 6.4 ml, 68 mmol) in Et_2O (10 ml) was added to 4-vinylbenzyl alcohol (5.9 g, 44.3 mmol) in Et_2O (500 ml) at 0 °C under N_2. After 1 h, additional PBr_3 (18.4 g, 6.4 ml, 68 mmol) was added. The reaction mixture was stirred for 1 h at room temperature. After the reaction, the reaction mixture was cooled to 0 °C and water (100 ml) was added slowly to control the temperature. The solution was extracted with Et_2O, and the Et_2O layer was washed with aqueous $NaHCO_3$, brine and dried with $MgSO_4$. The crude product was purified by vacuum distillation (0.65 mmHg) at 60 °C to obtain **1**. Yield 6.8 g (78%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.48 (s, 2H), 5.26 (dd, 1H, J=11.0, 1.0 Hz), 5.75 (dd, 1H, J=17.6, 1.0 Hz), 6.69 (dd, 1H, J=17.6, 11.0 Hz), 7.35 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 33.4, 114.6, 126.6, 129.2, 136.1, 137.2, 137.7.

4.1.3. Synthesis of macromonomer 2 (n=7.1). A solution of 4-vinylbenzyl bromide **1** (2.96 g, 15 mmol) in THF (10 ml) was added to a solution of silver hexafluorophosphate (4.55 g, 18 mmol) in THF (500 ml) at −10 °C and stirred for 8 min. After the reaction, NaOH (3 g, 75 mmol) in water (50 ml) was added to the reaction mixture. The solution was filtered to remove AgBr and the solution was concentrated to a volume of ca. 200 ml. The solution was then added drop-wise into water and extracted with ethyl acetate. The organic ethyl acetate layer was washed with NH_4Cl, brine, and dried with $MgSO_4$. Evaporation of the solvents afforded **2** (10.46 g, quant.) as a clear viscous oil that solidified upon standing at 4 °C, was pure according to NMR analysis, and was used without further purification (n=7.1 calculated by ^{1}H NMR). Macromonomer **2** (n=13.1) was prepared by a similar procedure. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.55–1.66 (br, 29.7H), 3.39–3.56 (br, 29.7H), 4.48 (s, 2H), 5.22 (d, 1H, J=11.0 Hz), 5.80 (dd, 1H, J=17.6, 1.0 Hz), 6.75 (dd, 1H, J=17.6, 11.0 Hz), 7.32 (d, 2H, J=8.1 Hz), 7.45 (d, 2H, J=17.6, 8.1 Hz); ^{13}C NMR (500 MHz, $CDCl_3$) δ 27.2, 62.3, 70.7, 71.0–71.2, 72.8, 113.9, 126.9, 128.5, 137.5, 137.6, 139.8.

4.1.4. Synthesis of of 4-[4-(vinyl)phenoxy]butyliodide 3. A mixture of NaOH (0.40 g, 10 mmol) and 4-acetoxystyrene (0.91 ml, 5 mmol) in DMSO (15 ml) was stirred at 60 °C for 2 h. The mixture was cooled to room temperature and 1,4-diiodobutane (1.32 ml, 10 mmol) in DMSO (15 ml) was added gradually. After 30 min, water (100 ml) was added and the solution extracted with ethyl acetate (100 ml×3). Ethyl acetate layer was washed with dilute HCl, aqueous $NaHCO_3$, and brine. The organic ethyl acetate layer was dried over Na_2SO_4, and filtered. After evaporation of the solvent, the residue was washed with methanol to

extract the 1,4-bis[4-(vinyl)phenoxy)]butane. The extract was evaporated and separated by column chromatography on silica gel to provide the desired compound in 41% yield (solvent: hexane). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 (d, J=8.7 Hz, 2H), 6.84 (d, J=8.7 Hz, 2H), 6.65 (dd, J=17.4, 11.0 Hz, 1H), 5.60 (dd, J=17.7, 1.0 Hz, 1H), 5.12 (dd, J=10.8, 1.1 Hz, 1H), 3.98 (t, J=6.0 Hz, 2H), 3.26 (t, J=6.6 Hz, 2H), 1.85–2.08 (m, 4H).

4.1.5. Synthesis of macromonomer 4. The monomer 4-[4-(vinyl)phenoxy]butyliodide **3** (1.86 g, 6.0 mmol) in THF (25 ml) was added in the solution of silver hexafluorophosphate (8.99 g, 30 mmol) in THF (250 ml) at −10 °C. After 1 h, NaOH (1.5 g, 38 mmol) in water (30 ml) was added in the reaction mixture. The generated solid material (AgI) was separated by filtration and evaporated to ca. 150 ml. Ethyl acetate (200 ml) was added to the reaction mixture, and ethyl acetate layer was washed with NH_4Cl, brine, and dried with $MgSO_4$. The organic layer was filtered and evaporated. The residue was separated by column chromatography on silica gel (hexane/EtOAc: 95:5 to THF) to obtain **4** in 81% yield. The polymerization degree of PTHF was n=17.0 determined by ^{1}H NMR. Macromonomer **4** (n=34.0) was prepared by a similar procedure. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (d, J=8.4 Hz, 2H), 6.84 (d, J=9.0 Hz, 2H), 6.65 (dd, J=17.7, 11.0 Hz, 1H), 5.60 (d, J=17.7 Hz, 1H), 5.11 (d, J=12.0 Hz, 1H), 3.98 (t, J=6.3 Hz, 2H), 3.64 (t, J=6.0 Hz, 2H), 3.50–3.49 (br), 1.73–1.86 (m, 2H), 1.56–1.70 (br).

4.1.6. Synthesis of macromonomer 6. 4-(5-Hydroxypentyl)styrene **5** was prepared using literature procedure.[16] A solution of **5** (490 mg, 2.79 mmol) in CH_2Cl_2 (10 ml) was added slowly to a solution of di-*tert*-butyl pyridine (0.80 g, 4.19 mmol) and trifluoromethanesulfonic anhydride (1.04 g, 3.69 mmol) at room temperature. The solution was stirred for 1 h and then cooled to −20 °C. THF (50 ml) was then added with strong stirring for 10 min. After the reaction, NaOH (3 g, 75 mmol) was added to the reaction mixture. The resulting solution was evaporated to 20% of the initial volume. Water (25 ml) was added to the solution, followed by three extractions with ethyl acetate. The combined organic phase was washed with brine (2×25 ml) and dried over $MgSO_4$. Evaporation of the solvent afforded the macromonomer **6** (1.87 g, 93.7% as a typical result) as a clear viscous oil. Small amounts of the solvent remained in the product and the material was used without further purification immediately for resin synthesis (n=6.9, as calculated by ^{1}H NMR and ESI). ^{1}H NMR (500 MHz, acetone-d_6) δ 7.59 (d, 2H), 7.35 (d, 2H), 6.70 (dd, 1H), 5.15 (d, 1H), 3.39 (m, 30H), 1.58–1.60 (m, 30H).

4.1.7. Preparation of 8a,b, 9a,b by suspension polymerization. Suspension polymerization was carried out by slight modification of the reported method.[2] A solution of styrene (6.8 ml, 60 mmol), **2** (6.90 g, 10.3 mmol, n=7.1), and **7** (406 mg, 1.4 mmol) in DME (16.1 ml) was heated to 45 °C until a homogeneous solution was obtained. The initiator (benzoyl peroxide, 120 mg) was added to the organic solution and the solution was added by syringe to aqueous phase (142 ml prepared by reported method[2]) under N_2 at 45 °C. The temperature of the reaction mixture was raised to 85 °C and stirring was continued for 20 h. The suspension was filtered to recover the polymer beads and washed with hot water. The resin was washed with THF in a soxhlet extractor for 20 h. The recovered beads **8a** were washed with ether and hexane and dried under vacuum for 24 h. Yield 9.39 g (69%). Sieve separation: 100–200 mesh: 5.03 g, 40–100 mesh: 1.41 g, <40 mesh: 1.54 g. Resins **8b**, **9a**, and **9b** were prepared using a similar procedure. ^{13}C NMR (150 MHz, $CDCl_3$) δ 26.0–27.0, 30.3, 40.3, 42.0–45.0, 62.6, 70.0–72.0, 125.0–134.0.

4.2. Preparation of 10 by suspension polymerization

Resin **10** was prepared using the same procedure as for resin **8**, but using a higher concentration of NaCl (10%) in water and divinyl benzene as the cross-linker to minimize problems of emulsion formation.

4.3. Measurement of swelling volume

Resins (100–200 mesh, 50 mg) were placed in a 1 ml syringe with filter and 0.8 ml of the desired solvent was added. The syringe was placed in a shaker for 1 h and the volume of the resin was measured.

4.4. Determination of the loading of 8a,b, 9a,b, and 10

The PTHF resin (100 mg), DIC (100 μL), DMAP (2 mg), and Fmoc-glycine (300 mg) in anhydrous CH_2Cl_2 (2 ml) was placed in screw-top vial, and shaken at room temperature for 1 h. The mixture was filtered and washed three times with CH_2Cl_2. The filtrate was returned to a screw-top vial and the reaction was carried out again. The mixture was washed three times each with CH_2Cl_2, THF, MeOH, Et_2O and hexanes. The produced resin was dried in vacuo overnight. Approximately 15 mg of each resin was added into 2 vials and 20% piperidine/DMF (3 ml) was added to the vial and shaked at room temperature for 1 h. A 100 μl aliquot of this solution was diluted to 3 ml with 20% piperidine/DMF and the UV adsorption at 290 nm measured.

4.5. Preparation of PTHF–grafted 5-hydroxypentyl *J*anda*J*el 13a–f

5-Hydroxypentyl *J*anda*J*el **11** (1.00 g, 1.07 mmol OH loading) was placed in a cylindrical reaction vessel, with sintered glass filter and a stopcock at one end and with a rubber-sealed screw-cap at the other end. The reaction vessel was charged with argon gas and sealed by closing the stopcock. The resin was swollen with anhydrous dichloromethane (20 ml). 2,5-Di-*tert*-butylpyridine (0.72 ml, 3.21 mmol) and trifluoromethanesulfonic anhydride (0.54 ml, 3.21 mmol) were added through syringe in sequence. The suspension was shaken for 15 min at room temperature. The solution containing excess reagents was drained through the sintered glass filter and the resin was dried by flowing argon gas. The resin was washed three times with anhydrous dichloromethane (10 ml) and dried by flowing argon gas for 5 min. THF (15 ml) was then added

into the reaction vessel via a syringe and the reaction vessel was shaken for 10–35 min at room temperature. Tetra-*n*-butylammonium hydroxide (40% in H_2O, 1 ml) was then added to terminate the living polymerization. After additional shaking for 1 h, the resulting resin was collected into a syringe equipped with polypropylene filter and washed several times with dichloromethane, Et_2O and *n*-hexane in sequence, and dried under reduced pressure to give a series of poly-THF-grafted *J*anda*J*el (**13a–f**).

4.6. Preparation of polyoxetane–grafted 5-hydroxypentyl *J*anda*J*el 14

The procedure is similar to the preparation of **13a–f**, except a 50/50 mixture of oxetane–dichloromethane (15 ml) was used instead of 15 mL of THF for grafting the activated complex.

4.6.1. Synthesis of 5-methyl-2-phenyl-2,4-dihydropyrazol-3-one 18.[22] TentaGel (0.32 mmol/g), and PTHF reins **8b** (0.35 mmol/g), **13b** (0.67 mmol/g), and **13e** (0.44 mmol/g)) were swollen in CH_2Cl_2 (12 ml) and treated with DIC (5 equiv), DMAP (1 equiv) and acetic acid (5 equiv). After shaking at room temperature for 3 h, these resins were filtered, and washed with CH_2Cl_2, MeOH and Et_2O and dried in vacuo. Under argon, 5 equiv of LiHMDS (1 M solution in THF, prepared from solid LiHMDS) was slowly added via syringe to a pre-cooled suspension at −78 °C of acetyl resin in THF, and stirred for 15 min at −78 °C. Acetyl chloride (5 equiv) was added dropwise, and the mixture was stirred for 15 min at −78 °C and then allowed to warm to room temperature. After 3 h, the resin was filtered, and washed with THF, CH_2Cl_2, MeOH and Et_2O, and dried in vacuo. These resulting resins were treated with phenylhydrazine (10 equiv) in THF (4 ml) and trimethyl orthoformate (4 ml) at 50 °C for 12 h, and filtered, and washed with THF, CH_2Cl_2, MeOH and Et_2O, and dried under vacuum. The desired product **18** was obtained by treating with 2% TFA/acetonitrile (7 ml) at room temperature for 30 min. The resulting filtrate was concentrated under reduced pressure, and purified by preparative TLC to give **18**; TentaGel (<1 mg, 1%), **8b** (15 mg, 48%), **13b** (27 mg, 47%), **13e** (16 mg, 42%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.13 (s, 3H), 3.37 (s, 2H), 7.13 (t, J=7.6 Hz, 1H), 7.35 (t, J=8.0 Hz, 2H), 7.81 (d, J=7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.9, 17.0, 42.9, 43.0, 43.1, 118.7, 118.8, 125.0, 128.7, 137.9, 156.3, 170.4; FTIR (cm^{-1}): 3064, 2924, 2852, 1714, 1594, 1561, 1498; MS (ESI) m/z=175 $[M+H]^+$.

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Di(2-pyridyl)methylamine–palladium dichloride complex covalently anchored to a styrene-maleic anhydride co-polymer as recoverable catalyst for C–C cross-coupling reactions in water

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Abstract—A new polymer-supported di(2-pyridyl)methylamine–palladium dichloride complex covalently anchored to a styrene-alt-maleic anhydride co-polymer is prepared. This complex catalyzes Heck, Suzuki and Sonogashira cross-coupling reactions in neat water with similar efficiency than the monomeric complex. The turnover number (TON) of this polymer reaches up to 10^4 for Heck reactions, whereas for Suzuki and Sonogashira couplings TONs up to 10^5 are achieved. There is low leaching of palladium after filtration of the polymer and the activity remains almost constant after fourth and five reaction cycles especially in Sonogashira reactions. In the case of the Suzuki reaction Pd nanoparticles are dispersed into the polymer after the first cycle according to TEM images and 2.4% of Pd are found by ICP-OES in the corresponding filtrate. Alternatively, these palladium-catalyzed reactions can also be performed under microwave heating. These couplings take place with better efficiency with polymer-supported di(2-pyridyl)methylamine–palladium dichloride complex than with the polyurea-encapsulated Pd EnCat™ 40.

1. Introduction

Palladium-catalyzed cross-coupling reactions have become a major area of interest in organic chemistry.[1] From the environmental point of view several practical and economical aspects of these reactions have to be developed for their industrialization. The use of water as solvent has important advantages in large-scale processes due to nontoxic, nonflammable and inexpensive features.[2] Additionally, the recovery[3] and recycling of the precious expensive catalyst and its complete removal from the products constitute essential problems to be solved.[4] Several methodologies have been developed to remove and recover the catalyst from the reaction medium, the filtration of a heterogeneous catalyst being the most simple procedure. The palladium metal, salt or complex can be for instance encapsulated,[5] incarcerated,[6] or entrapped in sol–gels,[7] inorganic supports,[8] block co-polymer matrices,[9] dendrimers,[10] and PEG-resins.[11] The preparation of covalently supported palladium catalysts either based on polymer or on silica gel-anchored ligands has experienced an important development in the last decade.[12] Some of these supported catalysts, derived from palladium–phosphine complexes,[14] palladacycles,[15] and *N*-heterocyclic carbene complexes,[16] have been used in aqueous media and in neat water,[13] mainly in Heck and Suzuki reactions. The leaching of palladium from the solid support and the lower reactivity in comparison with related homogeneous catalysis are important problems when employing these type of strategies.

