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Liquid-phase chemistry: recent advances in soluble polymer-supported catalysts, reagents and synthesis

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Chemistry on soluble polymer-matrices, termed liquid-phase organic synthesis, is emerging as a viable alternative or adjunct to the classical solid-phase approach across the broad spectrum of polymer-supported organic chemistry. This review details the significant advances in liquid-phase synthetic methodologies, reagents, catalysts and supports that have appeared from 1997 to the present.

Introduction

Cross-linked polymer supports are now ubiquitous throughout the fields of combinatorial chemistry, organic synthesis and catalysis.[1,2] However, emerging problems associated with the heterogeneous nature of the ensuing chemistry and with 'on-bead' spectroscopic characterisation[3] has meant that soluble polymers are being developed as alternative matrices for combinatorial library production[4] and organic synthesis.[5,6] Synthetic approaches that utilise soluble polymers, termed 'liquid-phase' chemistry, couple the advantages of homogeneous solution chemistry (high reactivity, lack of diffusion phenomena and ease of analysis) with those of solid phase methods (use of excess reagents and easy isolation and purification of products). Separation of the functionalized matrix is achieved by either solvent or heat precipitation, membrane filtration or size-exclusion chromatography.

Poly(alkene oxide)s such as poly(ethylene glycol) (PEG) are amongst the most studied soluble polymers for organic synthesis,[7,8] with polyethylene oligomers[9] and poly(styrene)s[10,11] also receiving considerable attention. The wide applicability of PEG is directly linked to its broad solubility profile: soluble in DMF, dichloromethane, toluene, acetonitrile, water and methanol, but insoluble in diethyl ether, *tert*-butyl methyl ether, isopropyl alcohol[12] and cold ethanol.

In liquid-phase chemistry, where a soluble polymer is being iteratively derivatized either terminally or on side-chain residues, a balance has to be reached between loading capacity (substitution per gram of polymer) and the solubility profile of the resulting polymer derivative. As the molecular weight of the matrix is lowered, the end-groups have a proportionally greater effect on the physical properties of the polymer derivative, which can result in non-quantitative precipitation and low polymer recoveries. PEG of molecular weight 3000 to 5000 is typically utilised in liquid-phase strategies. The polymer chains can be terminated with either two hydroxy groups (dihydroxy-PEG) or with one hydroxy group and one methyl ether (monomethoxy-PEG). Lower molecular weight PEG matrices give a correspondingly higher loading per gram of support and if dihydroxy-terminated PEG is chosen the loading is double that of a monomethoxy-PEG of the same molecular weight. Throughout this review *vide infra*, the balance of loading and polymer recovery is discussed with optimal conditions being described for a number of cases.

Soluble polymer-supported synthesis

Targeted synthesis

The utility of combinatorial chemistry within drug discovery is ultimately linked to the ability to rapidly construct complex molecules on polymer supports. With this in mind, a polymer-supported approach to the prostaglandin core was seen as an important benchmark in the progress of this chemistry. Chen and Janda have successfully utilised Noyori's[13] three component coupling strategy, in a 'liquid-phase' format, for the synthesis of PGE_2 methyl ester[10] **1a** and $PGF_{2\alpha}$[11] **1b** (Scheme 1).

The synthetic strategy hinged upon the choice of a soluble polymer support that could withstand extreme reaction and workup conditions. While PEG is ostensibly the polymer of choice for most facets of liquid-phase chemistry, its use in this case was contraindicated for two reasons: insolubility in THF at low temperatures and its solubility in water which precluded aqueous extraction/removal of organometallic byproducts. A non-crosslinked copolymer of styrene and chloromethylstyrene (3 mol%), previously used for peptide synthesis,[14] was prepared (0.3 mmol g^{-1} loading) and incorporated as the polymer matrix. This copolymer is soluble in THF, dichloromethane and ethyl acetate even at low temperatures, but is insoluble in methanol and water so that purification can involve both aqueous extraction and precipitation techniques.

The synthetic approach to PGE_2 methyl ester **1a** involved an initial attachment of the cyclopentanoid alcohol **2** to the soluble co-polymer *via* Ellman's tetrahydropyran linker.[15] The vinyl-

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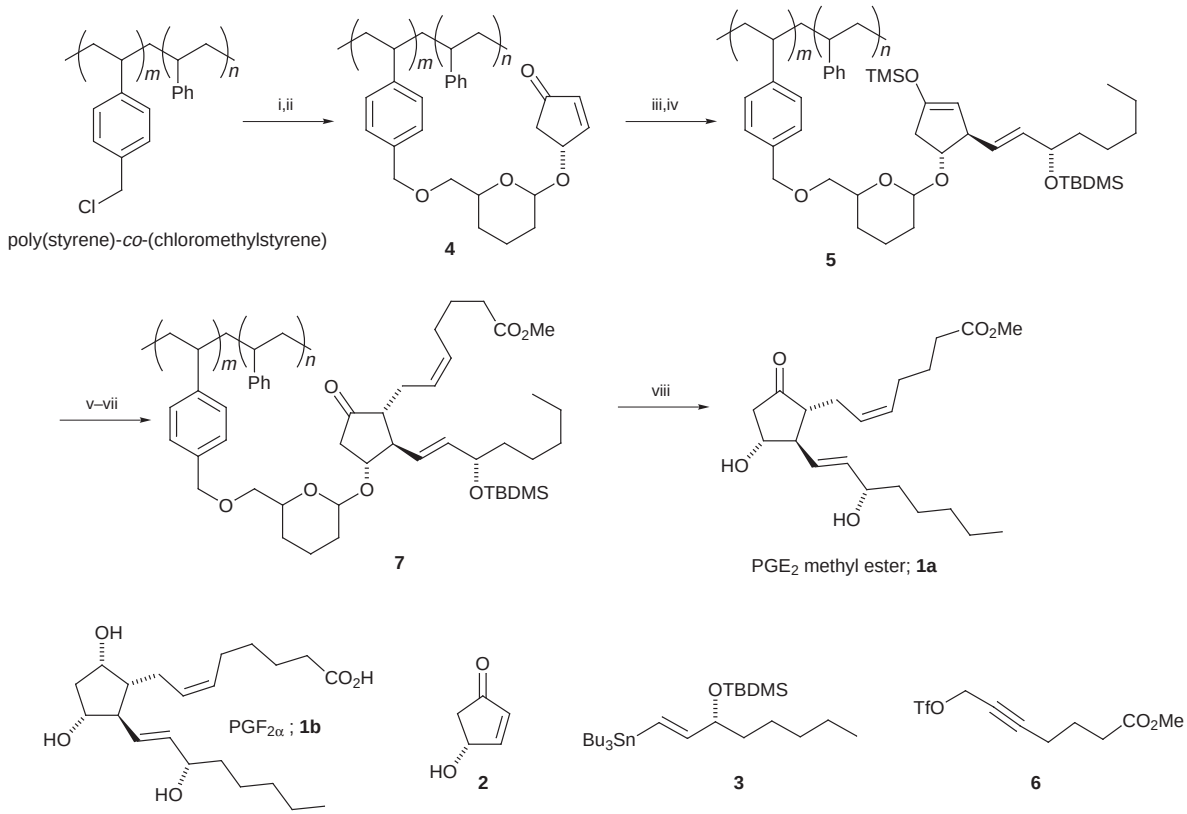


