Developing Soluble Polymers for High-Throughput Synthetic Chemistry

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Abstract: Soluble polymers have emerged as viable alternatives to resin supports across the broad spectrum of high-throughput organic chemistry. As the application of these supports become more widespread, issues such as broad-spectrum solubility and loading are becoming limiting factors and therefore new polymers are required to overcome such limitations. This article details the approach made within our group to new soluble polymer supports and specifically focuses on parallel libraries of block copolymers, *de novo* poly(styrene-*co*-chloromethylstyrene), PEG-'stealth' stars, and substituted poly(norbornylene)s.

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 developing as alternative matrices for combinatorial library production [4] and organic synthesis [5,6]. Soluble polymer-supported chemistry couples 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. Solvent or heat precipitation, membrane filtration or size-exclusion chromatography achieves separation of the functionalized matrix.

Throughout the evolution of the fields of combinatorial chemistry and high-throughput synthesis we have focussed on developing soluble polymer-supported approaches. This has led to (i) the generation of peptide [4], azatide [7] and prostanoid [8] libraries on soluble polymer supports; (ii) the development of a number of supported reagents, such as poly(ethylene glycol) (PEG)-supported triarylphosphines **1a-b** [9,10], PEG-supported *N*-phenyltriflimide **2** [11]; (iii) PEG-supported cinchona **3a** [12] and phthalazine ligands **3b** [13] for polymer-supported Sharpless' asymmetric dihydroxylation reactions; (iv) PEG-supported dialkylborane reagent **4** for a 'fish-out' strategy of β-amino alcohols [14]; (v) synthesis of prostaglandins E **5a** and F2α **5b** [15,16], six-membered prostanoids [8] and the C_{21}-C_{27} fragment of the bryostatin marine metabolites **6a-d** (Fig. **1**) [17].

In much the same way that Merrifield's [18] 1-2 % divinyl benzene (DVB) cross-linked poly(styrene) resin dominated the developing field of solid-phase chemistry, poly(alkene oxide)s such as PEG have been the most studied polymers for soluble polymer-supported organic synthesis [19]. Other supports, such as poly(ethylene) oligomers [20] and poly(styrene)s [15,16] being used only in more specialised cases. Whereas the recent rapid advances in solid-phase chemistry have been punctuated with the development of new resin classes such as Tentagel [21,22], PEGA [23,24] and *J*anda*J*el [25,26], soluble polymer-supported chemistry has witnessed very few additions to its existing matrices. This has led us along with a number of other groups to focus on developing new supports possessing unique properties within the 'liquid-phase' arena [27].

The broad utility of PEG is linked to its wide solubility profile: soluble in DMF, dichloromethane, toluene, acetonitrile, water and methanol, but insoluble in diethyl ether, *t*-butyl methyl ether, *i*-propyl alcohol [28] and cold ethanol. However, as the scope of soluble polymer-supported chemistry increases, limitations have emerged with the use of PEG such as (i) THF and ether insolubility limiting the use of Grignard and other carbanion-based chemistries; (ii) metal complexation that limits the effectiveness of transition-metal chemistries; (iii) instability of the PEG-backbone to strong Lewis acids.

A soluble polymer-supported approach to prostaglandin synthesis raised new challenges for its matrix. The synthetic strategy hinged upon the choice of a soluble polymer-support that could withstand extreme reaction and workup conditions. The use of PEG was contraindicated for two reasons: insolubility in THF at low temperatures and its solubility in water that precluded aqueous extraction/removal of organometallic byproducts. Therefore, a non-crosslinked copolymer of styrene and chloromethylstyrene (3 mol %), previously used for peptide synthesis [29], was prepared (0.3 mmol g^{-1} loading) and as the 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 **7a** involved an initial attachment of the cyclopentanoid alcohol **8** to the soluble co-polymer *via* Ellman's tetrahydropyran linker [30]. The vinylstannane ω-chain **9** was then added to