Dipyridyl- and dipyrimidyl-based ligands **1** and **2** showed excellent properties for palladium complexation and have proven to be efficient catalysts for C–C and C–N bond forming reactions.[17] When this type of complexes were covalently anchored to a polymeric matrix resulting from a ROMP polymerization, the resulting $PdCl_2$ complexes **3** present similar or even higher catalytic activity than the monomeric ones and no leaching of palladium being observed in organic solvents. We have recently chosen dipyridyl-based ligands derived from di(2-pyridyl)methylamine in order to have a primary amino group, which could be more easily anchored to a polymeric support than the di(2-pyridyl)amine used by Buchmeiser et al.[17] The corresponding $PdCl_2$ complexes **4** have shown as versatile catalysts for Heck, Suzuki, and Sonogashira reactions in organic and aqueous solvents.[18] Herein we report the preparation of a novel polymer-supported di-(2-pirydyl)methylamine-based $PdCl_2$ complex covalently anchored to a poly(styrene-alt-maleic anhydride) resin **5**.[19]

Keywords: Heck reaction; Suzuki reaction; Sonogashira reaction; Supported-catalyst; Water.
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This polymer has been widely used by our group for the preparation of different polymer-supported *N*-hydroxysuccinimide-derived reagents presenting good mechanical stability and solubility (Fig. 1)[20]

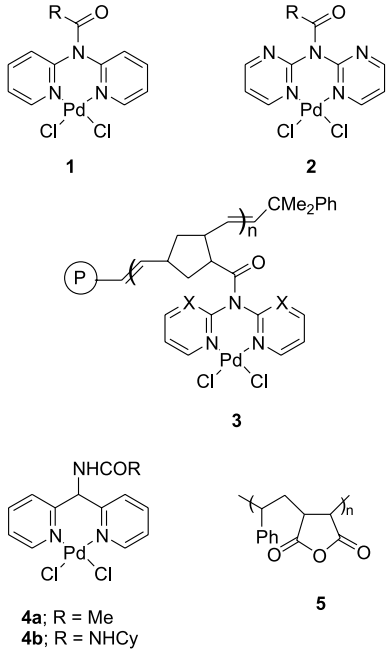
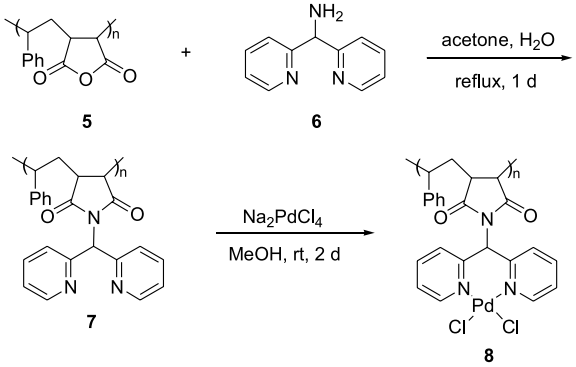


Figure 1.

2. Results and discussion

2.1. Synthesis of the polymer-supported palladium complex

The polymer-supported ligand **7** was prepared by reaction of poly(styrene-alt-maleic anhydride) resin **5**[19] with di-(2-pyridyl)methylamine (**6**)[18b,21] in a mixture of acetone–water (1/2) under reflux for 1 day (Scheme 1). Elemental analyses of three different batches of supported-ligand **7** showed similar nitrogen content in the range of 10.38–11.40%, revealing a rather high ligand loading (average 2.6 mmol/g). For the preparation of the palladium complex **8** a 0.5 M methanolic solution of Na_2PdCl_4 (ca. 2 equiv) was mixed with the polymer **7** and stirred for 2 days at room temperature. Elemental analysis of the corresponding three different batches of complex **8** gave a 5.84–6.20% of N content. Inductive coupled plasma-optic emission spectrometry (ICP-OES) revealed that resin **8** contained an average of 1.2 mmol/g of Pd, which supposes that ca. 46% of the di-(2-pyridyl)methylamine ligand participated in the formation of the $PdCl_2$ complex. The FT-IR spectra of polymeric ligand **7** and complex **8** are rather similar showing a sharp band at 1705 and 1712 cm^{-1}, respectively, for the imide carbonyls.[22]

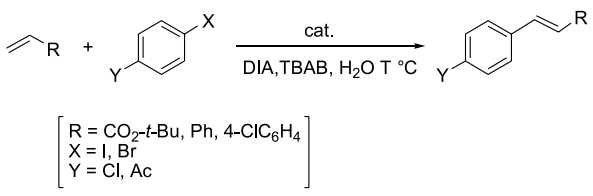


Scheme 1.

2.2. Use of the polymer-supported palladium complex 8 in cross-coupling reactions

The systematic study of the catalytic activity of the polymer-supported Pd-dipyridyl complex **8** for Heck, Suzuki, and Sonogashira reactions was investigated using water as solvent and compared with the same processes carried out with the monomeric complex **4b**.[18] In addition, the stability, recovery and leaching of the heterogeneous catalyst were studied in all these processes under aqueous conditions. Recycling experiments have been also carried out with the commercially available polyurea-encapsulated [Pd EnCat 40™][5,23] in order to compare with the results obtained with the polymeric complex **8**.

2.2.1. Heck reactions. Heck couplings were carried out with *tert*-butyl acrylate or styrenes as olefinic substrates and aryl halides. The reactions were performed in neat water as solvent with diisopropylamine as base in the presence of tetra-*n*-butylammonium bromide (TBAB, 0.5 equiv) (Scheme 2 and Table 1). The presence of TBAB in Pd-catalyzed cross-coupling reactions, especially in Heck reactions, increase the conversion rate by formation and stabilization of Pd colloids.[24] The arylation of *tert*-butyl acrylate and 4-chlorostyrene with 4-chloroiodobenzene in the presence of the polymeric complex **8** gave higher yields in similar or shorter reaction times than the monomeric **4b** (Table 1, entries 1–6). The loading of both catalyst can be lowered down to 10^{-2} mol% of Pd but the temperature must be raised to 140 °C to get full conversion after more than 1 day reaction time (Table 1, entries 5 and 6). Similar processes with aryl bromides must to be performed at higher temperature and loading of catalyst (Table 1, entries 7–10). In the coupling between 4-chlorobromobenzene and *tert*-butyl acrylate quantitative yields were obtained at 160 °C with both catalysts (Table 1, entries 7 and 8). In case of the arylation of styrene with 4-bromoacetophenone the reaction was faster with the monomeric catalyst **4b** (Table 1, entries 9 and 10). This reaction can be performed alternatively at 100 °C under microwave heating in 10 min in good yields (Table 1, entries 11 and 12). However, the vinylation of aryl chlorides under this reaction conditions failed.



Scheme 2.

Recycling and leaching experiments were assayed for the arylation of *tert*-butyl acrylate and 4-chlorostyrene with 4-chlorophenyl iodide using complex **8** (0.1 mol% Pd) at

Table 1. Heck reactions with polymeric **8** and monomeric **4b** di(2-pyridyl)methylamine-based $PdCl_2$ complexes[a]

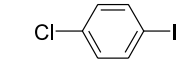
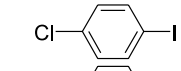
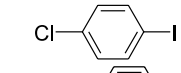
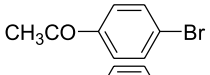
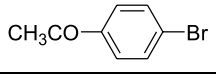
Entry	X	Y	R	Cat. (mol% Pd)	*T* (°C)	*t*	Yield (%)[b]
1	I	Cl	CO_2-*t*-Bu	**8** (0.1)	100	14 h	99
2	I	Cl	CO_2-*t*-Bu	**4b** (0.1)	100	1 d	98
3	I	Cl	4-ClC_6H_4	**8** (0.1)	100	2 d	99
4	I	Cl	4-ClC_6H_4	**4b** (0.1)	100	1 d	78
5	I	Cl	4-ClC_6H_4	**8** (0.01)	140	38 h	97
6	I	Cl	4-ClC_6H_4	**4b** (0.01)	140	31 h	95
7	Br	Cl	CO_2-*t*-Bu	**8** (0.1)	160	2 d	99
8	Br	Cl	CO_2-*t*-Bu	**4b** (0.1)	160	2 d	99
9	Br	CH_3CO	C_6H_5	**8** (0.5)	100	6.5 h	85
10	Br	CH_3CO	C_6H_5	**4b** (0.5)	100	4.5 h	99
11	Br	CH_3CO	C_6H_5	**8** (0.1)	100 (MW)	10 min	80
12	Br	CH_3CO	C_6H_5	**4b** (0.1)	100 (MW)	10 min	96

[a] Reaction conditions: aryl halide (1 mmol), alkene (1.5 mmol), *i*-Pr_2NH (3 mmol), TBAB (0.5 mmol), Pd complex and H_2O (2 mL).
[b] Determined by GLC using decane as internal standard.

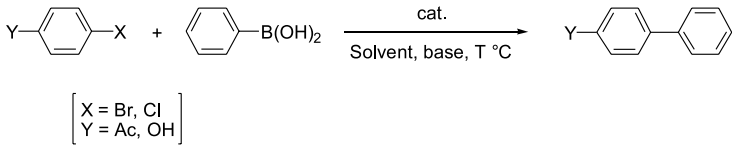
80 °C instead under reflux in order to prevent degradation of the polymer (Table 2, entries 1 and 2). The same catalyst batch was isolated by filtration (G-5) from the reaction medium and reused in 4 consecutive coupling reactions and only extended reaction time was observed after the first run in the case of *tert*-butyl acrylate (Table 2, entry 1). When the polyurea-encapsulated [Pd EnCat 40™][5,23] (0.1 mol% Pd) was used as catalyst for the coupling between 4-chloroiodobenzene and 4-chlorostyrene, a similar behaviour than complex **8** was observed after three cycles (Table 2, compare entries 2 and 3). Catalytic cycles for the arylation of *tert*-butyl acrylate and styrene with 4-bromoacetophenone were also carried out with complex **8** (1 and 0.5 mol% of Pd, respectively) at 100 °C (Table 2, entries 4 and 5). In the case of *tert*-butyl acrylate the reaction time increased after the first run and it was maintained in the next three consecutive cycles. In all cases, yields remained almost constant, however, in the arylation of styrene the yield decreased after the third run. Apparently, no leaching of Pd was observed because filtrates did not show catalytic activity in any case. When the arylation of styrene with 4-bromoacetophenone was performed under microwave heating degradation of the polymer and leaching of palladium was observed.

2.2.2. Suzuki reactions. The cross-coupling between phenylboronic acid and aryl bromides such as 4-bromoacetophenone and 4-bromophenol were carried out with K_2CO_3 as base under water reflux and in aqueous MeOH either at 60 °C or at room temperature using KOH as base (Scheme 3 and Table 3). The cross-coupling of 4-bromoacetophenone with phenylboronic acid under water reflux took place with similar TON using the polymeric **8** and the monomeric **4b** catalysts either with 0.1 or 0.001 mol% loading of Pd and slightly higher TOF ($TON \times h^{-1}$) of 10^5 (h^{-1}) with the polymeric complex (Table 3, entries 1–4). The same results were obtained with both complexes when couplings were performed in aqueous MeOH at 60 °C (Table 3, entries 5 and 6). In the case of the cross-coupling of 4-bromophenol with phenylboronic acid, no differences were observed with both complexes **8** and **4b** under the three essayed reaction conditions (Table 3, entries 7–12). When 4-chloroacetophenone was coupled with phenylboronic acid under water reflux with K_2CO_3 as base, TBAB (0.5 equiv) was added (Table 3, entries 13–16). In this case a higher Pd loading had to be used for the polymeric complex **8** (4.5 mol% Pd) than for the momomeric **4b** (0.1 mol% Pd). Under microwave heating 56 and 88% yield were obtained for the same catalyst loading (0.1 mol% Pd) when the

Table 2. Heck reactions with polymer **8** and Pd EnCat™ 40 over 3 or 4 cycles[a]

Entry	ArX	Alkene	Cat. (mol% Pd)	*T* (°C)	Cycle 1		Cycle 2		Cycle 3		Cycle 4	
					t (h)	Yield (%)[b]	*t* (h)	Yield (%)[b]	*t* (h)	Yield (%)[b]	*t* (h)	Yield (%)[b]
1		CH_2=$CHCO_2$-*t*-Bu	**8** (0.1)[c]	80	7	99	24	99	38	89	38	92
2		4-ClC_6H_4CH=CH_2	**8** (0.1)[c]	80	24	99	24	99	24	99		
3		4-ClC_6H_4CH=CH_2	Pd EnCat (0.1)[d]	100	15	99	15	91	23	95		
4		CH_2=$CHCO_2$-*t*-Bu	**8** (1)[d]	100	6	99	21	85	22	88	22	82
5		C_6H_5CH=CH_2	**8** (0.5)[e]	100	6	85	22	91	40	59		

[a] Reaction conditions: aryl halide (1 equiv), alkene (1.5 equiv), *i*-Pr_2NH (3 equiv), TBAB (0.5 equiv), Pd complex and H_2O (2 mL/equiv).
[b] Determined by GLC using decane as internal standard.
[c] Scale (3 mmol).
[d] Scale (1 mmol).
[e] Scale (2 mmol).



Scheme 3.

Table 3. Suzuki reactions with polymeric **8** and monomeric **4b** di(2-pyridyl)methylamine-based $PdCl_2$ complexes[a]

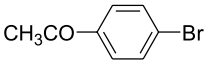
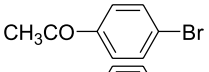
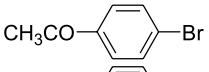
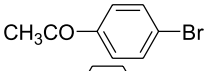
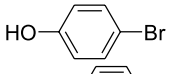
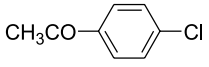
Entry	X	Y	Cat. (mol% Pd)	Solvent	Base	*T* (°C)	*t*	Yield (%)[b]
1	Br	CH_3CO	**8** (0.1)	H_2O	K_2CO_3	100	1 h	99
2	Br	CH_3CO	**4b** (0.1)	H_2O	K_2CO_3	100	30 min	98
3	Br	CH_3CO	**8** (0.001)	H_2O	K_2CO_3	100	1 h	99
4	Br	CH_3CO	**4b** (0.001)	H_2O	K_2CO_3	100	75 min	99
5	Br	CH_3CO	**8** (0.1)	MeOH/H_2O[c]	KOH	60	1 h	99
6	Br	CH_3CO	**4b** (0.1)	MeOH/H_2O[c]	KOH	60	30 min	99
7	Br	HO	**8** (0.1)	H_2O	K_2CO_3	100	30 min	88 (82)
8	Br	HO	**4b** (0.1)	H_2O	K_2CO_3	100	40 min	99 (87)
9	Br	HO	**8** (0.1)	MeOH/H_2O[c]	KOH	60	30 min	94
10	Br	HO	**4b** (0.1)	MeOH/H_2O[c]	KOH	60	30 min	99
11	Br	HO	**8** (0.1)	MeOH/H_2O[c]	KOH	Room temperature	6 d	86
12	Br	HO	**4b** (0.1)	MeOH/H_2O[c]	KOH	Room temperature	5 d	75
13	Cl	CH_3CO	**8** (4.5)	H_2O	K_2CO_3[d]	100	7 h	99
14	Cl	CH_3CO	**4b** (0.1)	H_2O	K_2CO_3[d]	100	6 h	68
15	Cl	CH_3CO	**8** (0.1)	H_2O	K_2CO_3[d]	120 (MW)	5 min	56
16	Cl	CH_3CO	**4b** (0.1)	H_2O	K_2CO_3[d]	120 (MW)	5 min	88

[a] Reaction conditions: aryl halide (1 mmol), $PhB(OH)_2$ (1.5 mmol), base (2 mmol), Pd complex, and H_2O (2 mL).
[b] Determined by GLC using decane as internal standard. In parenthesis isolated yield after flash chromatography.
[c] Volume ratio 2/3.
[d] TBAB (0.5 mmol) was added.

reaction was carried out with complex **8** at 100 °C and monomeric complex **4b** at 120 °C, respectively (Table 3, entries 15 and 16).

The recovery of the polymeric complex **8** was studied for the cross-coupling of phenylboronic acid with 4-bromoacetophenone and 4-bromophenol under different reaction

Table 4. Suzuki cross-coupling reactions between phenylboronic acid and aryl halides with polymer **8** and Pd EnCat™ 40 over 2, 3, 4 or 5 cycles[a]

Entry	ArX	Cat. (mol% Pd)	T (°C)	Cycle 1		Cycle 2		Cycle 3		Cycle 4		Cycle 5	
				t (h)	Yield (%)[b]	*t* (h)	Yield (%)[b]	*t* (h)	Yield (%)[b]	*t* (h)	Yield (%)[b]	*t* (h)	Yield (%)[b]
1		**8** (0.1)[c]	100[d]	1.5	99	2	99	2.5	93				
2		Pd EnCat (0.1)[c]	100[d]	2	88	2	80						
3[e]		**8** (0.1)	60[f]	1	99	1.5	99	2	99	2.5	99		
4[g]		**8** (0.1)	60[f]	7	80	7	98	7	97	7	94		
5		**8** (0.1)[h]	60[f]	0.5	94	2	73	3	93	3	92		
6		**8** (4.4)[i,j]	130[d]	3	76	14	41	14	39	15	49	15	47

[a] Reaction conditions: aryl halide (1 equiv), $PhB(OH)_2$ (1.5 equiv), base (2 equiv), Pd complex, and H_2O (2 mL/equiv).
[b] Determined by GLC using decane as internal standard.
[c] Scale (2 mmol).
[d] In H_2O and K_2CO_3 as base.
[e] The cycles were performed in situ without filtration of the polymer **8**.
[f] In MeOH/H_2O and KOH as base.
[g] The catalyst was recovered by filtration from the previous cycles of entry 3 and the new 4 cycles were performed in situ without filtration of the polymer **8**.
[h] Scale (3 mmol).
[i] Scale (1 mmol).
[j] In H_2O, K_2CO_3 as base and in the presence of TBAB.