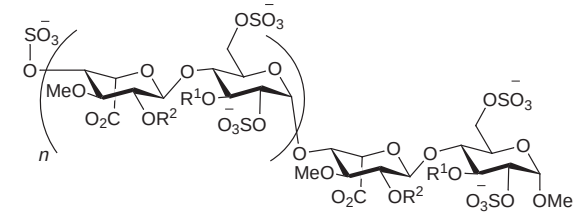
Scheme 1 *Reagents and conditions*: i, 6-(hydroxymethyl)-3,4-dihydro-2*H*-pyran (3 equiv.), NaH (3.3 equiv.), DMA, room temp., 24 h; ii, **2** (3.0 equiv.), PPTS (0.5 equiv.), CH_2Cl_2, 40 °C, 16 h; iii, **3** (4.2 equiv.), $Li_2CuCNMe_2$ (3.9 equiv.), THF, −78 °C, 15 min; iv, TMSCl (15 equiv.), −78 °C, 30 min; Et_3N (30 equiv.), 0 °C, 15 min; v, MeLi (3 equiv.), THF, −23 °C, 30 min; vi, **6** (6 equiv.), −78 °C, 10 min, then −23 °C, 30 min; vii, H_2, 5% Pd–$BaSO_4$, quinoline, benzene–cyclohexane (1 : 1), room temp., 48 h; viii, 48% aq. HF–THF (3 : 20, v/v), 45 °C, 6 h.

stannane ω-chain **3** was then added to **4** in the presence of $Li_2CuCNMe_2$ in THF at −78 °C. Following reaction of the intermediary enolate with TMSCl, the stable polymer-bound silyl enol ether **5** was isolated. The α-chain was then incorporated, as its respective triflate **6**, by trapping of the intermediate enolate formed following addition of MeLi to **5** in THF (−23 °C). Following partial reduction of the α-chain alkyne, the polymer-bound *Z* alkene **7** was cleaved from the support, with accompanying deprotection of the silyl ether protecting group to give **1a** in an overall yield of 37% for the eight step route. The main features to note are that the polymer recovery mass balance was > 97% and only one polymer-bound species was detected by routine NMR analysis, for each step of the synthesis.

Versatile and practical methodology for the construction of oligosaccharides of high structural complexity and in a combinatorial fashion is of tremendous interest. Solid-phase synthesis of oligosaccharides has improved dramatically over the past several years but can still suffer from problems such as decreased glycosylation rates, incomplete coupling and lowered stereoselectivities.[16] Building on an initial report by Krepinsky,[17] Dreef-Tromp and co-workers[18] utilised monomethoxy-PEG as a soluble polymer-support for their synthetic approach to heparan sulfate-like oligomers **8a**–**g**.

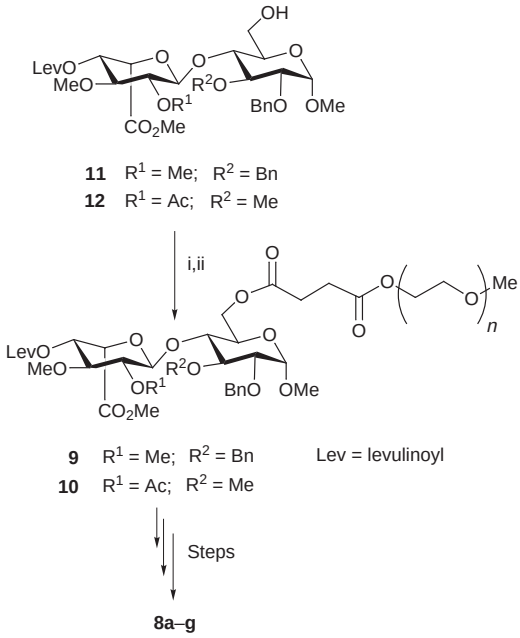
The PEG-supported acceptors **9** and **10** were prepared by an initial esterification of the free primary hydroxy group of the dissacharides **11** and **12** with succinic anhydride, followed by attachment to monomethoxy-PEG *via* esterification of the terminal carboxy group (Scheme 2). Subsequent glycosylations of the PEG-supported iduronic acids **9** and **10** were performed in an iterative three step cycle involving deprotection of the levulinoyl group, TMSOTf assisted coupling with disaccharide glycosyl donors as their respective trichloroacetimidates, and capping of the unreacted 4-hydroxy groups.

Optimisation studies led to excellent coupling efficiencies (> 95%) being achieved and the anomeric control (complete α-substitution) was comparable to that observed with the classical solution-phase approach. The PEG polymer support facilitated the synthetic strategy by allowing an excess of reagents to be used while ensuring that intermediates along the route could be purified by simple precipitation with high polymer recovery (> 95%). Furthermore, the extent of glycosylation could be followed routinely by ^{1}H NMR of the PEG-bound derivatives.