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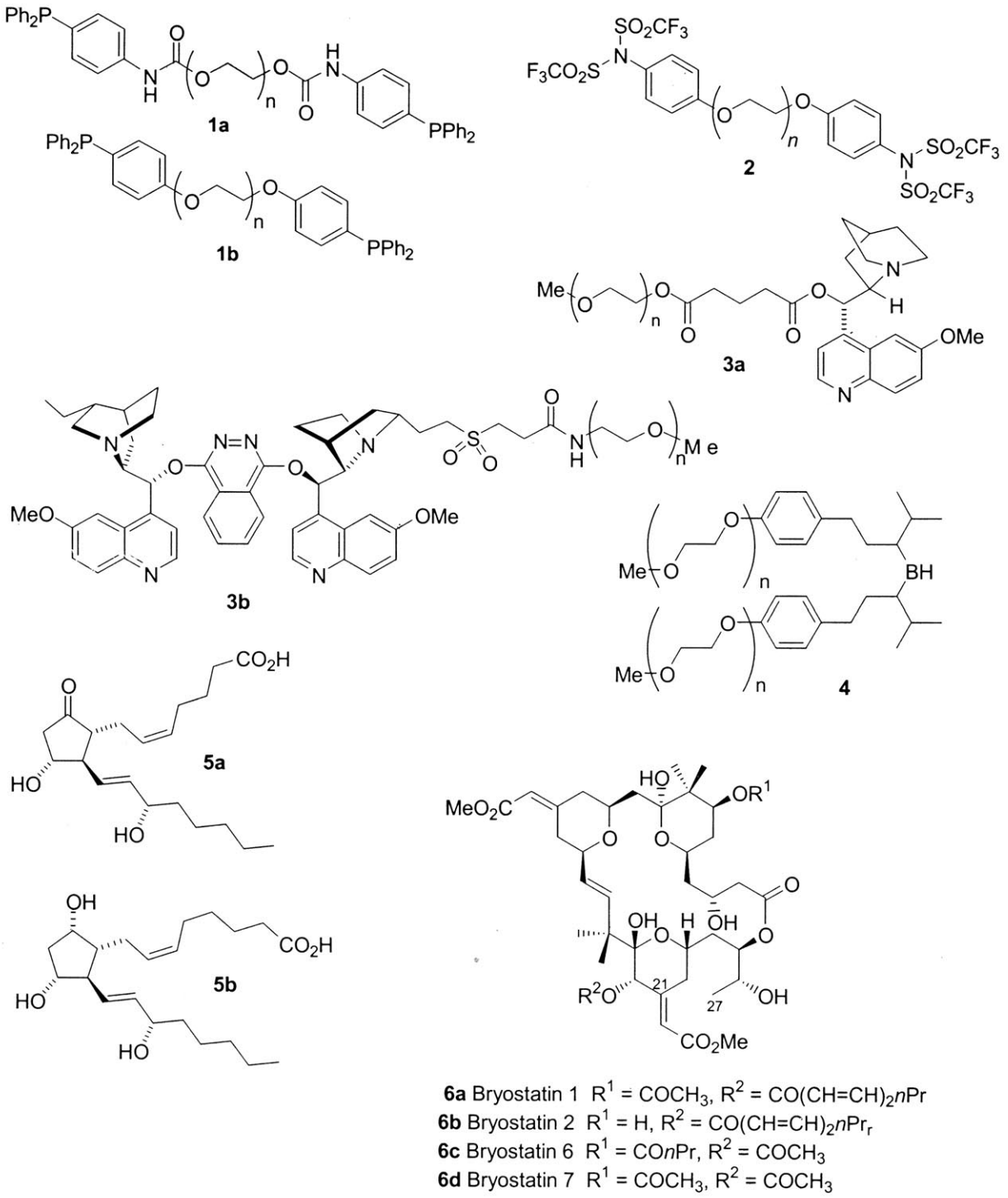
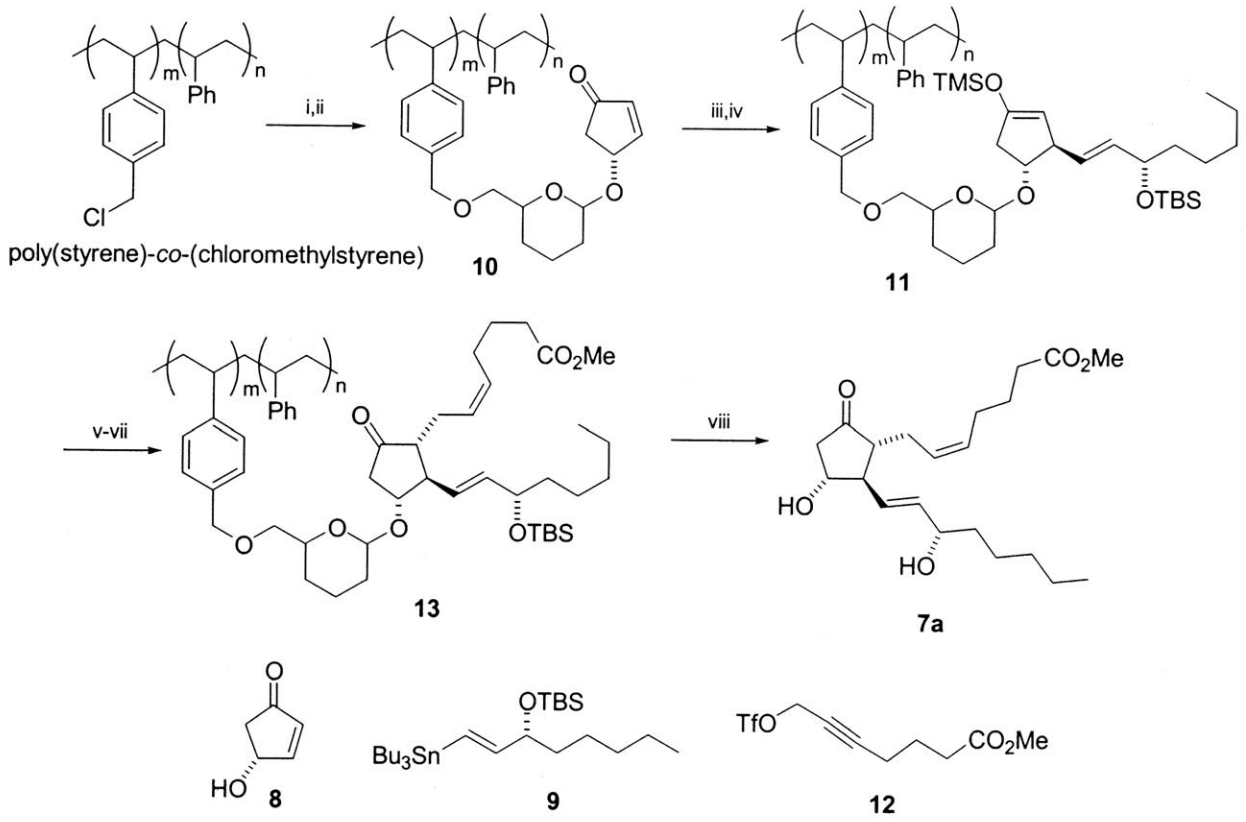