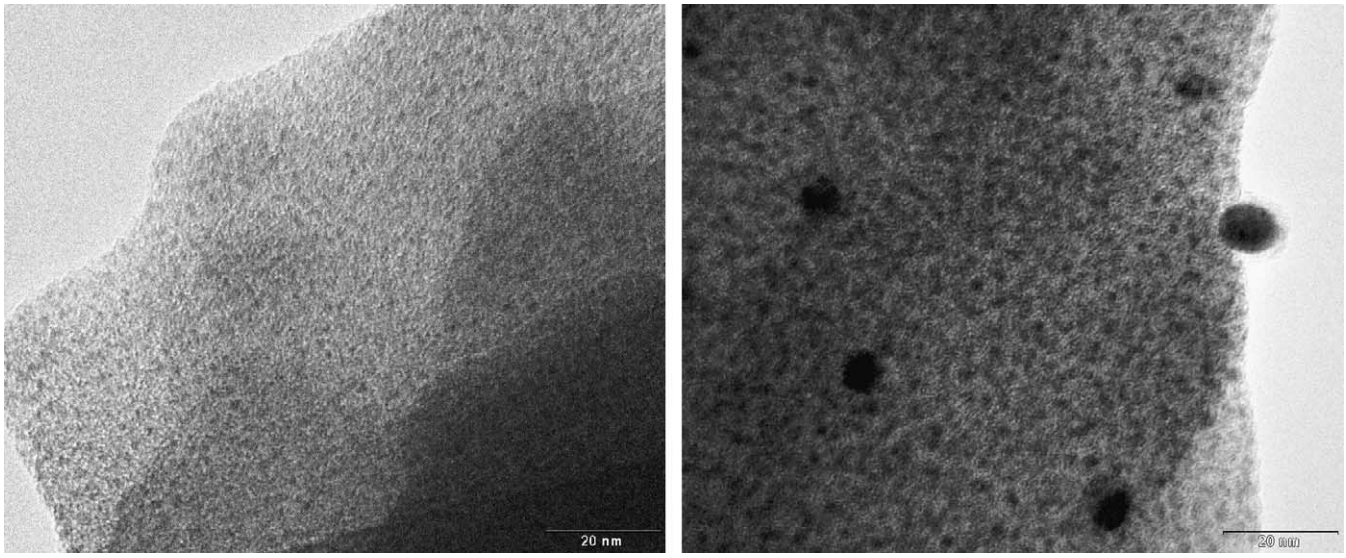


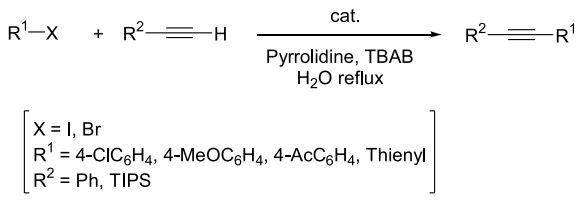
Figure 2. TEM images of the catalyst **8** before (left) and after (right) the first cycle of the Suzuki reaction (Table 4, entry 1).

conditions (Table 4). Slight variations were observed in the case of 4-bromoacetophenone under water reflux conditions when the catalyst was filtered off after three catalytic cycles (Table 4, entry 1). However, comparative recycling studies using Pd EnCat 40 (0.1 mol% Pd) in the cross coupling between phenylboronic acid and 4-bromoacetophenone under water reflux revealed lower yields, longer reaction times, and only 30% yield being obtained in the second run with total deactivation of the catalyst (Table 4, entry 2). Transmission electron microscopy (TEM) analysis of the polymer **8** before and after the 1st Suzuki coupling between 4-bromoacetophenone and phenylboronic acid in the absence of TBAB (Table 4, entry 1) showed the formation of some Pd nanoparticles (7–10 nm) in the surface of the polymer (Fig. 2). The filtrate of this reaction was analyzed by ICP-OES giving a low Pd leaching (2.4%).

For the recycling experiments in aqueous MeOH at 60 °C fourth consecutive cycles were performed in the same flask just adding all reagents with similar quantitative yields in 1–2.5 h (Table 4, entry 3). Then the polymer was filtered off and again fourth cycles were carried out in situ observing in this case that the reaction needed longer reaction times, 7 h in order to obtain 80–98% yield in each run (Table 4, entry 4).

The recycling experiments for the cross-coupling of 4-bromophenol and phenylboronic acid were studied using KOH as base in aqueous MeOH at 60 °C. Under this reaction conditions the reaction time increased from 0.5 to 3 h in the third run and remained constant for the fourth cycle (Table 4, entry 5). The catalytic cycles in the case of 4-chloroacetophenone were performed in water at 130 °C using K_2CO_3 as base and TBAB as additive to give in 3 h 76% yield. However, a lower conversion was observed in the second cycle in a longer reaction time. Similar results, around 39–49% yield in 14–15 h, were observed in four consecutive cycles (Table 4, entry 6). In all recycling experiments the filtrate showed no catalytic activity.

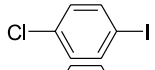
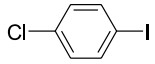
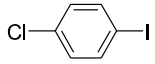
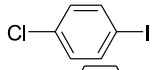
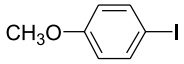
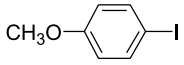
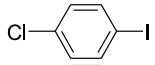
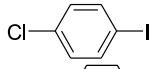
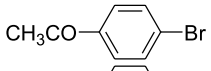
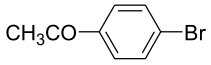
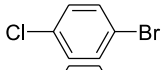
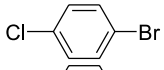
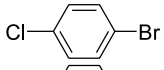
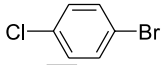
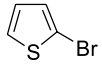
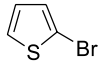
2.2.3. Sonogashira reactions. For the alkynylation of aryl iodides and bromides, a Sonogashira–Cassar–Heck copper-free protocol, set up recently by our group using complex **4b** and $PdCl_2$ as catalysts was used.[18c] The cross-coupling of activated and deactivated iodides and bromides with phenylacetylene and triisopropylsilylacetylene was performed with pyrrolidine (2 equiv) as base and TBAB as additive under water reflux (Scheme 4 and Table 5). For aryl iodides 0.1 mol % of Pd was employed with the polymeric **8** and the monomeric **4b** catalysts, whereas for aryl bromides a higher loading (0.2 mol% of Pd) gave better conversions. It is worthy to note that in general better efficiency, concerning yield and reaction rate, was observed for the polymeric than for the monomeric complex. In addition, the formation of secondary products from dimerization of the alkyne decreased when the polymer was used as catalyst. The Pd loading could be decreased to 10^{-3} mol% in the cross-coupling of phenylacetylene and 4-chloroiodobenzene but longer reaction times were necessary in order to get full conversion (Table 5, entries 1 and 3). Under these low Pd loading the polymer **8** showed a higher efficiency (TOF 3225 h^{-1}) than when using the monomer **4b** (TOF: 730 h^{-1}) (Table 5, entries 3 and 4). Under microwave heating the coupling between phenylacetylene and 4-chlorobromobenzene gave variable yields in the case of polymer **8** (between 13 and 47%) and lower than the monomer **4b** (Table 5, entries 11 and 12).



Scheme 4.

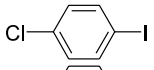
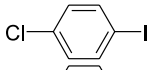
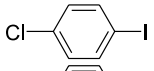
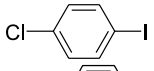
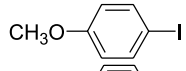
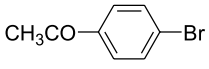
For the recycling studies of the polymer, alkynylation of 4-chloroiodobenzene with phenylacetylene was performed during 5 runs without appreciable lost of catalytic activity

Table 5. Sonogashira reactions with polymeric **8** and monomeric **4b** di-(2-pyridyl)methylamine-based $PdCl_2$ complexes[a]

Entry	R^1X	R^2	Cat. (mol% Pd)	*t*	Yield (%)[b]
1		Ph	**8** (0.1)	1 h	99
2		Ph	**4b** (0.1)	1 h	99
3		Ph	**8** (0.001)	31 h	99
4		Ph	**4b** (0.001)	4 d	70
5		Ph	**8** (0.1)	1 h	96
6		Ph	**4b** (0.1)	2 h	91
7		TIPS	**8** (0.1)	3 h	99
8		TIPS	**4b** (0.1)	6 h	94
9		Ph	**8** (0.2)	1.5 h	99
10		Ph	**4b** (0.2)	2 h	86
11		Ph	**8** (0.1)	10 min[c]	47
12		Ph	**4b** (0.1)	10 min[d]	66
13		TIPS	**8** (0.2)	14 h	99
14		TIPS	**4b** (0.2)	22 h	87
15		Ph	**8** (0.2)	1 h	92
16		Ph	**4b** (0.2)	2 h	90

[a] Reaction conditions: aryl halide (1 mmol), alkyne (1.2 mmol), pyrrolidine (2 mmol), TBAB (0.5 mmol), Pd complex, and H_2O (2.5 mL) reflux.
[b] Determined by GLC using decane as internal standard.
[c] The reaction was carried out under microwave heating at 100 °C (0.5 mmol scale).
[d] The reaction was carried out under microwave heating at 120 °C (0.5 mmol scale)

Table 6. Sonogashira reactions between phenylacetylene and aryl halides with polymer **8** and Pd EnCat™ 40 over 4 or 5 cycles[a]

Entry	ArX	Cat. (mol% Pd)	Cycle 1		Cycle 2		Cycle 3		Cycle 4		Cycle 5	
			t (h)	Yield (%)[b]	*t* (h)	Yield (%)[b]	*t* (h)	Yield (%)[b]	*t* (h)	Yield (%)[b]	*t* (h)	Yield (%)[b]
1		**8** (0.1)[c]	1	99	1	99	1	99	1	99	1	99
2		Pd EnCat (0.1)[c]	1.5	99	1.5	99	8	27				
3[d]		**8** (0.1)[c]	1	99	1	99	1	99	1	99	1	99
4[e]		**8** (0.1)[c]	1	99	1	99	1	99	1	99	1	99
5		**8** (0.1)[c]	1	96	1	92	1	92	1	94	1	92
6		**8** (0.2)[f]	1.5	99	1.5	99	2	88	2.5	91	2.5	93

[a] Reaction conditions: aryl halide (1 mmol), alkyne (1.2 mmol), pyrrolidine (2 mmol), TBAB (0.5 mmol), Pd complex, and H_2O (2.5 mL) reflux.
[b] Determined by GLC using decane as internal standard.
[c] Scale (3 mmol).
[d] The cycles were performed in situ without filtration of the polymer **8**.
[e] The catalyst was recovered by filtration from the previous cycles of entry 3 and the new 5 cycles were performed in situ without filtration of the polymer **8**.
[f] Scale (2 mmol).

(Table 6, entry 1). However, when recycling studies were performed with Pd EnCat 40 (0.1 mol% Pd) for the same cross-coupling under the same reaction conditions the catalytic activity was kept only during the two first cycles (Table 6, entry 2). In the case of 4-chloroiodobenzene the coupling was performed in situ during four quantitative cycles of 1 h by adding the reagents (except TBAB) to the flask. Then the polymer was filtered off and four more quantitative cycles were performed again during 1 h without loss of the catalytic activity (Table 6, entries 3 and 4). The alkynylation of the deactivated 4-iodoanisol with phenylacetylene gave practically the same yields in 1 h after five cycles (Table 6, entry 5). Even in the coupling of 4-bromoacetophenone and phenylacetylene good catalytic activity of the polymer was observed after five consecutive runs (Table 6, entry 6).

3. Conclusions

In conclusion, we have found that the new polymer-supported di(2-pyridyl)methylamine–palladium dichloride complex covalently anchored to a styrene-alt-maleic anhydride co-polymer showed similar catalytic activity than the monomeric palladium complex for Heck, Suzuki and Sonogashira reactions in water. This polymer maintains in general their efficiency especially in Sonogashira reactions through five recycle runs even better than the encapsulated Pd EnCat 40. The formation of Pd nanoparticles have been detected in the surface of the polymer by TEM analysis after a Suzuki reaction and 2.4% of Pd leaching was detected in the corresponding filtrate. On the other hand, the polymer cannot be recycled after microwave heating. In general, no appreciable catalytic activity was detected from the filtrates during recycling processes.

4. Experimental

4.1. General

The reagents and solvents were obtained from commercial sources and were generally used without further purification. Flash chromatography was performed on silica gel 60 (0.040–0.063 mm, Merck). Thin-layer chromatography was performed on Polygram® SIL G/UV_{254} plates. Gas chromatographic analyses were performed on a HP-6890 instrument equipped with a WCOT HP-1 fused silica capillary column. IR data were collected on a Nicolet Impact-400D-FT spectrophotometer in cm^{-1}. ICP-OES analyses were performed with a Perkin-Elmer Optima 4300. TEM analyses were performed with a JEOL JSM-840 and examples were dried, sonicated in hexane and supported on a carbon-coated copper grid. Elemental analyses were carried out by the corresponding services at the University of Alicante. The amounts of catalysts were weighed up in an electronic microscale (Sartorius, XM1000P) with precision of 1 μg. Microwave reactions were performed with a CEM Discover Synthesis Unit in glass vessels (10 mL) sealed with a septum under magnetic stirring at the temperature indicated on Tables 1, 3, and 5. All products have been previously described.[18]

4.2. Synthesis of polymer-supported complex 8

A mixture of di(2-pyridyl)methanamine (300 mg, 1.6 mmol)[18c] and poly(styrene-alt-maleic anhydride) resin (195 mg) was stirred under reflux during 24 h in H_2O/acetone (3 mL, 2/1). The solution was cooled to room temperature and water was added to precipitate the polymer. The solid was filtered, washed with H_2O and MeOH and dried under vacuum to yield 288 mg of a pale brown precipitate of polymer **7**. The average loading of amine (2.61 mmol/g) was determined by means of the nitrogen content from combustion analysis from three different batches. Without further purification, the modified polymer **7** (82 mg) was stirred for 2 days in MeOH (1 mL) with a 0.5 M methanolic solution of Na_2PdCl_4 (0.8 mL, 0.4 mmol). The mixture was filtered off (G-5) and washed with MeOH. The product was dried under reduced pressure and placed into an oven (130 °C) overnight to yield 130 mg of a brown solid. For the ICP-OES analysis, the resin was decomposed with HNO_3 giving 1.21 mmol/g of Pd.

4.3. General procedure for the Heck reactions

A suspension of aryl halide (1 mmol), alkene (1.5 mmol), diisopropylamine (0.420 mL, 3 mmol), tetra-*n*-butylammonium bromide (161 mg, 0.5 mmol), Pd complex (see Tables 1 and 2) and H_2O (2 mL) was stirred at the temperature indicated on Tables 1 and 2 in air, and the reaction progress was analyzed by GLC. After the reaction was completed and cooled to room temperature, the mixture was filtered off through a glass filter (G-5). The filtrate was extracted with ethyl acetate (3×15 mL) and the organic layer was dried over $MgSO_4$, evaporated (15 mmHg) and the resulting residue purified by flash chromatography.

4.4. General procedure for the Suzuki reactions in water

A solution of aryl halide (1 mmol), phenylboronic acid (183 mg, 1.5 mmol), potassium carbonate (276 mg, 2 mmol) tetra-*n*-butylammonium bromide (161 mg, 0.5 mmol, only for aryl chlorides), Pd complex (see Tables 3 and 4) in H_2O (2 mL) was stirred under reflux in air, and the reaction progress was analyzed by GLC. After the reaction was completed and cooled to room temperature, the mixture was filtered off through a glass filter (G-5). The filtrate was extracted with ethyl acetate (3×10 mL), the organic phases were dried over $MgSO_4$, and evaporated (15 mmHg). The subsequent residue was purified by recrystallization or by flash chromatography on silica gel to give pure products.

4.5. General procedure for the Suzuki reactions in methanol/water

A mixture of aryl halide (1 mmol), phenylboronic acid (183 mg, 1.5 mmol), potassium hydroxide (112 mg, 2 mmol), Pd complex (see Tables 3 and 4) and methanol/water: 2/3 (2.5 mL) was stirred at room temperature or at 60 °C (see Tables 3 and 4) and the reaction progress was analyzed by GC. After the reaction was completed and cooled to room temperature, the mixture was filtered off through a glass filter (G-5). When the product was not soluble in the solvent mixture the solid was dissolved in ethyl acetate. The filtrate was extracted with ethyl acetate

(3×10 mL), the organic phases were dried over $MgSO_4$, evaporated (15 mmHg) and the crude product purified by recrystallization (MeOH/H_2O:2:3) or flash chromatography on silica gel.