8a *n* = 2; $R^1 = SO_3^-$; R^2 = Me
8b *n* = 4; $R^1 = SO_3^-$; R^2 = Me
8c *n* = 5; $R^1 = SO_3^-$; R^2 = Me
8d *n* = 2; R^1 = Me; $R^2 = SO_3^-$
8e *n* = 3; R^1 = Me; $R^2 = SO_3^-$
8f *n* = 4; R^1 = Me; $R^2 = SO_3^-$
8g *n* = 5; R^1 = Me; $R^2 = SO_3^-$

Enzyme-assisted strategies for the synthesis of oligosaccharides is recognised as a promising alternative to chemical synthesis because of high regio- and stereo-selective reactions without the need for protecting groups. An efficient methodology for the construction of carbohydrates, including oligosaccharide and sphingoglycolipids, has been developed by Nishimura and Yamada.[19,20] They synthesised a vinylic oligosaccharide monomer **13** which, when treated with acrylamide under radical polymerisation conditions, formed a water-soluble copolymer **14** (Scheme 3). This water-soluble conjugate (**14**), was then used as a primer for a regioselective sialylation reaction catalysed by rat liver βGal1→3/4GlcNAc α-2,3-sialyltransferase, in the presence of CMP-NeuAc,[21] to generate the soluble polymer-supported trisaccharide **15** in quantitative yield.

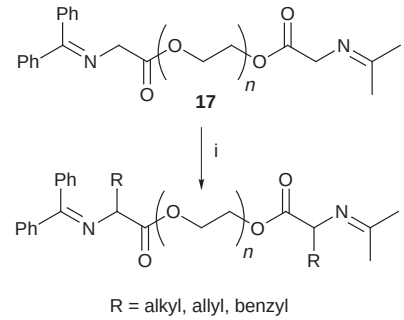


Scheme 2 *Reagents and conditions*: i, succinic anhydride, DMAP, pyridine; ii, MeO-PEG-OH, 1-(3-dimethyaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC), DMAP, CH_2Cl_2.

Purification of **15** from the enzyme and excess sugar building block by gel-filtration chromatography was facilitated by the presence of the poly(acrylamide) support. Subsequent treatment of **15** with leech ceramide glycanase in the presence of an excess of ceramide as an acceptor generated the transglycosidated product GM3 (**16**) in 61% yield. Thus this polymer-supported enzyme approach afforded the glycolipid GM3 in 56% yield from the readily available precursor/monomer **13**, a remarkable improvement in both the ease of synthesis and overall yield when compared to that of chemical synthesis.[22]

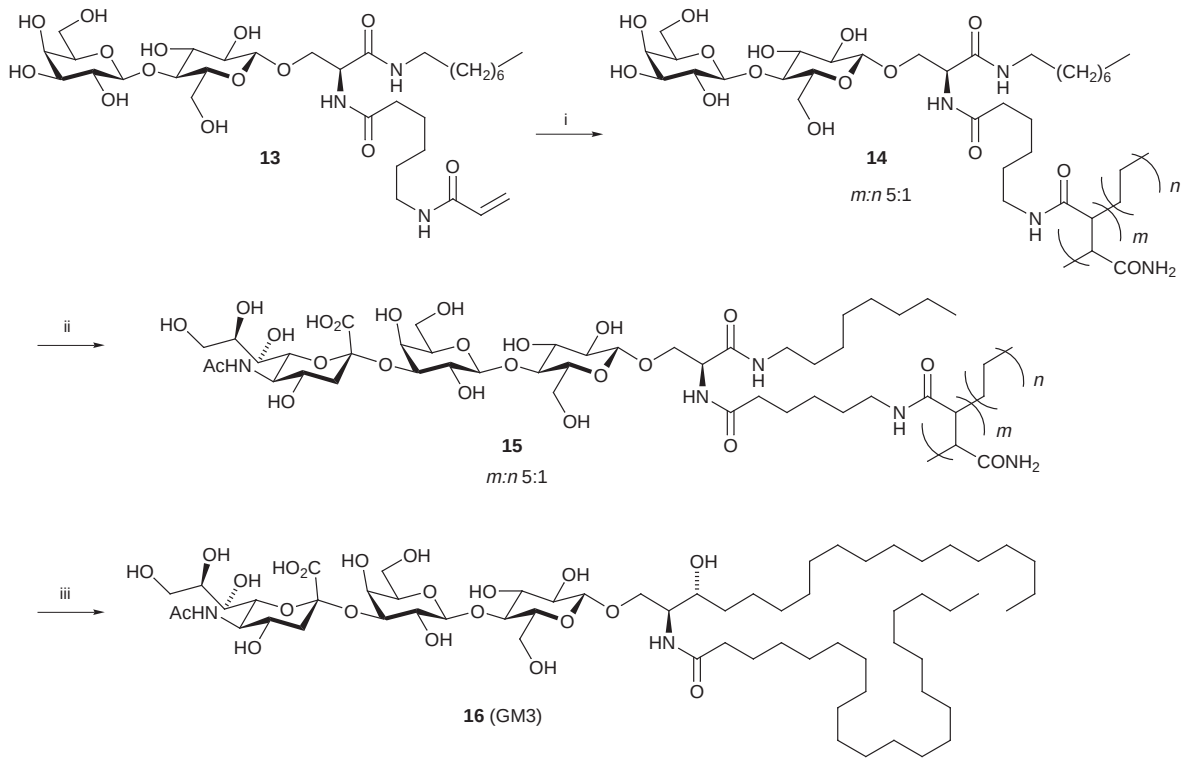
Synthetic methodology

C–C Bond formation. In addition to the extended synthetic strategies *vide supra*, exploration into chemical methodology on soluble supports continues to make significant advances. The development of efficient methods of forming carbon–carbon bonds is an important objective for any polymer-supported methodology. The reactions of stabilised carbanions with carbon centred electrophiles is one of the most common approaches in this area and Lamaty and co-workers[23] have exploited this methodology on PEG. Alkylation of the imine **17** was achieved with a range of electrophiles (RX) with K_2CO_3 as a base (Scheme 4). In the solution phase, a quaternary



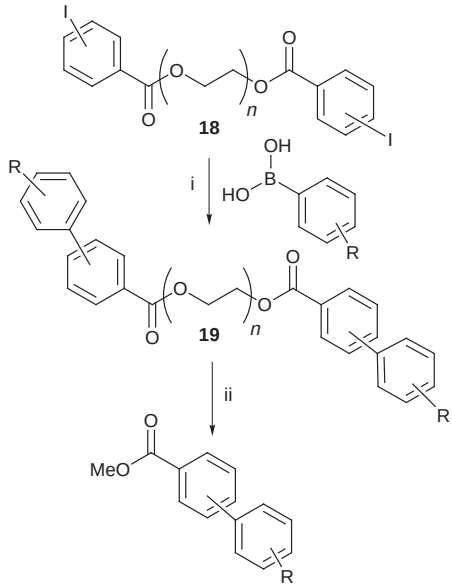
Scheme 4 *Reagents and conditions*: i, RX (2 equiv.), K_2CO_3 (4 equiv.), MeCN, reflux, 14 h (54–75%).

ammonium salt is required as a phase-transfer catalyst (PTC) to ensure complete alkylation. Interestingly the PEG support acted as a sufficiently powerful PTC under the conditions of the reaction that no ammonium salt was required. Dihydroxy-PEG_{2000} was utilised as the matrix of choice in this system which resulted in high loading capacities (1.0 mmol g^{-1}). However the authors note that the precipitation and recovery of the matrix after each reaction step was difficult and sometimes low yielding.