4.6. General procedure for the Sonogashira reactions

A 10 mL round-bottom flask was charged with palladium catalyst (see Tables 5 and 6), aryl halide (1 mmol), alkyne (1.5 mmol), pyrrolidine (0.164 mL, 2 mmol), tetrabutylammonium bromide (161 mg, 0.5 mmol) and water (2.5 mL). The mixture was stirred under reflux during the reaction time indicated in Tables 5 and 6. The reaction progress was analyzed by GLC. After the reaction was completed and cooled to room temperature, the mixture was filtered off through a glass filter (G-5). The filtrate was extracted with EtOAc (3×15 mL), washed with 2 M HCl, dried over $MgSO_4$, concentrated in vacuo and the residue purified by flash chromatography on silica gel.

4.7. General procedure for recycling reactions

When the corresponding Heck, Suzuki or Sonogashira reaction was finished the suspension was cooled down to room temperature and filtered off (G-5). The polymer was washed with water and ethyl acetate, dried under vacuum and reused.

Acknowledgements

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Polymer-micelle incarcerated ruthenium catalysts for oxidation of alcohols and sulfides

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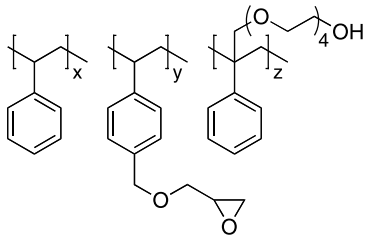
Abstract—Highly active immobilized ruthenium catalysts, which can be used for oxidation of alcohols and sulfides, were developed on the basis of the polymer-micelle incarcerated (PMI) method. The catalysts could be recovered and reused several times without loss of activity and no metal leaching was observed. Selection of micelle-forming conditions and polymer structures were key in achieving high activities. TEM and SEM analyses were conducted to observe the structures of PMI-Ru.

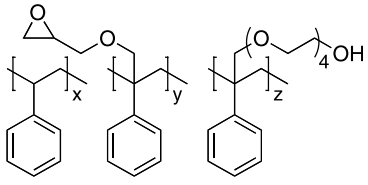
1. Introduction

Immobilized catalysts are now of great interest for two principle reasons. First, they are crucial for achieving environmentally benign chemical synthesis,[1] the catalysts are readily recovered and reused, and total waste is decreased. Secondly, immobilized catalysts play a key role for combinatorial library synthesis.[1d,2] Synthetic procedures are simplified using immobilized catalysts, and their application to automation is facile. However, whereas various immobilized catalysts have been developed, many are less active than the original non-immobilized catalysts. Oxidation reactions are very important transformations in organic synthesis,[3] and whilst several metal-based oxidizing reagents have been developed, in many cases stoichiometric amounts of metal oxidants are needed, and thus large amounts of metal-containing waste is formed. In this aspect, oxidation reactions using a catalytic amount of a metal reagent are very attractive[4] and several successful examples of catalytic oxidation of alcohols have been reported.[5] Among these catalysts, some ruthenium species have been widely developed and used as efficient catalysts for oxidation reactions.[6] Quite recently we have reported a novel immobilized ruthenium catalyst for the oxidation of alcohols and sulfides.[7] In the course of our investigation to develop efficient immobilized catalysts, we have found that choice of micelle-forming conditions and polymer structures plays a key role in obtaining higher catalytic activities in the polymer-micelle incarcerated (PMI) method. In this article, we describe efficient immobilized ruthenium catalysts, which have high activity for oxidation reactions (Figs. 1 and 2).



P$_1$ (x:y:z=79:15:6)

Figure 1.



P$_2$ (x:y:z=91:5:4)

Figure 2.

2. Results and discussion

Recently we have developed a novel polymer incarceration immobilization method for metal catalysts using

Keywords: Ruthenium catalysts; Oxidation of alcohols and sulfides; Polymer-micelle incarcerated (PMI) method.
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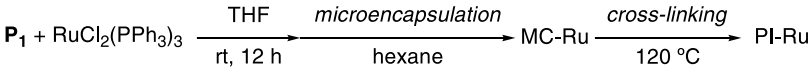
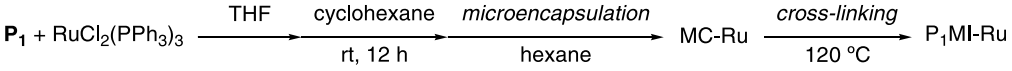
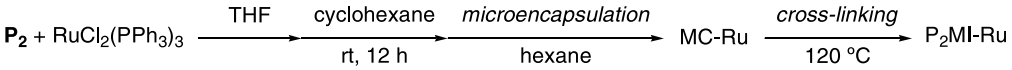


Scheme 1.



Scheme 2.



Scheme 3.

epoxide-containing copolymer (**P$_1$**), which is based on microencapsulation and cross-linking, and is successful in immobilizing highly active, metal-based catalysts such as palladium, platinum and scandium species.[8] We applied these methods to immobilization of dichlorotris(triphenylphosphine)ruthenium ($RuCl_2(PPh_3)_3$)[9] and successfully obtained an active ruthenium catalyst, so-called polymer incarcerated ruthenium (PI-Ru) (Schemes 1–3).[7]

While PI-Ru was found to be effective for catalytic oxidation of alcohols and sulfides, we then decided to investigate the structure of PI-Ru, mainly by electron microscopy.

PI-Ru was prepared from copolymer (**P$_1$**) and $RuCl_2(PPh_3)_3$ in a THF-hexane system. Epoxide-containing copolymer (**P$_1$**) was dissolved in tetrahydrofuran (THF) at room temperature, and $RuCl_2(PPh_3)_3$ was added to this solution. Transmission electron microscopic (TEM) analysis was conducted to observe this solution, and a membrane-like morphology without distinguishable clusters was confirmed (Fig. 3). Hexane was then added to form microencapsulated ruthenium (MC-Ru), which was filtered, washed and dried. MC-Ru was next heated at 120 °C for 3.5 h to afford PI-Ru (**2**). MC-Ru was observed by TEM analysis, and a spherical structure containing some craters was observed (Fig. 4). In addition, PI-Ru supported on a glass was observed by scanning electron microscopy (SEM), and a membrane-like structure with many submicrometer holes was observed (Fig. 5).

In heterogeneous catalysts, the interfacial surface area of the catalysts is a key to obtain high activity. Recently, we have developed a highly active Pd(0) catalyst[10] having subnanometer clusters and a Sc catalyst[11] containing well-regulated polymer micelles. In both cases a solvent system

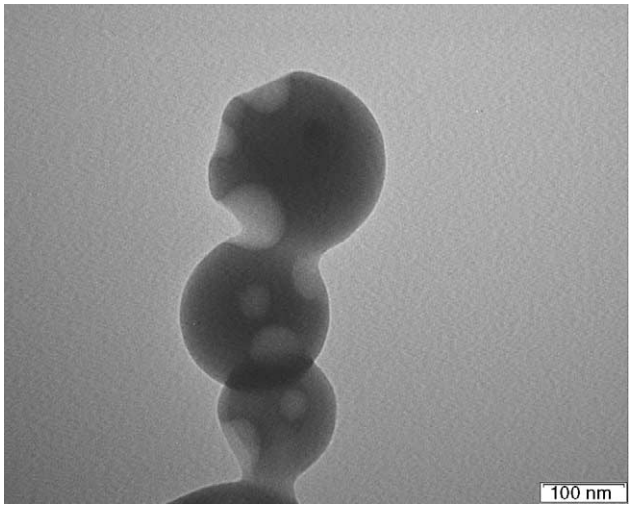


Figure 4. TEM image of MC-Ru.

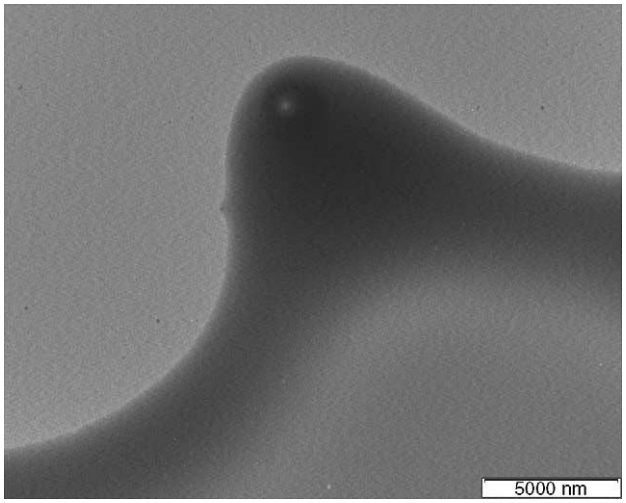


Figure 3. TEM image of a **P$_1$**-$RuCl_2(PPh_3)_3$ solution in THF.

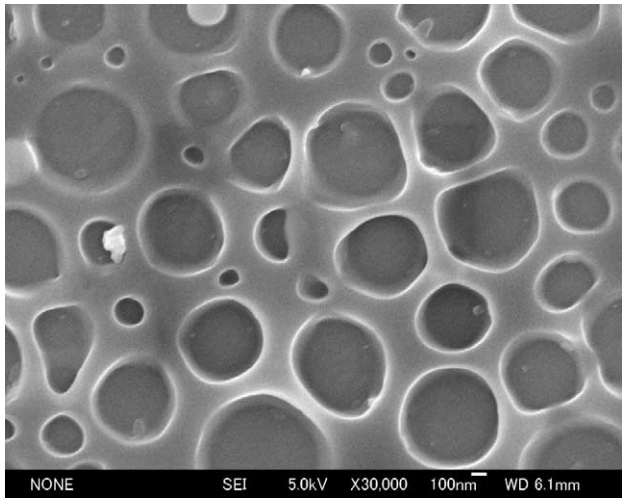


Figure 5. SEM image of PI-Ru on glass.

Table 1. Solvent systems for the preparation of MC-Ru

Conditions of microencapsulation (solvent/poor solvent)	Loaded ruthenium (%)
THF/hexane	90
CH_2Cl_2/MeOH	69
THF–cyclohexane/hexane	89

in which the catalysts were prepared played an important role to regulate the catalyst structure. We then examined several solvent systems for the preparation of MC-Ru (Table 1). In the case of a THF–hexane system, in which the hydrophobic domains of the polymer chains should be orientated towards the exterior, 90% of ruthenium was loaded on the polymer support. On the other hand, in the case of a CH_2Cl_2–MeOH system, in which hydrophilic zones of the polymer chains should be orientated towards the exterior,[12] only 69% of ruthenium was loaded. These results suggest that the ruthenium may be located in both the hydrophilic and hydrophobic area of the polymer, but on-balance prefer hydrophilic interactions. Therefore, we chose the former conditions for microencapsulation, and modified

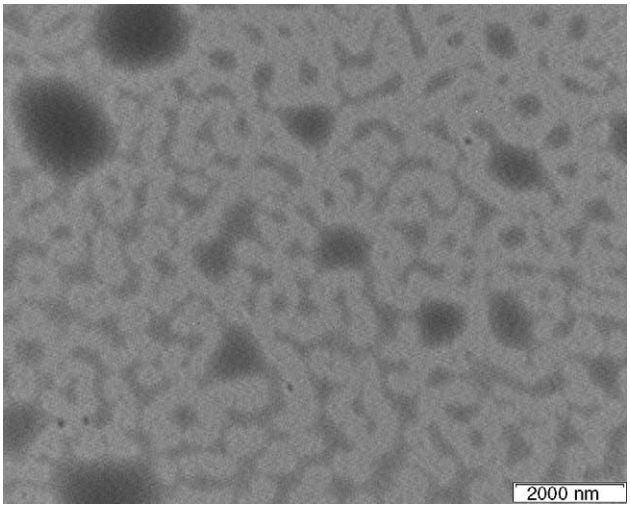


Figure 6. TEM image of a $\mathbf{P_1}$-$RuCl_2(PPh_3)_3$ solution in THF–cyclohexane.

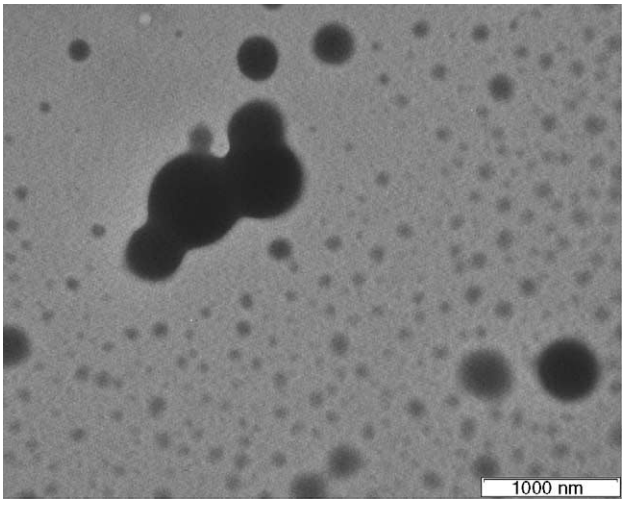


Figure 7. TEM image of a $\mathbf{P_2}$-$RuCl_2(PPh_3)_3$ solution in THF–cyclohexane.

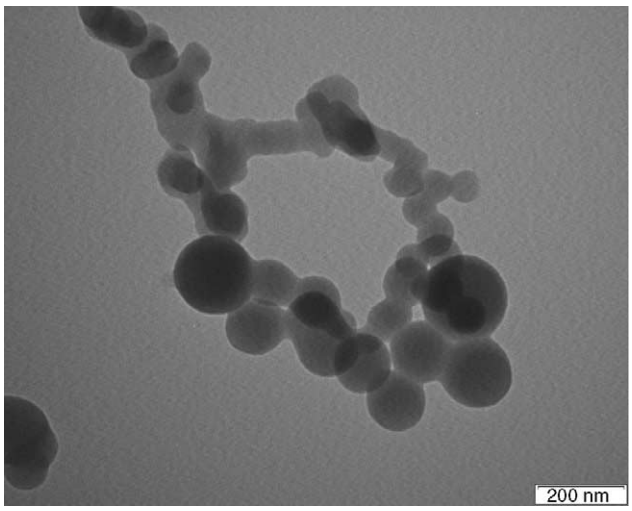


Figure 8. TEM image of MC-Ru using $\mathbf{P_1}$ under micelle-forming conditions.

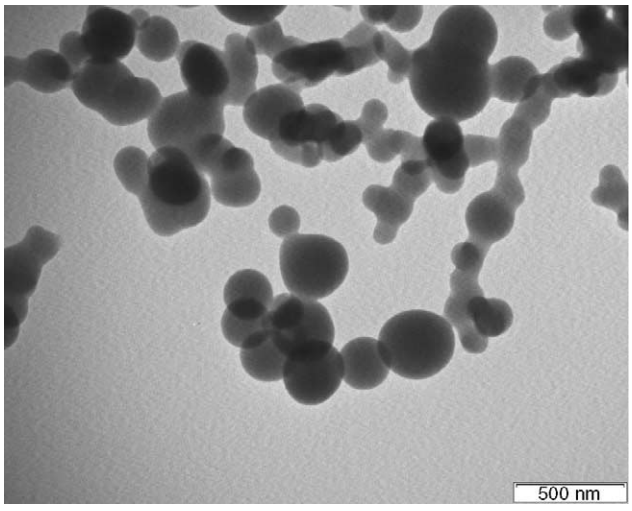


Figure 9. TEM image of MC-Ru using $\mathbf{P_2}$ under micelle-forming conditions.

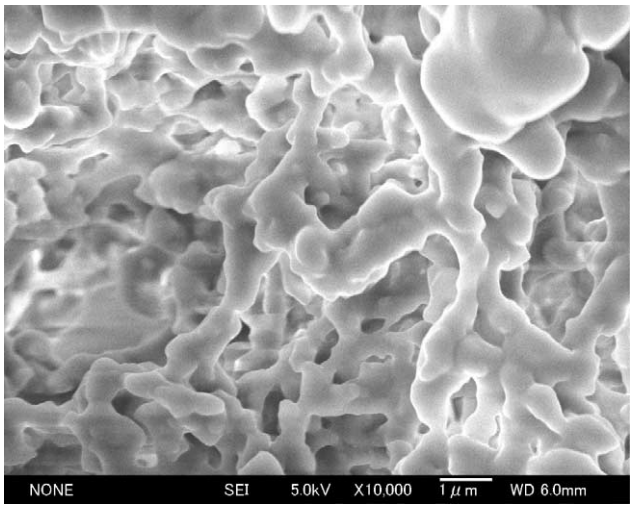


Figure 10. SEM image of P_2MI-Ru on glass.

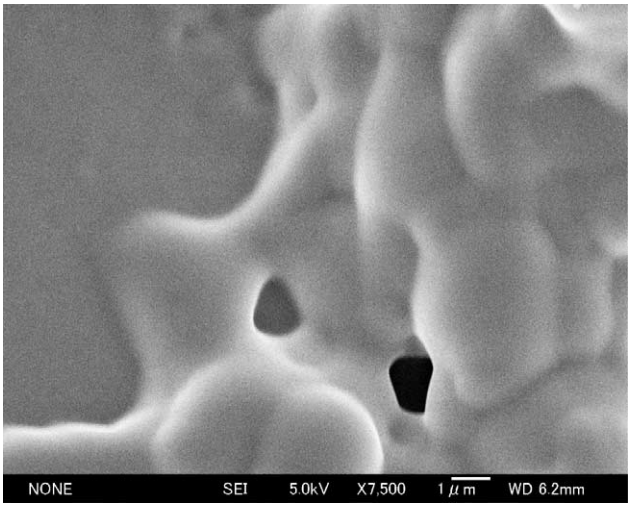


Figure 11. SEM image of P_1MI-Ru on glass.

the conditions to form micelles. Copolymer **P_1** or **P_2** (1 g), which were effective for micelle formation in the cases of Pd and Sc catalysts, was dissolved in THF (20 mL), and $RuCl_2(PPh_3)_3$ (400 mg) was added. Cyclohexane (60 mL) was slowly added to this solution, and after the mixture was stirred for 12 h at room temperature, the solution was observed by TEM analysis. In the case of **P_1**, spherical capsules were not observed (Fig. 6), whilst spherical capsules were formed in the case of **P_2** (Fig. 7). Next, the solution was added to hexane and observed by TEM analysis. In both cases, chains consisting of a series of clear spherical micelles (100–500 nm) were formed (Figs. 8 and 9). To the mixture, glass as a support was added and the whole mixture was allowed to stand overnight to form precipitations of micelles on the glass. The glass support was washed with hexane and heated at 150 °C for 5 h. After subsequent washing with THF, the support was observed by SEM analysis. In the case of **P_2**, micelles were fixed by the cross-linking and the original size of micelles (300–2000 nm) was maintained to afford highly dispersed 3D networked morphologies (Fig. 10). On the other hand, in the case of **P_1**, a series of larger spherical micelles (2–4 μm) were observed (Fig. 11). In either case, the structure is very different from the membrane-like morphologies of PI-Ru, which is prepared in a THF–hexane solvent system. To distinguish these two catalysts from the original PI-Ru, they were named polymer **1**-micelle incarcerated ruthenium (P_1MI-Ru) and polymer **2**-micelle incarcerated ruthenium (P_2MI-Ru). When hexane was added to the micelle solutions, precipitates were formed and after heating at 120 °C for 3.5 h PMI-Ru was generated. In the case of P_1MI-Ru, 89% of ruthenium was loaded, same level as that of PI-Ru prepared in THF–hexane.

We thought that the difference of the morphologies between PI-Ru and PMI-Ru could be ascribed to the solvent systems used in the microencapsulation. In the cases of PMI-Ru, stable micelles were formed in THF–cyclohexane before precipitation and the micelle morphologies were approximately maintained after cross-linking. The difference between **P_1** and **P_2** could be ascribed to facility of phase separation. In the case of **P_2**, more well defined and more stable micelles might be formed by phase separation between the hydrophobic benzene rings and the hydrophilic epoxy or tetraethyleneglycol moieties along the polymer backbone.[10]

P_1MI-Ru and P_2MI-Ru were first used in the oxidation of a sulfide to compare their catalytic activities. When PI-Ru, P_1MI-Ru and P_2MI-Ru were used as the catalysts, reactions proceeded smoothly in an acetone–water co-solvent system in the presence of 2.2 equiv of iodobenzene diacetate ($PhI(OAc)_2$) to afford the desired sulfone in high yields. The reaction profile in the presence of P_2MI-Ru is shown in Figure 12. The reaction proceeded via two steps; the first

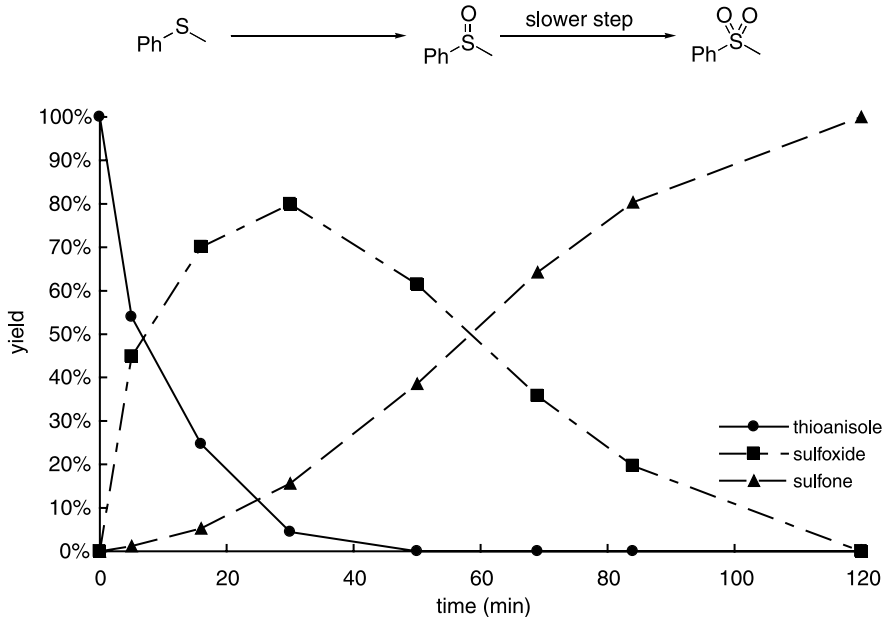


Figure 12. Reaction profile of oxidation of thioanisole in the presence of 0.5 mol% of P_2MI-Ru. The yields were determined by GC analysis with reference to an internal standard (IS = anisole). Reaction conditions: thioanisole (2 mmol), P_2MI-Ru (0.5 mol%), $PhI(OAc)_2$ (4.4 mmol), acetone (18 mL), water (2 mL) and anisole (100 mg) at room temperature.

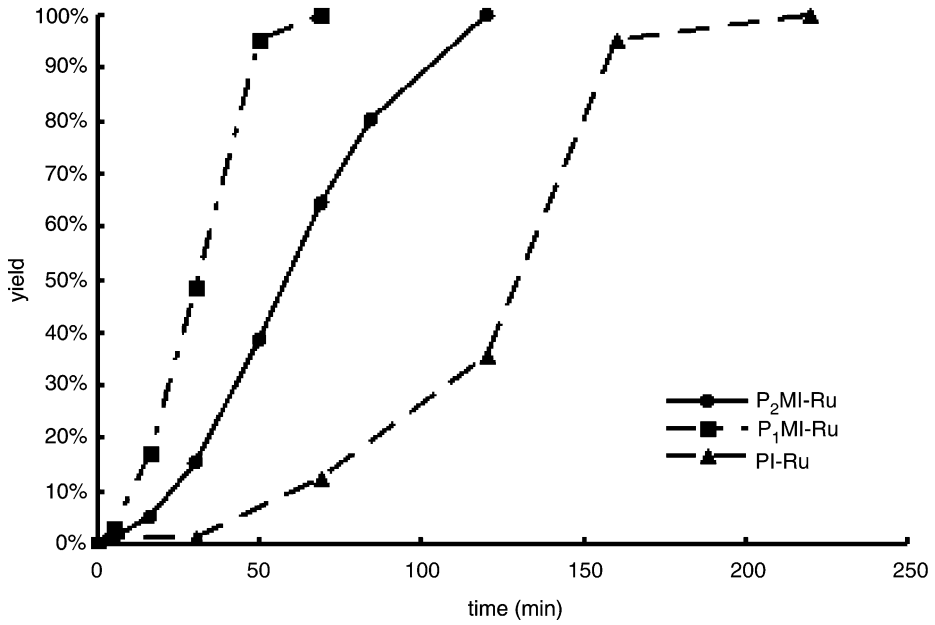


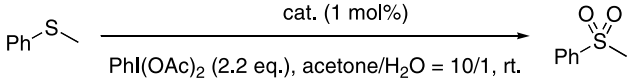
Figure 13. Formation of phenyl–methyl sulfone in the presence of 0.5 mol% of P_1MI-Ru, P_2MI-Ru and PI-Ru. The yields were determined by GC analysis with reference to an internal standard (IS=anisole). Reaction conditions: thioanisole (2 mmol), PI-Ru, P_1MI-Ru or P_2MI-Ru (0.5 mol%), $PhI(OAc)_2$ (4.4 mmol), acetone (18 mL), water (2 mL) and anisole (100 mg) at room temperature.

step was oxidation of the sulfide to the sulfoxide, the second step was oxidation of the sulfoxide to the sulfone. Judging from the chart, it seems that the second step is slower and that there is no induction period in the first step. The reactions proceeded smoothly using all the three catalysts tested as shown in Figure 13, but there are differences in reaction rate. In the presence of 0.5 mol% of each catalyst, the reaction was complete within 220 min in the case of PI-Ru, 70 and 120 min in the case P_1MI-Ru and P_2MI-Ru, respectively. All the catalysts could be recovered and reused several times by simple filtration and washing (Table 2). It is noted that no leaching of ruthenium was observed by fluorescence X-ray (XRF) analysis. In the cases of PI-Ru and P_2MI-Ru, longer reaction times were needed for reactions to get to complete in the 2nd use, while in the case of P_1MI-Ru the reactivity was completely maintained for at least 4 uses. The higher activity advantages of P_1MI-Ru and P_2MI-Ru compared with the previously reported PI-Ru could be ascribed to the formation of stable micelle morphologies with a large surface area. Although P_2MI-Ru has a larger surface area than P_1MI-Ru, P_1MI-Ru has a higher catalytic activity in the oxidation of sulfides. This could be explained by quantity of hydrophilic parts in the polymers (21% of hydrophilic parts in **P_1** vs 9% in **P_2**). As described above, ruthenium is mainly located in the hydrophilic parts of the polymer, which are at the outer layer of micelles when a THF(-cyclohexane)/hexane microencapsulation system was employed. In the slower second step, oxidation of a sulfoxide to a sulfone, the hydrophilic sulfoxide and $PhI(OAc)_2$ might be located at a hydrophilic catalytic site. On the other hand, the generated sulfone and iodobenzene, which are relatively hydrophobic, might be easily eliminated from the catalytic site to the outer layer. Therefore, in P_1MI-Ru derived from **P_1** containing more hydrophilic parts, there are more ruthenium metals located in the hydrophilic parts than in P_2MI-Ru, and the catalytic turn-over frequency is also higher.

Under these conditions, aromatic (even with electron withdrawing group), aliphatic and cyclic sulfides were smoothly oxidized in the presence of either P_1MI-Ru or P_2MI-Ru to afford the desired products in high yields (Table 3).

Next, P_1MI-Ru and P_2MI-Ru were used in the oxidation of alcohols in the presence of 2 equiv of *N*-methylmorpholine-*N*-oxide (NMO). PI-Ru, P_1MI-Ru and P_2MI-Ru were

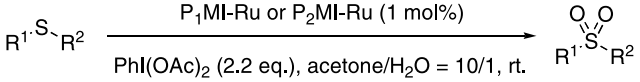
Table 2. Oxidation of a sulfide using PI-Ru and PMI-Ru

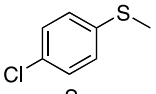
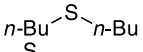


Entry	Catalyst	Yield (%)[a] [Time (h)[b]]			
		1st	2nd	3rd	4th
1	PI-Ru	quant. (2.0)	95 (2.5)	80 (2.5)	94 (2.5)
2	P_1MI-Ru	quant. (0.5)	87 (0.5)	97 (0.5)	99 (0.5)
3	P_2MI-Ru	96 (0.5)	96 (1.0)	89 (1.1)	quant. (1.3)

[a] Isolated yield. No peaks of ruthenium were observed by XRF analysis (<1.1%).
[b] Time until sulfoxide was completely consumed (confirmed by TLC).

Table 3. Oxidation of sulfides



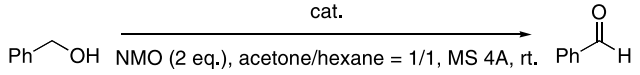
Entry	Substrate	P_1MI Ru		P_2MI Ru	
		Time (h)	Yield (%)[a]	Time (h)	Yield (%)[a]
1		0.5	quant.	0.5	96[b]
2		2	98	0.75	99
3		2	96	0.5	99
4		2	quant.[c]	2	quant.[c]
5		2	quant.[c]	2	quant.[c]

[a] Isolated yield. No peaks of ruthenium were observed by XRF analysis (<1.1%).
[b] Quantitative yield, using 0.1 mol% of P_2MI-Ru for 11 h.
[c] Determined by GC.

preliminarily treated with 20 equiv of NMO in an acetone-isopropyl alcohol (^{i}PrOH) (1/9) solvent at room temperature for 12 h before application to the oxidation reactions. Both PI-Ru and P_2MI-Ru did not work well in the oxidation of benzyl alcohol without molecular sieves 4A (MS 4A) (Table 4, entries 1, 2). When 0.5 g/mmol of MS 4A were added to the reaction mixture, P_2MI-Ru worked well to afford benzaldehyde in high yield (entry 5). In the cases of PI-Ru and P_1MI-Ru, the desired product was obtained in moderate yields (entries 3, 4). P_2MI-Ru could be reused several times after recovery by simple filtration and washing, although after 2nd use 7.5 h was needed to complete the reaction. Lower catalyst loading of P_2MI-Ru also produced the product in high yield, albeit with prolonged reaction time (entry 7). That P_2MI-Ru was the best catalyst for oxidation of alcohols was thought to be due to the greater surface area as well as hydrophilicity of the polymers that determined the reactivities in the case of oxidation of sulfides.

Under these conditions, the substrate scope was surveyed using P_1MI-Ru and P_2MI-Ru (Table 5). In most cases, high to excellent yields were obtained in the oxidation of both

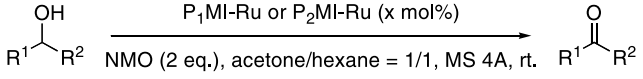
Table 4. Oxidation of an alcohol using PI-Ru and PMI-Ru

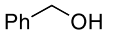
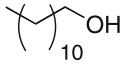
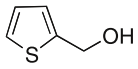
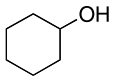


Entry	Catalyst (mol%)	MS 4A (0.5 g/mmol)	Time (h)	Yield (%)[a]
1	PI-Ru (1.0)	−	2.5	47
2	P_2MI-Ru (1.0)	−	2.5	51
3	PI-Ru (1.0)	+	2.5	59
4	P_1MI-Ru (1.0)	+	2.5	75
5	P_2MI-Ru (1.0)	+	2.5	93
6	P_2MI-Ru (2.0)	+	2.5	93[b]
7	P_2MI-Ru (0.3)	+	24	91

[a] Determined by GC. No peaks of ruthenium were observed by XRF analysis.
[b] 2nd; 85% for 7.5 h, 3rd; 85% for 7.5 h.

Table 5. Oxidation of alcohols



Entry	Substrate	P_1MI-Ru			P_2MI-Ru		
		x	Time (h)	Yield (%)[a]	x	Time (h)	Yield (%)[a]
1		1	2.5	75	1	2.5	93
2		1	12	66	1	2.5	67
3		1	2.5	74	1	2.5	81
		1	12	83			
4		1	12	73	1	12	82
					2	12	96
5		1	12	50	1	12	45
					2	12	83
6		1	12	65	1	12	60
					2	12	85

[a] Determined by GC. No peaks of ruthenium were observed by XRF analysis.

primary and secondary alcohols.[13] Moreover, no ruthenium leaching was observed in all cases.

3. Conclusion

In summary, we have developed a novel effective immobilization method for ruthenium, the polymer-micelle incarcerated (PMI) method. The solvent system for the preparation of the catalysts was found to be very important to the morphologies obtained. We gained an insight into the structure of PMI-Ru by TEM and SEM analyses, the micelle 3D cross-linked networks were observed, whilst PI-Ru had membrane-like morphologies. PMI-Ru was effective in oxidation of sulfides and alcohols and had higher activity than PI-Ru. Moreover, the catalyst could be recovered by simple filtration and reused several times without loss of catalytic activity, no Ru leaching was observed in both systems. The higher catalytic activity of PMI-Ru was ascribed to the greater surface area that was enabled by well-regulated 3D network. Further investigations of other reactions using PMI-Ru as a catalyst are now in progress.