Scheme 3 *Reagents and conditions*: i, acrylamide (4.0 equiv.), *N,N,N'N'*- TMEDA (0.4 equiv.), ammonium peroxodisulfate (APS), 50 °C, 2 d (92%); ii, CMP-NeuAc (1.2 equiv.), α-2,3-sialyltransferase (0.3 unit), bovine serum albumin, $MnCl_2$, calf intestinal alkaline phosphate (20 unit), sodium cacodylate buffer (50 mM, pH 7.49), 37 °C, 3 d (> 99%); iii, ceramide (4 85 equiv.), ceramide glycanase (0.01 unit), Triton CF-54 (1 drop), sodium citrate buffer (50 mM, pH 6.0), 37 °C, 17 h (61%).

The biaryl subunit is an important pharmacophore in a variety of biologically active compounds. Blettner and co-workers[24] utilised the first example of a Suzuki cross-coupling reaction on PEG, in a parallel array format, to generate libraries of substituted biaryls (Scheme 5). They studied a range of



Scheme 5 *Reagents and conditions*: i, arylboronic acid (2 equiv.), $Pd(PPh_3)_4$ (0.05 equiv.), aq. Ma_2CO_3 (2 M; 2.5 equiv.), DMF, 110 °C, sealed tube, 10 h; ii, Et_3N–MeOH (1 : 4), 85 °C, sealed tube, 2 d.

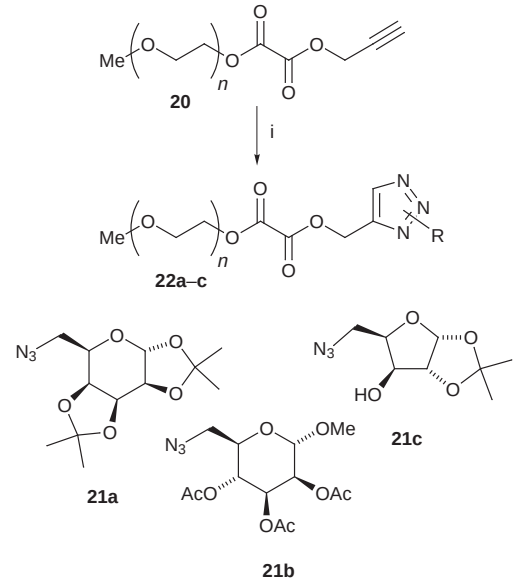
molecular weight PEGs and found that dihydroxy PEG_{6000} (0.33 mmol g^{-1}) and monomethoxy PEG_{5000} (0.2 mmol g^{-1}) supported aryl iodides **18** and biaryls **19** could be purified by precipitation, but that dihydroxy PEG_{4000} (0.5 mmol g^{-1}) derivatives had to be purified by parallel flash column filtration. Polymer recovery by precipitation ranged from 90–98%, whereas due to the polydispersity of PEG, recovery by column filtration was only variable (52–74 %).

Heterocycle formation. There is considerable precedence describing solution-phase dipolar cycloaddition reactions with alkenes and alkynes for the synthesis of aromatic and non-aromatic five-membered ring heterocycles.[25] Several examples of solid-phase cycloaddition reactions have also been reported.[26] Recently, the first example of a liquid-phase 1,3-dipolar cycloaddition reaction was reported (Scheme 6).[27]

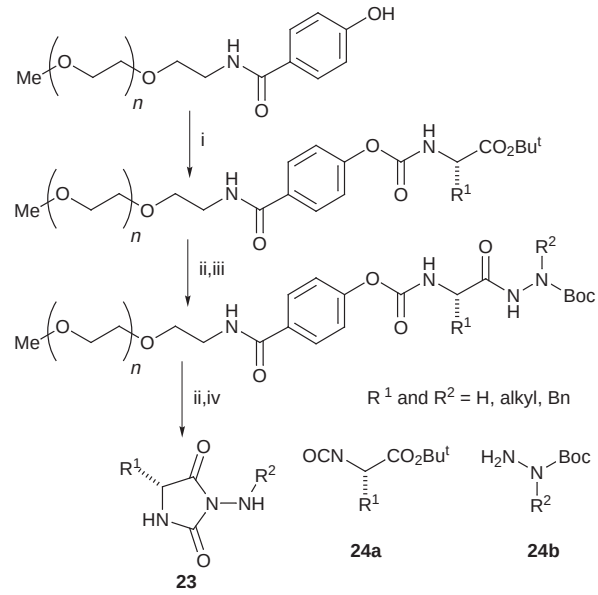
The PEG-supported alkyne **20** underwent smooth cycloaddition with a range of carbohydrate-derived primary azides **21a**–**c** to generate the regioisomeric, polymer-bound triazoles **22a**–**c** in good yields (73–86%).

The search for novel scaffolds on which molecular diversity can be constructed is an ongoing challenge throughout the field of combinatorial chemistry.[28] Janda and co-workers have synthesised a 3-aminoimidazoline-2,4-dione library[29] **23** on a monomethoxy-PEG_{5000} support (Scheme 7). The aminoimidazolinedione core is a rigid five-membered ring heterocycle with two points of diversification. The first diversity element R^1 was introduced as an amino acid isocyanate **24a**, the second as a Boc-aza-amino acid **24b**. The last step in the route involved a smooth cyclization–cleavage reaction, with maintenance of the stereochemical integrity of C-5, which furnished the scaffold **23** free in solution.