4. Experimental

4.1. General

^{1}H and ^{13}C NMR spectra were recorded on a JEOL JNM-LA300, JNM-LA400 spectrometer in $CDCl_3$. Tetramethylsilane was used as an internal standard ($\delta=0$) for 1H NMR, and the $CDCl_3$ solvent peak was used as the internal standard ($\delta=77.0$) for ^{13}C NMR. 2-Phenylpropene, *N*-bromosuccineimide (NBS), bromobenzene, glycidol, styrene, iodobenzene diacetate and tetraethyleneglycol

were purchased from Tokyo Chemical Industry. 2-Thiophenemethanol, dodecanol, cyclohexanol, butyl sulfide, tetrahydrothiophene, diphenyl sulfide, benzyl alcohol, 4-chlorophenyl methyl sulfide, thioanisole, anisole, 2-octanol and phenethyl alcohol were purchased from Tokyo Chemical Industry and distilled before use. Di-*n*-butyl sulfone, dodecanal, cyclohexanone, 2-octanal, acetophenone and tetrahydrothiophene-1, 1-dioxide were purchased from Tokyo Chemical Industry and distilled before use. AIBN was purchased from Wako Pure Chemical Industry. $RuCl_2(PPh_3)_3$ was purchased from Strem Chemicals. MS 4A were purchased from Aldrich and dried in vacuo at 200 °C for 3 days. The glass used as a support was purchased from MATSUNAMI Glass. Dry solvents (THF, DCM, DMF) were purchased from Wako Pure Chemical Industry. Tetraethyleneglycol mono-2-phenyl-2-propenyl ether was prepared according to the literature.[8a] Dehydrated acetone and cyclohexane were purchased from Kanto Chemical. Hexane was purchased from Kanto Chemical and dried over MS 3A that were purchased from Wako Pure Chemical Industry. Water was treated by MILLIPORE Elix-UV before use. Column chromatography was performed on silica gel 60 (Merck), and preparative TLC was carried out by using Wakogel B-5F (Wako Pure Chemical Industry). XRF analysis was performed on Shimadzu EDX-800 equipment. GC analysis was performed on Shimadzu GC-17A apparatus (column = J & W SCIENTIFIC DB-1). The structures of the known compounds were confirmed by comparison with commercially available compounds or literature data.

4.2. Microscopic analysis

TEM images were obtained using a JEOL JEM-1010 instrument operated at 80 kV. All TEM specimens were prepared by placing a drop of the solution on carbon-coated Cu grids and allowed to dry in air (without staining). SEM images were obtained using a JEOL JSM-6700F instrument operated at 5.0 kV. All SEM specimens were coated with platinum for 60 s in a sputter coater (JFC-1600).

4.2.1. Preparation of vinyl monomer. 3-Bromo-2-phenylpropene.[14] A mixture of 2-phenylpropene (22.4 g, 190 mmol), NBS (23.7 g, 133 mmol) and bromobenzene (76 mL) was rapidly heated in an oil bath at 160 °C until NBS was dissolved. After cooling to room temperature, the precipitate was removed by filtration and washed with chloroform. The filtrate was purified by distillation (bp 80–85 °C/3 mmHg) to afford 3-bromo-2-phenylpropene containing 1-bromo-2-phenylpropene (15.5 g). The purity was found to be 78.0% (determined by ^{1}H NMR). ^{1}H NMR ($CDCl_3$) δ=4.39 (s, 2H), 5.49 (s, 1H), 5.56(s, 1H), 7.33–7.51 (m, 5H); ^{13}C NMR ($CDCl_3$) δ=34.2, 117.2, 126.1, 128.3, 128.5, 137.6, 144.2.

4.2.2. 2-[(2-Phenylallyloxy)methyl]oxirane. To sodium hydride (60% in mineral oil, 1.6 g, 40 mmol) suspended in dry DMF (75 mL) was added glycidol (7.4 g, 100 mmol) in DMF (5 mL) at 0 °C. Then a solution of 3-bromo-2-phenylpropene (78% purity, 5.05 g, 20 mmol) in DMF (10 mL) was added at the same temperature, and the mixture was stirred for 24 h at room temperature. After the mixture was cooled to 0 °C and diluted with diethyl ether, saturated aqueous ammonium chloride was added to quench the reaction, the aqueous layer was extracted with diethyl ether. The combined organic layers were dried over sodium sulfate, and the solvent was removed in vacuo. The residue was purified by flash chromatography (silica, hexane/EtOAc) to afford 2-[(2-phenylallyloxy)methyl]oxirane (2.66 g, 70%). ^{1}H NMR ($CDCl_3$) δ=2.59 (dd, 1H, J=2.7, 5.1 Hz), 2.78 (dd, 1H, J=4.2, 5.1 Hz), 3.13–3.17 (m, 1H), 3.46 (dd, 1H, J=5.8, 11.5 Hz), 3.77 (dd, 1H, J=3.2, 11.5 Hz), 4.41 (ddd, 1H, J=0.7, 1.2, 12.9 Hz), 4.48 (ddd, 1H, J=0.5, 1.2, 12.9 Hz), 5.34–5.36 (m, 1H), 5.53–5.54 (m, 1H), 7.45–7.48 (m, 5H); ^{13}C NMR ($CDCl_3$) δ=44.3, 50.8, 70.5, 73.2, 114.6, 126.0, 127.8, 128.4, 138.6, 143.9; IR (KBr) 3000, 2924, 2867, 1911, 1812, 1701, 1630, 1512, 1479, 1407, 1337, 1254, 1205, 1107, 991, 909, 839 cm^{-1}; HRMS (EI): Calcd for $C_{13}H_{16}O_2$ (M+), 190.0994; found, 190.0998.

4.3. Preparation of tetraethyleneglycol mono-2-phenyl-2-propenyl ether

To sodium hydride (60% in mineral oil, 1.82 g, 45.4 mmol) suspended in tetrahydrofuran (70 mL), tetraethyleneglycol (8.81 mL, 45.4 mmol) was added at 0 °C. After the reaction mixture was stirred for 1 h at room temperature, 3-chloro-2-phenylpropene (3.46 g, 22.7 mmol) was added and the mixture was further stirred for 12 h. The mixture was cooled to 0 °C and diluted with diethyl ether, saturated aqueous ammonium chloride was added to quench the reaction and the aqueous layer was extracted with diethyl ether. The combined organic layers were dried over sodium sulfate and the solvent was removed in vacuo. The residue was purified by flash chromatography to afford tetraethyleneglycol mono-2-phenyl-2-propenyl ether (4.52 g, 64%) and tetraethyleneglycol di-2-phenyl-2-propenyl ether (621 mg, 13%).

4.3.1. Tetraethyleneglycol mono-2-phenyl-2-propenyl ether. ^{1}H NMR ($CDCl_3$) δ=2.72 (s, 1H), 3.58–3.74 (m, 16H), 4.42 (s, 2H), 5.34 (d, 1H, J=1.2 Hz), 5.53 (d, 1H, J=0.5 Hz), 7.25–7.36 (m, 3H), 7.44–7.52 (m, 2H); ^{13}C NMR δ=61.7, 69.2, 70.3, 70.53, 70.58, 72.4, 73.1, 114.4, 126.1, 127.7, 128.3, 138.7, 144.0.

4.3.2. Tetraethyleneglycol di-2-phenyl-2-propenyl ether. ^{1}H NMR ($CDCl_3$) δ=3.55–3.75 (m, 16H), 4.41 (s, 4H), 5.33 (d, 2H, J=1.0 Hz), 5.51 (s, 2H), 7.23–7.36 (m, 6H), 7.43–7.50 (m, 4H); ^{13}C NMR δ=69.2, 70.47, 70.51, 73.0, 114.3, 126.0, 127.6, 128.2, 138.7, 144.0.

4.4. Preparation of copolymer P_1

Styrene (40.2 mL, 351 mmol), 4-vinylbenzyl glycidyl ether (8.42 g, 43.9 mmol), tetraethyleneglycol mono-2-phenyl-2-propenyl ether (13.6 g, 43.9 mmol) and 2,2′-azobis(isobutyronitrile) (393 mg) were combined in chloroform (50.0 mL). The mixture was stirred for 24 h under reflux, then cooled to room temperature. The resulting polymer solution was slowly pored into cold methanol (0 °C). The precipitated polymer was filtered and washed with methanol several times and dried for 24 h in vacuo to afford the desired copolymer (**P_1**, 37.0 g). The molar ratio of the monomers was determined by ^{1}H NMR analysis (styrene: 4-vinylbenzyl

glycidyl ether: tetraethyleneglycol mono-2-phenyl-2-propenyl ether=79: 15: 6). M_w: 42,798, M_n: 14,649, $M_w/M_n=2.922$ (gel permeation chromatography).

4.5. Preparation of copolymer P_2

Styrene (7.53 g, 72.3 mmol), 2-[(2-phenylallyloxy)methyl]-oxirane (1.72 g, 9.04 mmol), tetraethyleneglycol mono-2-phenyl-2-propenyl ether (2.81 g, 9.04 mmol) and AIBN (105.9 mg) were combined in chloroform (11.5 mL). The mixture was stirred for 24 h at reflux and then cooled to room temperature. The resulting polymer solution was slowly poured into methanol. The precipitated polymer was filtered and washed with methanol several times and dried for 24 h in vacuo to afford the desired copolymer (**P_2**, 7.35 g, 61% yield). The molar ratio of the components was determined by ^{1}H NMR analysis (x:y:z=91:5:4). M_w: 31 912, M_n: 19 468, $M_w/M_n=1.64$ (gel permeation chromatography).

4.6. Preparation of PI-Ru

Copolymer (**P_1**, 6.29 g) was dissolved in tetrahydrofuran (THF, 125 mL) at room temperature, to this solution dichlorotris(triphenylphophine)ruthenium(II) ($RuCl_2(PPh_3)$, 2.52 g) was added, the mixture was stirred for 24 h at that temperature. Hexane (800 mL) was slowly added to the mixture at room temperature. Coaservates were found to envelop the metal dispersed in the medium. The mixture was left to stand at room temperature for 12 h. The resultant capsules were washed with hexane several times and dried at room temperature for 12 h. The capsules were then heated at 120 °C for 3.5 h to prepare polymer incarcerated ruthenium (PI-Ru, 7.74 g, 0.302 mmol/g, 90% of ruthenium metal was loaded). The washings were concentrated to determine loading of ruthenium metal by fluorescence X-ray analysis.

4.7. Preparation of P_1MI-Ru

Copolymer (**P_1**, 1.00 g) was dissolved in tetrahydrofuran (THF, 20 mL) at room temperature, to this solution dichlorotris(triphenylphophine)ruthenium(II) ($RuCl_2(PPh_3)$, 0.41 g) was added, after the polymer and metal were completely dissolved, cyclohexane (60 mL) was slowly added, and stirred for 24 h at that temperature. Hexane (140 mL) was slowly added to the mixture at room temperature, coaservates were found to envelop the metal dispersed in the medium. The mixture was left to stand at room temperature for 12 h, the resultant capsules were then washed with hexane several times and dried at room temperature for 12 h. The capsules were heated at 120 °C for 3.5 h to generate polymer incarcerated ruthenium (PI-Ru, 1.16 g, 0.329 mmol/g, 89% of ruthenium metal was loaded). The washings were concentrated to determine loading of ruthenium metal by fluorescence X-ray analysis.

4.8. Preparation of P_2MI-Ru

Copolymer (**P_2**, 1.02 g) was dissolved in tetrahydrofuran (THF, 20 mL) at room temperature, to this solution dichlorotris(triphenylphophine)ruthenium(II) ($RuCl_2(PPh_3)$, 0.41 g) was added, after the polymer and metal were completely dissolved, cyclohexane (60 mL) was slowly added, and stirred for 24 h at this temperature. Hexane (140 mL) was slowly added to the mixture at room temperature, coaservates were found to envelop the metal dispersed in the medium. The mixture was left to stand at room temperature for 12 h, the capsules were then washed with hexane several times and dried at room temperature for 12 h, then heated at 120 °C for 3.5 h to form polymer incarcerated ruthenium (PI-Ru, 1.12 g, 0.275 mmol/g, 72% of ruthenium metal was loaded). The washings were concentrated to determine loading of ruthenium metal by fluorescence X-ray analysis.

4.9. PMI-Ru on glass

Copolymer (**P_1** or **P_2**, 54 mg) and $RuCl_2(PPh_3)_3$ (10 mg) were dissolved in THF (1 mL), cyclohexane (3 mL) was slowly added to this mixture to form polymer micelles. To this solution, glass (microscope cover glass, borosilicate glass (SiO_2 64.2%, B_2O 8.9%, Na_2O 7.2%, ZnO 7.1%, K_2O 6.4%, washed with 1 N NaOH aq./EtOH (1/1), water and EtOH, successively, before use) was added, and the mixture was allowed to stand overnight to precipitate the micelles onto the glass. The glass with micelles was washed with hexane and dried and then heated for 5 h at 150 °C. The resulting glass was washed with THF, PMI-Ru on glass was obtained.

4.10. PI-Ru on glass

Copolymer (**P_1**, 54 mg) and $RuCl_2(PPh_3)_3$ (10 mg) were dissolved in THF (1 mL). To this solution, glass (microscope cover glass, borosilicate glass (SiO_2 64.2%, B_2O 8.9%, Na_2O 7.2%, ZnO 7.1%, K_2O 6.4%, washed with 1 N NaOH aq./EtOH (1/1), water and EtOH, successively, before use) was added, the mixture was allowed to stand overnight to precipitate the micelles onto the glass. The glass with micelles was washed with hexane and dried, then heated for 5 h at 150 °C. The resulting glass was washed with THF, PI-Ru on glass was obtained.

4.11. Preliminary treatment before oxidation of alcohols

Acetone (5.4 mL) and ^{i}PrOH (0.6 mL) were added to P_1MI-Ru (0.32 g) at room temperature, and to this mixture 4-methylmorpholine *N*-oxide (NMO, 0.26 g) was added. The mixture was stirred for 24 h at this temperature. The catalyst capsules were filtered and washed with acetone several times and dried at room temperature for 12 h to prepare treated polymer incarcerated ruthenium (0.30 g, 0.310 mmol/g). The washings were concentrated to determine loading of ruthenium metal by fluorescence X-ray analysis.

4.12. A typical procedure for oxidation of sulfides

Thioanisole (120.9 mg, 0.98 mmol), $PhI(OAc)_2$ (708.2 mg, 2.10 mmol) and P_1MI-Ru (0.329 mmol/g, 31.4 mg, 1 mol%) were combined in acetone (10 mL) and water (1.0 mL). The mixture was stirred for 30 min at room temperature. The catalyst was collected by filtration and washed with acetone. The crude mixture was purified by TLC to afford methyl phenyl sulfone[15] (152.2 mg, 0.98 mmol, qunat.). ^{1}H NMR ($CDCl_3$) $\delta=3.05$ (s, 3H),

7.5–8.0 (m, 5H). ^{13}C NMR ($CDCl_3$) δ=44.6, 127.4, 129.5, 131.0, 140.6. No leaching of Ru in the reaction mixture was confirmed by XRF analysis. The collected catalyst was dried and reused (2nd; 87%, 3rd; 97%, 4th; 99%).

4.12.1. Diphenyl sulfone.[15] ^1H NMR ($CDCl_3$) δ= 7.48–7.60 (m, 6H), 7.93–7.97 (m, 3H). ^{13}C NMR ($CDCl_3$) δ=127.6, 129.3, 133.2, 141.5.

4.12.2. 4-Chloro methyl sulfone. ^1H NMR ($CDCl_3$) δ= 3.08 (s, 3H), 7.54–7.57 (m, 2H), 7.89–7.91 (m, 2H). ^{13}C NMR ($CDCl_3$) δ=44.5, 129.0, 129.8, 139.1, 140.4.

4.13. Typical procedure determining yield by GC analysis

Di-*n*-butyl sulfide (142.7 mg, 0.98 mmol), $PhI(OAc)_2$ (708.2 mg, 2.10 mmol) and P_1MI-Ru (0.329 mmol/g, 31.4 mg, 1 mol%) were combined in acetone (10 mL) and water (1.0 mL). The mixture was stirred for 2 h at room temperature. The catalyst was collected by filtration and washed with acetone. Yield was determined by GC analysis with reference to an internal standard (IS=anisole). After determining the yield, the solvents of the filtrate were removed in vacuo, then the volume of the residue was adjusted to 5mL using THF to give a sample for XRF analyses for the measurement of the leaching of the ruthenium.