Pyrazolidine-3,5-diones **25a** are a class of heterocyclic compounds with four potential sites for diversification (Scheme 8). They are used for the treatment of arthritis but gastric irritation can limit their therapeutic application.[30] Therefore analogues are being sought that maintain the therapeutic profile but possess reduced side-effects. Janda and co-workers[12] have developed a liquid-phase approach to the synthesis of the



Scheme 6 *Reagents and conditions*: i, RN_3 (**21a**–**c**) (2 equiv.), toluene, reflux, 12 h.



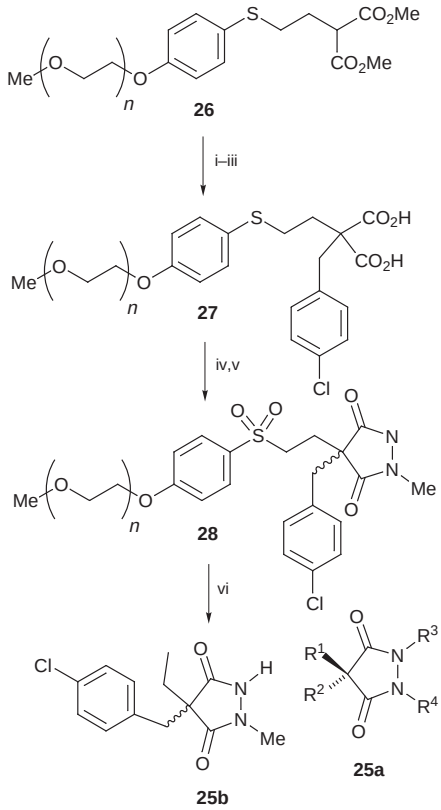
Scheme 7 *Reagents and conditions*: i, **24a**, Et_3N; ii, TFA, CH_2Cl_2; iii, **24b**, DCC; iv, dilution, Pr^i_2NEt (1.1 equiv.).

pyrazolidine-3,5-dione **25b** which involves an initial preparation of malonate **26** which is attached to PEG *via* Janda's ethyl phenyl sulfide traceless linker.[31,32] The malonate **26** was alkylated and de-esterified under standard conditions to give the polymer-supported diacid **27**. Ring closure to form the heterocyclic core was followed by oxidation of the sulfide linker and cleavage of sulfone **28** with Na–Hg amalgam to give *rac*-**25b** in excellent overall yield (61% for six steps).

Soluble polymer-supported reagents and catalysts

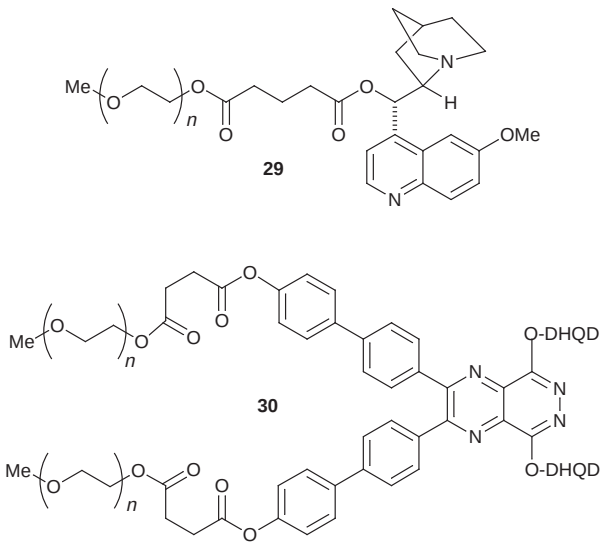
Combinatorial library construction has to date occurred almost exclusively on solid polymer supports. However, to reduce the effort involved in transferring solution-phase chemical methodology onto polymers, a notable shift towards solution-phase chemical library generation is occurring. However, to facilitate rapid library generation and purification, a whole new generation of functional polymer reagents and catalysts are being developed.[33–35]

An important application of soluble polymer-supports has been the use of PEG-supported hydroquinidine cinchona

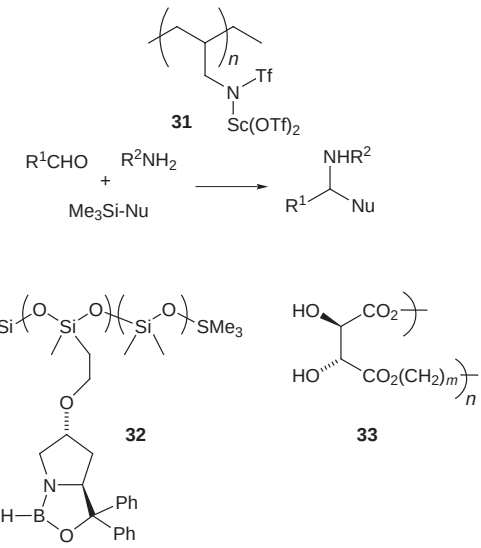


Scheme 8 *Reagents and conditions*: i, 4-chlorobenzyl chloride, Cs_2CO_3, DMF, room temp., 17 h; ii, NaOH, H_2O, room temp., 5 h; iii, Amberlite® IR-120 (plus), room temp., 1 h (94% from **26**); iv, methylhydrazine, benzotriazol-1-yloxytrispyrrolidinophosphonium (PyBOP), Pr^i_2NEt, DMF, room temp., 43 h (98%); v, $KHSO_5$, H_2O, room temp., 3 h (90%); vi, 5% Na–Hg, Na_2HPO_4, MeOH–DMF (1 : 8), room temp., 18 h, (74%).

alkaloid ligands **29** in the Sharpless asymmetric dihydroxylation reaction of olefins.[36,37] Following their seminal reports in this area, Han and Janda[38] have studied the dihydroxylation of *trans*-cinnamic acid on different polymer-supports: Merrifield and Wang resins, Tentagel and PEG. Various reaction parameters were modified: the amount of ligand/metal and reaction time. Under all conditions, the liquid-phase PEG support provided the best results and compared favourably with the dihydroxylation of a solution-bound cinnamic acid derivative. Bolm and Gerlach[39] have further improved the liquid-phase asymmetric dihydroxylation reaction, by utilising cinchona alkaloid–pyridazine–PEG conjugates **30** as ligands. This new strategy led to shortened reaction times, good yields and improved enantioselectivities (up to 99% ee).



A soluble polymer-supported scandium catalyst, poly(allylscandium triflylamide) ditriflate **31** was used for three-component condensation reactions between aldehydes, amines and silylated nucleophiles, to generate β-amino ketones, β-



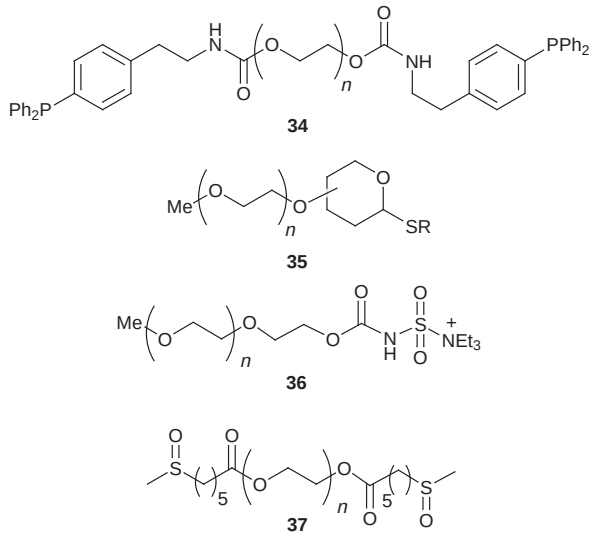
amino esters and α-amino nitriles in excellent yields.[40] The polymer-supported catalyst was recovered by precipitation in hexanes, and could be reused without loss in activity. The scandium catalyst **31** also catalysed aldimine selective reactions in the presence of aldehydes.[41] In the presence of **31**, aldimines reacted almost exclusively with silyl enolates without forming adducts with aldehydes, a common side-reaction using the more conventional $Sc(OTf)_3$ catalyst. The authors attributed this unique chemoselectivity to the stability of the aldimine–polymer–supported catalyst complex.

The recovery and reuse of polymer-supported catalysts is one of the major benefits associated with this strategy, especially when dealing with chiral catalysts which can be tremendously expensive to prepare. The commercially available copolymer of methylhydrosiloxane and dimethylsiloxane was utilised as a soluble support for Corey's chiral oxazaborolidine.[42] The reduction of a family of prochiral ketones was catalysed by polymer-adduct **32** with > 98% ee, comparable to the solution-phase oxazaborolidine counterpart. The polymer-supported catalyst, in contrast to most of the cases discussed *vide supra* is not a solid, and so was removed from the reaction mixture by size-exclusion filtration, rather than by precipitation. The strategy is compatible with automation and could see ultimate application in a continuous flow reactor system.

The linear poly(tartrate ester) **33** has been successfully applied in a liquid-phase variant of the enantioselective Sharpless epoxidation reaction.[43] The active polymer species was prepared by treating L-(+)-tartaric acid with a variety of diols under standard polycondensation conditions. However, the observed enantioselectivity for the epoxidation of *trans*-hex-2-en-1-ol was moderate (up to 79% ee), the solution-phase reaction with L-(+)-dimethyltartrate gave 98% ee showing that there exists some scope for improvement.

A number of examples of liquid-phase reagents have appeared recently. Janda and co-workers[44] synthesised a PEG-functionalized triarylphosphine **34** and showed that it is a more reactive reducing agent in the Staudinger and Mitsunobu etherification reactions than a Merrifield resin-bound counterpart. A number of PEG-matrices were studied and dihydroxy-PEG_{3400} (0.58 mmol g^{-1}) was found to be the lowest molecular weight matrix that consistently afforded excellent polymer phosphine recovery (> 97%) following precipitation from diethyl ether.

A monomethoxy-PEG-supported scialic acid glycosyl donor **35** has been utilised in a liquid-phase glycosylation reaction



with galactose analogues to give α-linked disaccharides.[45] A PEG-supported variant of the Burgess reagent **36** has been developed for application in a soluble polymer-supported approach to the cyclodehydration of β-hydroxyamides and thioamides.[46] Interestingly, the PEG-supported reagent was found to be much more stable than the solution-phase counterpart and had an extended shelf-life. Vederas and co-workers[47] have synthesised a PEG-supported sulfoxide **37** as a recyclable and odourless alternative for the Swern oxidation. The sulfoxide facilitated the oxidation of a range of alcohols in yields comparable to that of DMSO in solution. The reagent was also recyclable as the spent polymer could be smoothly and quantitatively oxidised back to **37** by treatment with sodium metaperiodate.

In a soluble-polymer strategy analogous to resin-capture,[48] Hori and Janda[49] facilitated the purification of a solution-phase library of β-amino alcohols with a monomethoxy-PEG_{5000}-supported dialkyl borane reagent **38** (Fig. 1). Simple addition of

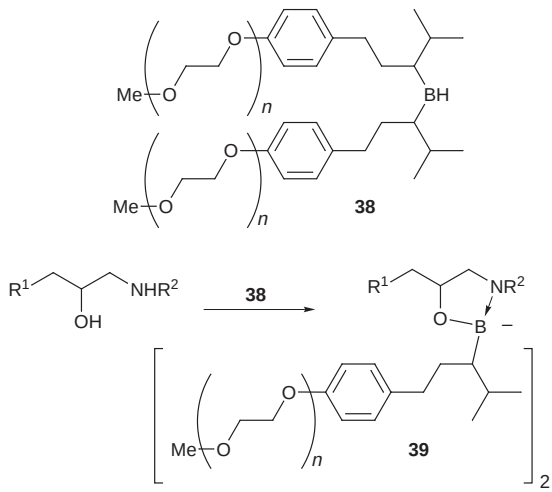


Fig. 1 Liquid-phase 'fishing-out' strategy: PEG-supported dialkylborane **38** facilitates the purification of β-amino alcohols by removal from crude reaction mixtures as polymer-supported 1,2-oxazaborolidines **39**.

38 to a crude reaction mixture containing the required product, followed by precipitation into diethyl ether, gave the polymer-supported 1,3,2-oxazaborolidine **39** from which the amino alcohol was released by acid treatment. By using this 'fishing-out' strategy amino alcohols were isolated greater than 95% pure.

Development of new soluble polymer supports

In comparison with the plethora of supports commercially available for solid-phase synthesis, there is a relative dearth of soluble polymers available to satisfy the increasing demands of liquid-phase chemistry. This reality has lead a number of groups to focus on the development of new supports possessing unique properties within the liquid-phase arena.