4.14. Typical procedure for oxidation of alcohols

Benzyl alcohol (54.0 mg, 0.5 mmol), MS 4A (250 mg), NMO (117.0 mg, 1.0 mmol) and P_2MI-Ru preliminarily treated (0.270 mmol/g, 2 mol%) were combined in acetone/hexane=1/1 (3.0 mL). After the mixture was stirred for 2.5 h under an Ar atmosphere at room temperature, the catalyst was collected by filtration and washed with hexane and acetone, then dried and reused. Yield was determined by GC analysis with reference to an internal standard (IS= anisole). After determining the yield, the solvents of the filtrate were removed in vacuo, then the volume of the residue was adjusted to 5 mL using THF to give a sample for XRF analyses for the measurement of the leaching of the ruthenium.

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Polymer-bound diazonium salts for the synthesis of diazoacetic esters

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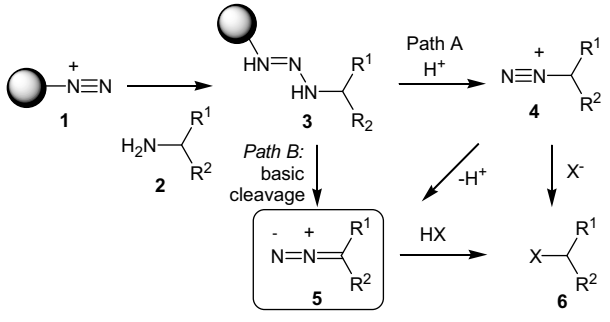
Abstract—Starting from Merrifield resin, various polymer-bound diazonium salts were prepared. Upon treatment with amino acid esters, resulting the appropriate triazenes, the corresponding diazoacetic esters were formed by basic cleavage. Scope and limitation of this transformation were investigated.

1. Introduction

Polymer-bound reagents are versatile tools for the modern high-throughput synthesis of medium- to large-sized compound collections. Although many reagents have been developed in the past,[1] an azo-transfer reagent to transform amines into diazo compounds is not available to our knowledge.[2]

In several reports,[3] we and others[4] demonstrated the use of triazenes **3** as linker moieties in solid-phase organic synthesis to detach amines,[5] guanidines,[6] ureas and amides[7] from solid supports. In addition, we have demonstrated that immobilized primary triazenes derived from an aromatic diazonium ion and primary amines are suitable for the alkylation of acids and for the synthesis of alkyl halides **6** (X=Hal) (Path A, Scheme 1).[8] In a preceding communication, we have described the use of polymer-bound triazenes based on the T2* linker in the synthesis of alkyl sulfonates **6** (X=RSO_3) starting from the corresponding sulfonic acid and in extension from sodium sulfonates.[9] Extension to phosphonates **6** (X=$(RO)_2PO_2$) and phosphinates **6** (X=$RPHO_2$) was also possible (Scheme 1).[10] In a related context, the ability of polymer-bound triazene linkers as alkylating agents was demonstrated in the synthesis of various carboxylic esters starting from the corresponding acids.[11]



Scheme 1. Cleavage of polymer-bound disubstituted triazenes.

In all these cases, the triazene moiety serves as a capped diazoalkane equivalent, delivering the alkyl group upon protonation.[12] Earlier, we proposed[8c] that polymer-bound triazenes might also deliver diazoalkanes upon cleavage, however, this transformation remained elusive (Path B, Scheme 1).

Diazonium ions were synthesized previously on cellulose[13,14] and macroporous supports.[15] They were used for the immobilization of enzymes.[15] Beněs et al. showed,[16] that (*p*-aminophenylsulfonyl)ethyl modified cellulose could be diazotized to give a diazonium salt, which is, according to the authors, unstable. This can be coupled with β-naphthol to the corresponding azo dye. Lipophilic supports are being used in a sequence consisting of diazotation and subsequent reduction for the synthesis of hydrazines.[17] The diazotation of aliphatic amines in the presence of halide ions is a convenient method and has been used for the synthesis of Merrifield-type resins on a Multipin-support™.[18]

We have synthesized diazonium ions with different substitution pattern, determined their thermophysical properties[19] and used them for the synthesis of triazenes.[9,10,20,21]

Keywords: Diazonium salts; Diazoacetic esters; Merrifield resin.
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Rademann et al. used the T2-*para* resin for the synthesis of triazenes,[11] while Struber et al. developed solid-phase bound triazenes based on nitration and further functionalization of polystyrene and investigated their chemical and thermophysical properties.[22]

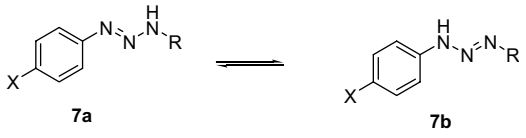
2. Synthesis of α-diazoacetic esters from polymeric diazonium ions

Diazoacetic esters are very reactive building blocks for organic syntheses. They can be used for cyclopropanation reactions,[23] [1,3]-dipolar cycloaddition ('Huisgen reaction')[24] and N–H, O–H and S–H insertion reactions.[25,26] These esters have been synthesized by nitroxylation,[27] alkylation[28] or diazotransfer.[26,29]

To the best of our knowledge, no practical approach for a one-step conversion of amines into diazo compounds has yet been reported. Herein, we present in detail, the development of this methodology and further extensions.

The goal of this project was to prepare α-diazoacetic esters from the corresponding α-aminoacid esters with a polymeric diazonium ion as nitrogen donor. Reaction of an aromatic diazonium ion with a primary amine results in a triazene.[12] First discovered by Baumgarten, the basic cleavage of triazenes derived from glycine being substituted with a *para*-nitroaryl group gave diazoacetic ester and left an amine function at the original diazonium position.[30] It is known that triazenes based on amino acids having a free carboxylic moiety are only relatively stable.[31] Only triazenes of proline and cysteine were reported so far. However, when the carboxylic terminus of these amino acids are esterificated, triazenes derived from the latter are stable to be isolated.

1,3-Substituted triazenes exist in two tautomeric forms[32,33] (allyl isomers) (Scheme 2).



Scheme 2. Tautomerism of triazenes. X = NO_2, OMe, Hal.

In case of electron-withdrawing groups at the aromatic ring (X = NO_2), the dominant form is the one where the double bond is not conjugated with the phenyl ring (b). For the base induced preparation of diazoacetic esters, we used electron-poor triazenes prepared before.[19b] However, basic cleavage of amino acids attached to these resins did not lead to any product with the exception of a nitro substituted resin which gave small amounts of the diazoacetic esters (vide infra). Therefore we synthesized a few new T2* like diazonium-ions having electron-withdrawing groups based on the building blocks **8a–d** (Fig. 1). A series of new polymer-bound resins were designed to take the influence of substituents into account.

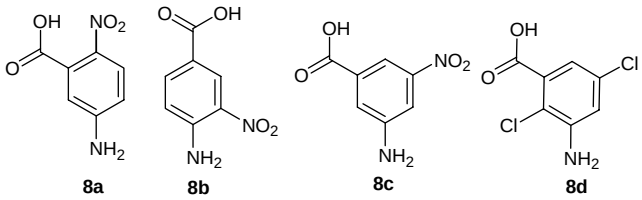
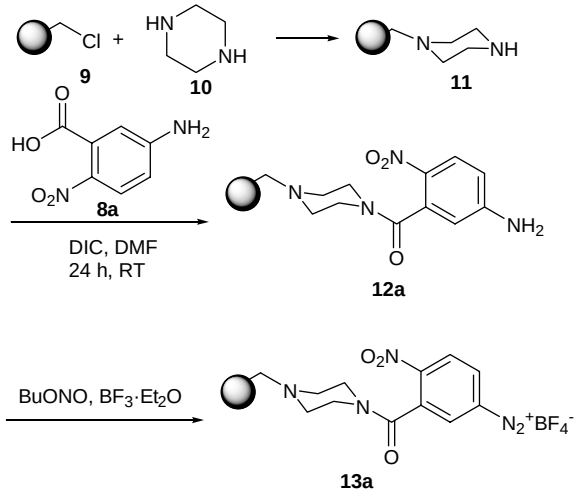


Figure 1. Building blocks for resin synthesis (all commercial available).

Piperazine (**10**) was used as spacer for a better coupling of the anthranilic acids to the Merrifield resin (**9**, approx. 1 mmol/g, 1–2% cross-linked). The former method of coupling benzoic acids or phenols with Cs_2CO_3 or NaH to Merrifield resin,[19b] gave, in the cases of electron-poor anthranilic acids, only low yields. Coupling of the benzoic acids with DIC (without protecting the amino function) to the resin **11**, which is commercially available, resulted in a complete loading of the resin (Scheme 3). The loadings of the resins **12a–d** were determined by CHN analysis.



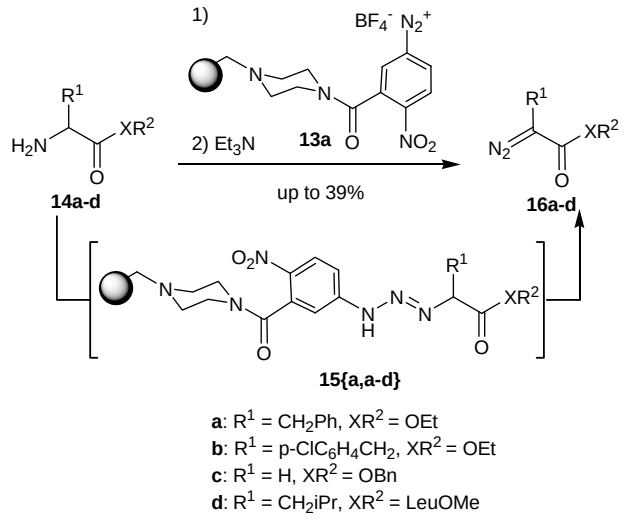
Scheme 3. Preparation and diazotation of the T2*-like piperazine aryl amino resin **12a**.

The subsequent diazotation reaction of these amino resins with *tert*-butyl nitrite (*t*BuONO) and bortrifluoride etherate ($BF_3 \cdot Et_2O$) in THF between 0 and −10 °C led to polymer-bound diazonium ions **13a–d**. In analogy to the electron-poor resins synthesized and characterized before,[19b] they display a high temperature stability and can be stored at room temperature for several days or even weeks.

For the attachment to these resins, amino acid esters were liberated from their hydrochloride salts with KOH in water and extracted with diethylether and added directly to the diazonium resins **13**. After 1 h, an excess of triethylamine was added. Shaking this mixture for 2 h gave a new UV active spot on the TLC. Filtration of the solution, and chromatographically workup of the filtrate gave the desired diazo acetic ester, but only in a very low yield of 5%.

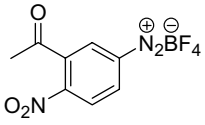
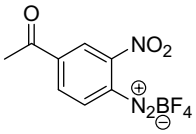
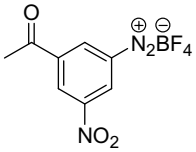
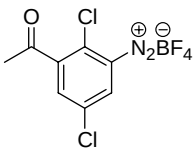
Another method to prepare the triazenes is to liberate the amino acid ester from its hydrochloride with sodium carbonate in a mixture of water/methylene chloride at 0 °C, and addition of the diazonium resin to this mixture. In this case, we could

isolate and analyze the triazene resin. This resin was cleaved with triethylamine in THF and gave the diazoacetic ester **16a** (R^1=Ph, XR^2=OEt), after filtrating the solution over a small amount of silica gel in excellent purities and in an overall yield of 38% based on the loading of the resin. This transformation worked also with substituted phenylalanine ester (R^1=*p*-ClC_6H_4, XR^2=OEt). Remarkably, azotransfer proceeded also well with the dipeptide HLeuLeuOMe (R^1=*i*Pr, XR^2=LeuOMe) and thus gave access to labeled peptides such a **16d** (Scheme 4).



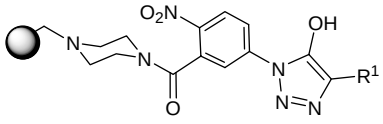
Scheme 4. Synthesis of diazoesters **16**.

Table 1. Yields (regarding the loadings of the amine resins **12a–d**) of the nitrogentransfer from different diazonium resins (**13a–d**) to phenylalanine ethylester

Entry		Yield (%) of 2-diazo-3-phenyl-propionic acid ethyl ester (**16a**)
13a		31
13b		37
13c		0
13d		2.5

The resins **13a–d** were tested on their diazo-transfer-capability (Table 1). Therefore, we used phenylalanine ethylester as the reference reagent. All resins form the desired triazene **15**{**a**,**a–d**}. Only **15**{**c**,**a**} gave no product after cleavage with triethylamine. Resins **15**{**a**,**a**} and **15**{**b**,**a**} gave a good yield of of 2-diazo-3-phenyl-propionic acid ethyl ester (**16a**). This is a nice evidence for our assumption, that the nitrogen transfer happens with electron withdrawing groups regarding the triazene function. Resin **15**{**d**,**a**} gave also the desired α-diazo ester, but in a very low yield (2.5%).

However, extension to glycine ethyl ester failed. Although being attachable to the resin, basic cleavage gave no detectable product. IR-stretches and elemental analysis indicated that a new product is formed on the resin. It appears that a Dimroth cyclization[34] took place to give triazoles **17**,[35,36] which are not detached from the resin under these conditions (Fig. 2). Apparently, a smaller substituent favors cyclization rather than cleavage. On the other hand, the benzyl ester of glycine **14c** does not undergo this cyclization on the resin. After cleavage, it gives the azo-acetic ester benzyl ester **16c** in a good yield. Amides did not undergo this cyclization. Therefore, peptides ought to be substrates of choice.



17

Figure 2. Viable product formed by cyclization prior cleavage.

In conclusion, we synthesized novel and bench-stable electron-poor diazonium salts and used them for the first azo-transfer to amino acids mediated by polymer-bound reagents. Although this transformation is not fully explored, this method should enable the synthesis of labeled amino acids and peptides. Since diazoacetic esters are valuable building blocks for the synthesis of heterocycles[37] and cyclopropanes[38] and can be used in combinatorial chemistry, we are directing efforts in our group toward applications of these important synthons.

3. Experimental

3.1. General

^{1}H NMR: Bruker DP 300 (300 MHz), Bruker DP 400 (400 MHz); δ=2.50 ppm for [D_5] dimethylsulfoxide, 3.31 ppm for [D_3] methanol, 7.24 ppm for $CHCl_3$. Description of signals: s=singlet, bs=broad singlet, d=doublet, t=triplet, q=quartet, m=multiplet, mc=centered multiplet, dd=doublet of doublet, ddd=doublet of dd, dt=doublet of triplets, dq=doublet of quartets, tt=triplet of triplets, ca=complex area. The spectra were analyzed according to first order. All couplings constants are absolute values. Abbreviations for signals: Ar-H=Ar. ^{13}C NMR: Bruker DP 300 (75 MHz), Bruker DP 400

(100 MHz); $\delta = 39.52$ ppm for perdeuterodimethylsulfoxide, 77.20 ppm for deuterochloroform, 49.00 for perdeuteromethanol. The signal structure was analyzed by DEPT and described as follows: + = primary or tertiary C-atom (positive signal), − = secondary C-atom (negative signal),) and q = quaternary C-atom (no signal). IR (infrared-spectroscopy): Perkin Elmer FT-IR 1750. The substances were dissolved in distilled dichloromethane. The resins were measured as KBr pellets on a Bruker IFS88 IR. ps = polystyrene. -MS (mass spectroscopy): EI-HRMS (electronic ionization-high resolution mass spectroscopy): Kratos MS 50 (70 eV) and Thermo Quest Finnigan MAT 95 XL (70 eV). GC (gas chromatography) analytical: Hewlett–Packard HP 5890 Series II 12 m × 0.25 mm capillary column HP I (carrier gas N_2). TLC (Thin layer chromatography): Silica gel coated aluminium plates (Merck, silica gel 60, F_{254}). Detection under UV-light at 254 nm, displayed with molybdato phosphate (5% phosphor molybdic acid in ethanol, dipping solution), and potassium permanganate (0.45 g potassium permanganate and 2.35 g of sodium carbonate in 90 ml of water, dipping solution). Elemental analysis: elementar vario EL at the Mikroanalytisches Labor of the Institute for Organic Chemistry, Universität Karlsruhe (TH). Descriptions without nominated temperature were done at room temperature (rt). Solid materials, except resins, were powdered. All Chemicals, solvents, and reagents were purchased from Acros, Aldrich, Fluka, Janssen, or Merck. The Merrifield resin (1–2% cross-linked, 200–400 mesh) was obtained from Polymer-Laboratories with loading = 1.06 g mol^{-1}. All resins were washed sequentially by using a vacuum reservoir connected to a sintered glass frit. Cleavage was conducted either using Teflon tubes with a frit connected to a vacuum line, with a glass pipette filled with glass wool, or simply paper-filtered. Evaporation of the solvent was achieved using a rota-vapor and/or under a high vacuum (ca. 0.1 mbar). All solvents were dried by conventional methods and distilled under argon. General washing procedure: (methanol, THF, pentane, dichloromethane) three times; (methanol, DMF, pentane, THF) once and (pentane, dichloromethane, pentane) two times.