By incorporating a sequential normal/living free radical polymerisation strategy with bifunctional initiator **40**[50] and the styryl and vinyl monomers **41a**–**e**, Janda and co-workers[51] have generated linear block copolymer libraries (Fig. 2).

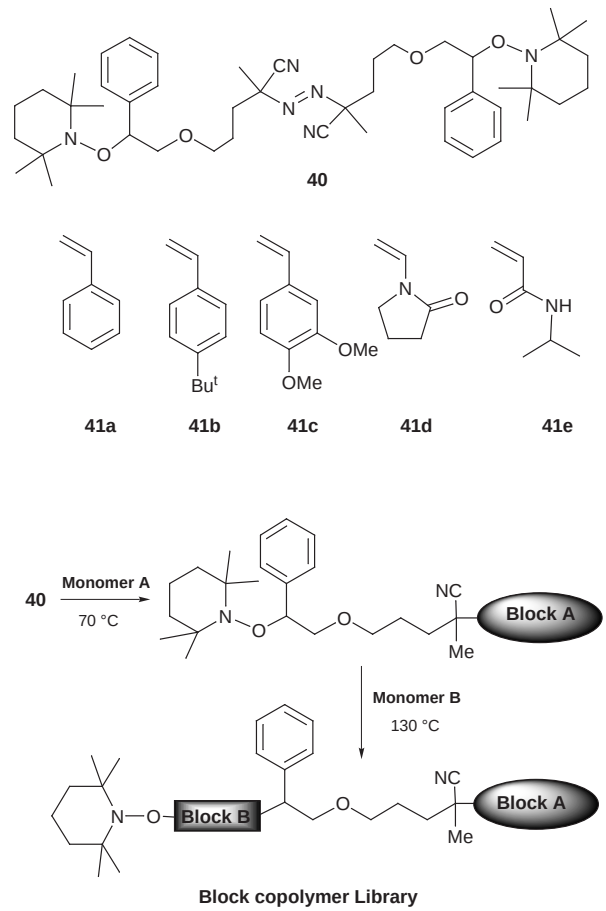
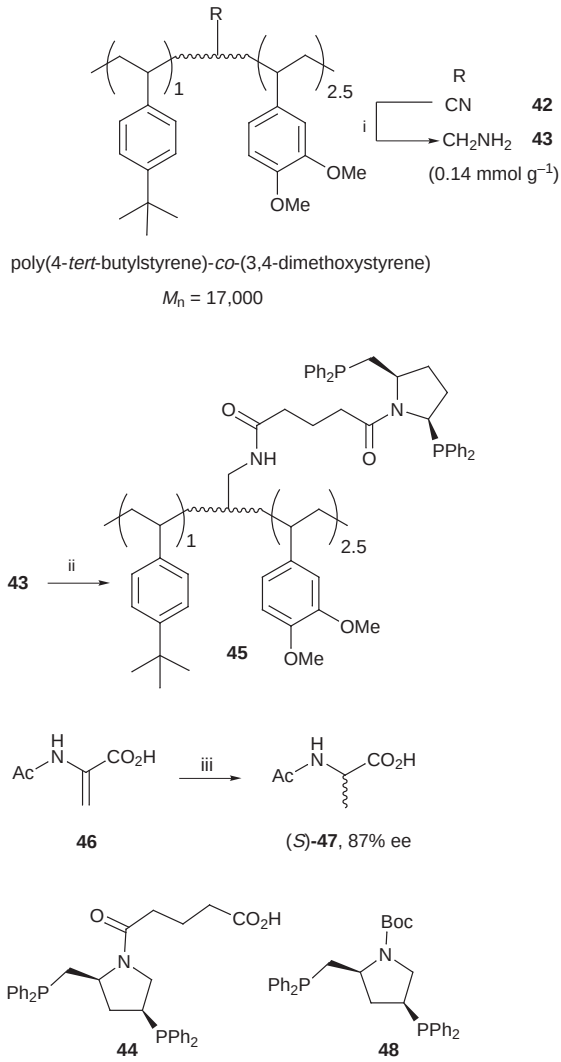


Fig. 2 Bifunctional initiator **40** and monomers **41a**–**e** utilised in a parallel format for block copolymer library generation.

The solubility profile of each library member was then determined in a broad range of organic solvents and water. A copolymer of 4-*tert*-butylstyrene and 3,4-dimethoxystyrene **42** was found to have a solubility profile complementary to that of PEG: soluble in THF and diethyl ether, but insoluble in methanol and water, and was studied as a potential new matrix for liquid-phase chemistry (Scheme 9). The nitrile moieties, located between the two polymer chains, could be smoothly reduced with either $LiAlH_4$ or by catalytic reduction, to generate amino groups as loci for chemical derivatization.

The resulting amino groups of **43** possessed comparable reactivity to that of cyclohexylamine in solution as determined by an imine forming reaction. Derivatization of the amine groups of **43** with a diphosphine ligand **44** gave the polymer-supported chiral diphosphine **45**. The extent of derivatization and oxidation state of the phosphine ligands was routinely monitored by ^1H and ^{31}P NMR spectroscopy. Exchange of $[Rh(cod)Cl]_2$ with the diposphine **45** generated a polymer-supported rhodium(I) species which catalysed the homogeneous enantioselective hydrogenation of dehydroamino acid **46**. The observed ee, stereochemical preference, and kinetics of formation of amino acid **47**, determined by ^1H NMR spectroscopy,



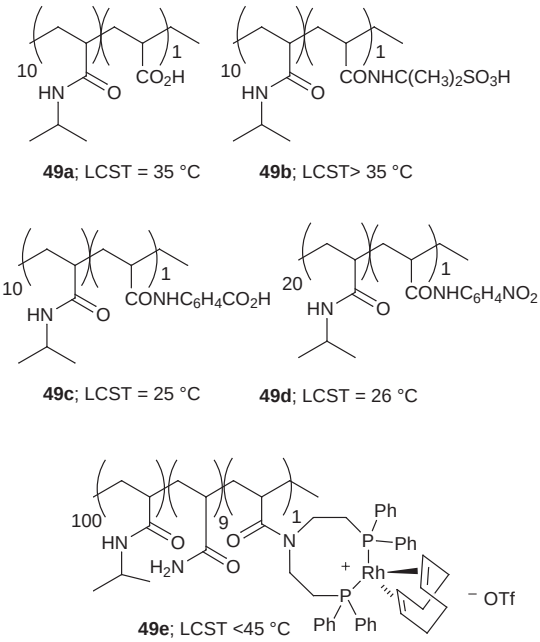
Scheme 9 *Reagents and conditions*: i, $LiAlH_4$ (76 equiv.), THF, reflux, 2 h (quant.); ii, **44** (4 equiv.), DMAP (6 equiv.), EDC (8 equiv.), THF, room temp., 4 h (quant.); iii, **45** (0.04 equiv.), $[Rh(cod)Cl]_2$ (0.02 equiv.), THF, room temp., 4 h, then **46** (1.0 equiv.), H_2 (20 psi), THF, 2 d.

were comparable to that observed with the solution-phase ligand **48**. Isolation of (*S*)-**47** was facilitated in the liquid-phase strategy as the polymer-supported catalyst was removed by simple precipitation into methanol while the solution-phase reaction required silica gel chromatography.

The block copolymer library approach shows how rapidly new linear supports can be assimilated using combinatorial chemistry methods. The only disappointing feature is the low loading capacity of the new materials (*ca.* 0.15 mmol g^{-1}), a result of the uncontrolled nature of the radical polymerisation process. However, the authors note that by increasing the initiator to monomer ratio the polymer chain length will be reduced and so the loading can be improved.

Bergbreiter and co-workers[52] have generated a number of co- and ter-polymers of *N*-isopropylacrylamides **49a–e** which are soluble in water below their lower critical solution temperature (LCST), but precipitate quantitatively at temperatures above their LCST. Thus they can be used as matrices for so-called 'smart' reagents and catalysts.

A concern when generating polymer-supported species where the functional groups are not substituted at the termini, but rather on side-chains along the polymer backbone, is that the reactivity and accessibility of these groups may not be the same as if the reaction were performed in solution. However the rate of catalytic reduction of the nitroarene groups of the poly(*N*-isopropylacrylamide) PNIPAM derivative **49d** below its LCST was equivalent to that of a solution-phase reduction of



3-acetamidonitrobenzene. The reduction of **49d** effectively ceased on heating above its LCST, showing the 'smart' nature of these polymers as substrate supports. Several PNIPAM-bound rhodium(I) catalysts were prepared including the cationic phosphine-ligated catalyst **49e**. Interestingly the rate of hydrogenation of allyl alcohol catalysed by **49e** was found to be considerably lower than that of a non-polymer bound catalyst, this was found to be caused by hydrogen bonding of the PNIPAM side-chain residues to the cationic rhodium centre. However, replacing the cationic rhodium(I) centre of **49e** with a neutral rhodium(I) core nullified this effect and the soluble-polymer supported approach was as effective as its solution-phase variant.

As discussed *vide supra* the successful use of liquid-phase supports has always been a compromise between loading and solubility profile. By comparison with solid-phase approaches this can appear to be a drawback, as a relatively large weight of polymeric material has to be utilised for a small return of product at the end. However, Cozzi and co-workers[53] have linked dendrimer chemistry to that of PEG chemistry and produced new soluble PEG-supports with expanded functional group capacity. A dihydroxy-PEG_{4600} core (0.43 mmol g^{-1}) was functionalized as a *m*-dicarboxyphenyl derivative which, following standard transformations, yielded a tetrahydroxyaryl-PEG_{4600} **50** with a loading capacity of 0.86 mmol g^{-1} (Scheme 10). This high-loading PEG-derivative was then utilised in a synthetic scheme to generate β-lactam **51**, all of the intermediates being purified by precipitation into diethyl ether with excellent polymer recovery. This shows that the solubility profile of the PEG_{4600} core has not been compromised by the higher terminal substitution. The second generation dendrimer **52** (loading of 1.73 mmol g^{-1}) was also prepared, although its solubility characteristics and utility in synthesis has yet to be demonstrated.

The past two years have seen an explosion in the utility of soluble polymers as supports in combinatorial and organic chemistry. Their unique properties which facilitate purification and easy analysis are making them increasingly useful to academics and industrialists alike and the increasing scope and removal of associated limitations of these matrices can only serve to increase their incorporation into the broad field of polymer-supported chemistry.

Acknowledgements

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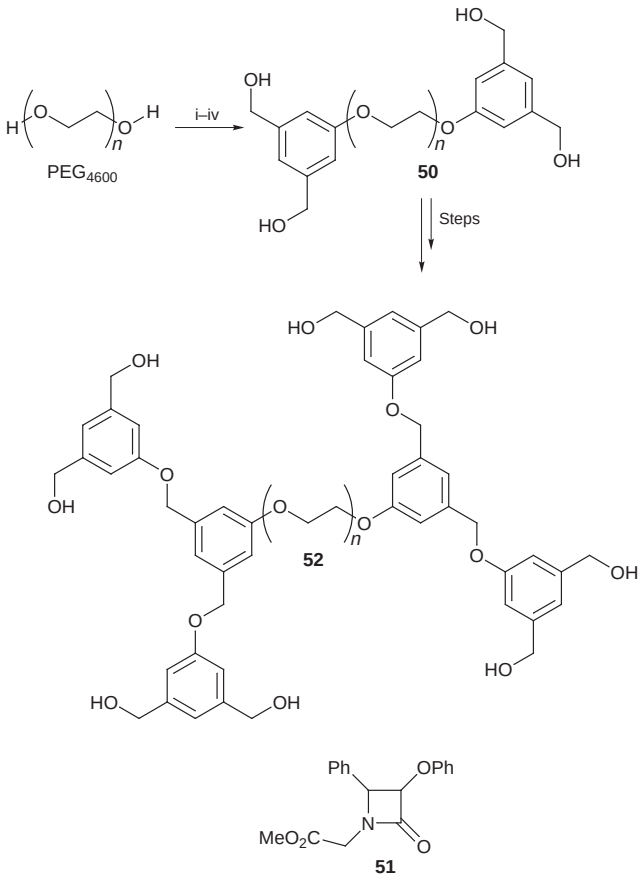

Scheme 10 *Reagents and conditions*: i, MsCl; ii, dimethyl 5-hydroxyisophthalate (3 equiv.), Cs_2CO_3 (3 equiv.), DMF, 50 °C, 15 h (95%); iii, aq. KOH (2 M), room temp., 15 h (70 %); iv, DIBAL-H (10 equiv.), toluene, reflux, 15 h (60%).

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