All resins were characterized by IR spectroscopy, loading and conversions were valued by CHN combustion analysis. Experimental examined loading of the resins can be correlated very well with the results from CHN-combustion analysis.

Typical loadings of the used chloromethylpolystyrene were between 0.6 and 1.4 mmol g^{-1}. All new compounds were characterized completely or compared to known substances.

3.1.1. Procedure for the preparation of piperazine resin 11. In a 250 ml three-necked round bottom flask equipped with a mechanical stirrer, 17.2 g (200 mmol) of piperazine were suspended in 100 ml of DMF and dissolved at 60 °C. Then, 8 ml of triethylamine (60 mmol) and 20 g of Merrifield resin (approx. 1 mmol/g) were added. The mixture was stirred for 48 h at 60 °C. The hot resin was filtered off and washed along the general washing procedure and dried under high vacuum. IR (neat): $\nu = 3340$ [m, ν_s(N–H)], 2802 [s, $\nu(CH_2)$], 2759 (s), 1688 [s, ν(C=O)], 1134 (m), 1009 (m), 808 (m). $C_{80}H_{84}N_2$ (1074 g/mol) calcd C 89.50, H 7.90, N 2.60, found C 88.69, H 7.78, N 3.07; loading: quant.

3.2. General procedure for the attachment of amino benzoic acids with electron withdrawing group to the piperazine resin

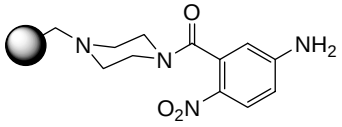
In a 500 ml round bottom flask, 80 mmol of the amino benzoic acid was dissolved in 200 ml of DMF. Then, 20 g (ca. 20 mmol) of the piperazine resin **11** (approx. 1 mmol/g) were added and the mixture was shaken at room temperature. During the shaking, 10.1 g (80 mmol) of DIC were slowly added with a syringe. After 48 h, the resin was filtered off, washed with DMF, THF and methanol, and dried under vacuum.

3.3. General procedure for the preparation of diazoacetic acids

In a 50 ml round bottom flask, 0.138 g (1.3 mmol) of Na_2CO_3 was solved in 3 ml of water. Then, 8 ml of methylene chloride were added and the mixture was cooled in an ice bath. At 0 °C, 2.5 mmol of the amino acid ester were added carefully. After 10 min stirring, the diazonium resin was added and the mixture was shaken for 2 h. Then, the resin was filtered off, and washed with water, methylene chloride and THF, and finally dried under vacuum.

This triazene resin was given into 10 ml of THF and while shaking, 1 ml of triethylamine was added. After 12 h, the resin was filtered off and the filtrate was rotavaporated and the remaining product (yellow oil) was dried under high vacuum.

3.3.1. (3-Amino-6-nitrophenyl)-*N*-carboxypiperazinyl-*N′*-methylpolystyrene (12a).



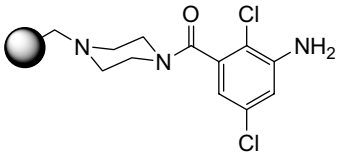
According to the general procedure, the reaction starting from 5.70 g (31.3 mmol) of 2-nitro-5-amino benzoic acid (**8a**), 8.4 g (7.8 mmol) of piperazine resin and 4.0 g (31.7 mmol) of DIC in ca. 100 ml DMF (abs.) at rt for 24 h yields a black/brown resin. IR (neat): $\nu = 3477$ [s, ν_{as}(N–H)], 3341 [s, ν_s(N–H)], 3227 (s), 2801 [m, $\nu(CH_2)$], 2767 (m), 1688 [s, ν(C=O)], 1642 [s, ν_{Ar}(C=C)], 1567 (m), 1526 (m), 1402 [m, δ(C–H)], 1233 [m, ν_s(N=O)], 1133 (m), 996 (m), 857 (m). $C_{87}H_{88}N_4O_3$ (1244 g/mol) calcd C 84.45, H 7.18, N 4.51, found C 83.80, H 7.41, N 4.09; loading: 90%.

3.3.2. (4-Amino-3-nitrophenyl)-*N*-carboxypiperazinyl-*N′*-methylpolystyrene (12b). Similarly, the reaction starting from 2.73 g (15 mmol) of 4-amino-3-nitro benzoic acid (**8b**), 5.00 g (4.66 mmol) piperazine resin and 1.89 g (15 mmol) of DIC in ca. 100 ml DMF (abs.) at rt for 24 h yields a brown resin. IR (KBr): $\nu = 3473$ [s, ν_{as}(N–H)], 3384 (s), 3325 [s, ν_s(N–H)], 3185 (s), 2801 [m, $\nu(CH_2)$], 2766 (m), 1689 [s, ν(C=O)], 1641 [s, ν_{Ar}(C=C)], 1561 (s), 1525

(s), 1408 [m, δ(C–H)], 1229 [m, ν_s(N=O)], 1133 (m), 996 (w), 858 (m). $C_{87}H_{88}N_4O_3$ (1244 g/mol) calcd C 84.45, H 7.18, N 4.51, found C 85.62, H 7.31, N 3.54; loading: 75%.

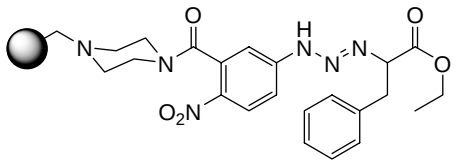
3.3.3. (3-Amino-5-nitrophenyl)-*N*-carboxypiperazinyl-*N′*-methylpolystyrene (12c). Similarly, the reaction starting from 2.73 g (15 mmol) of 3-amino-5-nitro benzoic acid (**8c**), 5.00 g (4.66 mmol) of piperazine resin **11** and 1.89 g (15 mmol) of DIC in ca. 100 ml DMF (abs.) at rt for 24 h yields a green resin. IR (neat): ν=3474 [s, ν_{as}(N–H)], 3350 [s, ν_s(N–H)], 3233 (s), 2802 [m, ν(CH_2)], 2767 (m), 1688 [s, ν(C=O)], 1640 [s, ν_{Ar}(C=C)], 1530 (s), 1399 [m, δ(C–H)], 1229 [m, ν_s(N=O)], 1135 (m), 996 (m), 857 (m). $C_{87}H_{88}N_4O_3$ (1244 g/mol) calcd C 84.45, H 7.18, N 4.51, found C 86.04, H 7.22, N 3.30; loading: 70%.

3.3.4. (3-Amino-2,5-dichlorophenyl)-*N*-carboxypiperazinyl-*N′*-methylpolystyrene (12d).



Similarly, the reaction starting from 3.09 g (15 mmol) 3-amino-2,5-dichloro benzoic acid (**8d**), 5.00 g (4.66 mmol) of piperazine resin **11** and 1.89 g (15 mmol) DIC in ca. 100 ml DMF (abs.) at rt for 24 h yields a light beige resin. IR(neat): ν=3483 [s, ν_{as}(N–H)], 3346 [s, ν_s(N–H)], 3221 (s), 2803 [m, ν(CH_2)], 2767 (m), 1688 [s, ν(C=O)], 1641 [s, ν_{Ar}(C=C)], 1567 (m), 1470 (w), 1399 [m, δ(C–H)], 1133 (m), 997 (m), 855 (m), $C_{87}H_{87}N_3OCl_2$ (1262 g/mol) calcd C 82.86, H 6.97, N 3.32, found C 84.73, H 6.84, N 2.57; loading: 74%.

3.3.5. Resin 15{a,a}.

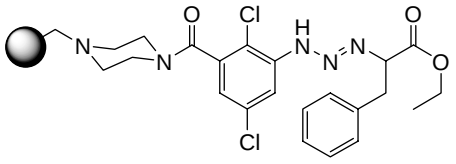


Similarly, the reaction starting from 0.50 g of amino resin **12a** (0.36 mmol), 0.40 ml (3.0 mmol) of $BF_3\cdot OEt_2$ and 0.40 ml (3.2 mmol) of *tert*-BuONO in 10 ml of THF at rt for 1.5 h yields a brown diazonium resin **13a**. To an ice-cooled mixture of 0.138 g (1.3 mmol) of Na_2CO_3 dissolved in 3 ml of water and 8 ml of methylene chloride, were slowly added 0.575 g (2.5 mmol) of phenylalanine ethylester hydrochloride, and stirred for 10 min. Then, at 0 °C the diazonium resin **13a** was added and shaken for 2 h. The resulting triazene resin was filtered off and washed with water, CH_2Cl_2, THF. IR (neat): ν=3316 [s, ν_{as}(N–H)], 2985 (w), 2802 [s, ν(CH_2)], 2767 (s), 1737 [s, ν(C=O)], 1688 s, ν(C=O)], 1642 [s, ν_{Ar}(C=C)], 1568 (m), 1528 (m), 1404 [m, δ(C–H)], 1231 [s, ν_s(N=O)], 1133 (m), 996 (m), 858 (m). $C_{98}H_{100}N_6O_5$ (1442 g/mol): calcd C 81.66, H 7.01, N 5.81, found C 80.97, H 7.10, N 4.76;

3.3.6. Resin 15{b,a}. Similarly, the reaction starting from 0.50 g of amino resin **12b** (0.30 mmol), 0.4 ml (3.0 mmol) of $BF_3\cdot OEt_2$ and 0.40 ml (3.2 mmol) of *tert*-BuONO in 10 ml of THF at rt for 1.5 h yields the brown diazonium resin. To an ice-cooled mixture of 0.138 g (1.3 mmol) of Na_2CO_3 dissolved in 3 ml of water and 8 ml of methylene chloride, were slowly added 0.575 g (2.5 mmol) of phenylalanine ethylester hydrochloride, and stirred for 10 min. Then, at 0 °C the diazonium resin **13b** was added and shaken for 2 h. The resulting triazene resin was filtered off and washed with water, CH_2Cl_2, THF. IR (neat): ν= 3322 [s, ν_{as}(N–H)], 2985 (w), 2802 [s, ν(CH_2)], 2766 (s), 1738 [s, ν(C=O)], 1688 s, ν(C=O)], 1643 [s, ν_{Ar}(C=C)], 1566 (m), 1530 (m), 1406 [m, δ(C–H)], 1222 [s, ν_s(N=O)], 1132 (m), 997 (w), 859 (w). $C_{98}H_{100}N_6O_5$ (1442 g/mol): calcd C 81.66, H 7.01, N 5.81, found C 83.95, H 7.53, N 3.88;

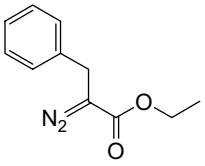
3.3.7. Resin 15c. Similarly, the reaction starting from 0.50 g of amino resin **12c**, 0.40 ml (3.0 mmol) of $BF_3\cdot OEt_2$ and 0.4 ml (3.2 mmol) of *tert*-BuONO in 10 ml THF at rt for 1.5 h yields the yellow diazonium resin. To an ice-cooled mixture of 0.138 g (1.3 mmol) of Na_2CO_3 dissolved in 3 ml of water and 8 ml of methylene chloride, were slowly added 0.575 g (2.5 mmol) of phenylalanine ethylester hydrochloride, and stirred for 10 min. Then, at 0 °C the diazonium resin **13c** was added and shaken for 2 h. The resulting triazene resin was filtered off and washed with water, CH_2Cl_2, THF. IR (neat): ν=3257 [s, ν_{as}(N–H)], 2985 (w), 2802 [s, ν(CH_2)], 2766 (s), 1749 [s, ν(C=O)], 1689 s, ν(C=O)], 1644 [s, ν_{Ar}(C=C)], 1562 (m), 1530 (m), 1407 [m, δ(C–H)], 1225 [s, ν_s(N=O)], 1134 (m), 996 (w), 859 (w). $C_{98}H_{100}N_6O_5$ (1442 g/mol): calcd C 81.66, H 7.01, N 5.81, found C 83.07, H 7.38, N 3.94;

3.3.8. Resin 15{d,a}.



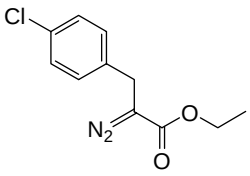
Similarly, the reaction starting from 0.50 g (0.29 mmol) of amino resin **12b**, 0.40 ml (3.0 mmol) of $BF_3\cdot OEt_2$ and 0.40 ml (3.2 mmol) of *tert*-BuONO in 10 ml THF at rt for 1.5 h yields the yellow diazonium resin. To an ice-cooled mixture of 0.138 g (1.3 mmol) of Na_2CO_3 dissolved in 3 ml of water and 8 ml of methylene chloride, were slowly added 0.575 g (2.5 mmol) of phenylalanine ethylester hydrochloride, and stirred for 10 min. Then, at 0 °C the diazonium resin **13d** was added and shaken for 2 h. The resulting triazene resin was filtered off and washed with water, CH_2Cl_2, THF. IR (neat): ν=3261 [s, ν_{as}(N–H)], 2985 (w), 2802 [s, ν(CH_2)], 2767 (s), 1738 [s, ν(C=O)], 1689 s, ν(C=O)], 1642 [s, ν_{Ar}(C=C)], 1562 (m), 1523 (m), 1404 [m, δ(C–H)], 1226, 1133 (m), 996 (w), 864 (m). $C_{98}H_{99}N_5O_3Cl_2$ (1466 g/mol): calcd C80.34, H 6.82, N 4.76, found C 82.82, H 7.39, N 3.25;

3.3.9. 2-Diazo-3-phenyl-propionic acid ethyl ester (16a).



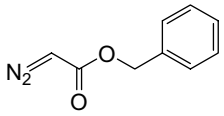
The triazene resin **15**{**a**-**d**,**a**} was added into 10 ml of THF and 0.5 ml of triethylamine was also added. The mixture was shaken for 4 h. The resin was filtered off and the filtrate was liberated from the solvent by rotavaporation and yielded 22.3 mg (0.11 mmol, 31%) of 2-diazo-3-phenyl-propionic acid ethyl ester; ^{1}H NMR (250 MHz, $CDCl_3$) δ= 7.15–7.32 (m, 5 H), 4.18 (q, 2 H, J=7.15 Hz), 3.56 (s, 2 H), 1.19 (t, 3 H, J=7.15 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ= 167.0, 136.3, 128.4, 127.8, 127.3, 126.1, 60.0, 28.3, 13.5 ppm; EI-MS *m*/*z* (relative intensity): 204.1 (15), 176 (14), 148 (17), 103 (100), 91 (89); HRMS (*m*/*z*) calculated for $C_{11}H_{12}N_2O_2$ 204.089878 found 204.0896.

3.3.10. 3-(4-Chloro-phenyl)-2-diazo-propionic acid ethyl ester (16b).



Similarly, the modificated triazene resin **15**{**a**,**b**} was added into 10 ml of THF and 0.5 ml of triethylamine was also added. This mixture was shaken for 12 h. The resin was filtered off and the filtrate was liberated from the solvent by rotavaporation and yielded 12.7 mg of 3-(4-chloro-phenyl)-2-diazo-propionic acid ethyl ester (15%); ^{1}H NMR (250 MHz, CDC_{l3}) δ=7.09–7.24 (m, 4 H), 4.16 (q, 2 H, J=7.15 Hz), 3.53 (s, 2 H), 1.21 (t, 3 H, J=7.15 Hz); ^{13}C NMR (100 MHz, CDC_{l3}) δ=167.0, 135.9, 132.4, 130.7, 128.9, 61.0, 28.9, 14.5 ppm.

3.3.11. 2-Diazo-acetic acid benzyl ester (16c).



Similarly, the modificated triazene resin **15a**″ (instead of the phenylglycine ethyl ester, there is a glycine benzyl ester bound as a triazene) was added into 10 ml of THF and 0.5 ml of triethylamine was also added. This mixture was shaken for 12 h. The resin was filtered off and the filtrate was liberated from the solvent by rotavaporation and yielded 25 mg of 2-diazo-acetic acid benzyl ester (39%); ^{1}H NMR (250 MHz, CDC_{l3}) δ=7.21–7.35 (m, 5 H), 5.12 (s, 2 H), 4.72 (s, 1 H); ^{13}C NMR (100 MHz, C_6D_6) δ=166.0, 142.0, 136.6, 127.4, 127.0, 66.3 ppm; 16d.

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