Fig. (1). The broad utility of soluble polymer-supported chemistry has resulted in supported-reagents (**1a-b**, **2**, **4**), ligands (**3a-b**) and natural product synthesis (**5a-b**, **6**).

10 in the presence of $Li_2CuCNMe_2$ in THF at -78 °C. Reaction of the intermediary enolate with TMSCl, furnished the stable polymer-bound silyl enol ether **11**. The α-chain was then incorporated, as its respective triflate **12**, by trapping of the intermediate enolate formed following addition of MeLi to **11** in THF (-23 °C). Following partial reduction of the α-chain alkyne, the polymer-bound *Z* alkene **13** was cleaved from the support, with accompanying deprotection of the silyl ether protecting group to give **7a** in an overall yield of 37 % for the eight step route. Polymer recovery mass balance was > 97 % and only one polymer-bound species was detected by routine NMR analysis for each step of the synthesis.



Scheme 1 *Reagents and conditions*: i. 6-(hydroxymethyl)-3,4-dihydro-2*H*-pyran (3 equiv), NaH (3.3 equiv), DMA, rt, 24 h; ii. **8** (3.0 equiv), PPTS (0.5 equiv), CH_2Cl_2, 40 ^oC, 16 h; iii. **9** (4.2 equiv), $Li_2CuCNMe_2$ (3.9 equiv), THF, -78 ^oC, 15 min; iv. chlorotrimethylsilane (15 equiv), -78 ^oC, 30 min; triethylamine (TEA, 30 equiv), 0 ^oC, 15 min; v. MeLi (3 equiv), THF, -23 ^oC, 30 min; vi. **12** (6 equiv), -78 ^oC, 10 min; -23 ^oC, 30 min; vii. H_2, 5 % Pd-$BaSO_4$, quinoline, benzene/cyclohexane (1:1), rt, 48 h; viii. 48 % aqueous HF/THF (3:20, v/v), 45 ^oC, 6 h.

In an alternative approach to generating new soluble-polymers we incorporated a sequential normal/living free radical polymerisation strategy with bifunctional initiator **14** and the styryl and vinyl monomers **15a-e**. This facilitated the production of linear, ABA, block copolymer libraries (Fig. **2**) [31].

The solubility profile of each library member was determined in a broad range of organic solvents and water. From within this library a copolymer of 4-*tert*-butylstyrene and 3,4-dimethoxystyrene **16** was found that has 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 synthesis (Scheme 2). The nitrile moieties, located between the two polymer chains, were deliberately incorporated so that they could be converted, with $LiAlH_4$ or by catalytic reduction, into amino groups as points for chemical derivatization.

Derivatization of the amine groups of **17** by acylation with a diphosphine ligand **18** furnished the polymer-supported chiral diphosphine **19**. The extent of derivatization and oxidation state of the phosphine ligands was routinely monitored by ^1H and ^{31}P NMR. Exchange of [Rh(1,5-cyclooctadiene)Cl]$_2$ with the diphosphine **19** generated a polymer-supported rhodium (I) species which catalysed the homogeneous enantioselective hydrogenation of dehydro-aminoacid **20**. The observed *ee*, stereochemical preference, and kinetics of formation of amino acid **21**, determined by ^1H NMR, were comparable to that observed with the solution-phase ligand **22**. Amino acid *S*-**21** was facilely isolated by precipitation and removal of **19**. The block copolymer library approach offers a rapid route into new linear supports utilizing parallel chemistry methods.

Olefin metathesis is a highly effective method for the construction of telechelic polymers [32,33]. In our most recent approach to the development of soluble polymer supports for organic synthesis we have moved our attention to terminally functionalized poly(dihydronorbornylene) matrices. These polymers can be rapidly accessed by ring-opening metathesis polymerization (ROMP) [34] of norbornene in conjunction with a functionalized chain transfer agent. We envisaged, as a starting point, the generation of a telechelic polymer that had a terminal hydroxyl group and that contained a hydrophobic backbone. The hydroxyl group could then be functionalized for subsequent utilization in organic chemistry. We have synthesized the hydroxy and methylsulfonate ester derivatized poly(dihydronorbornene) polymers **23a** and **23b** (Scheme 3).

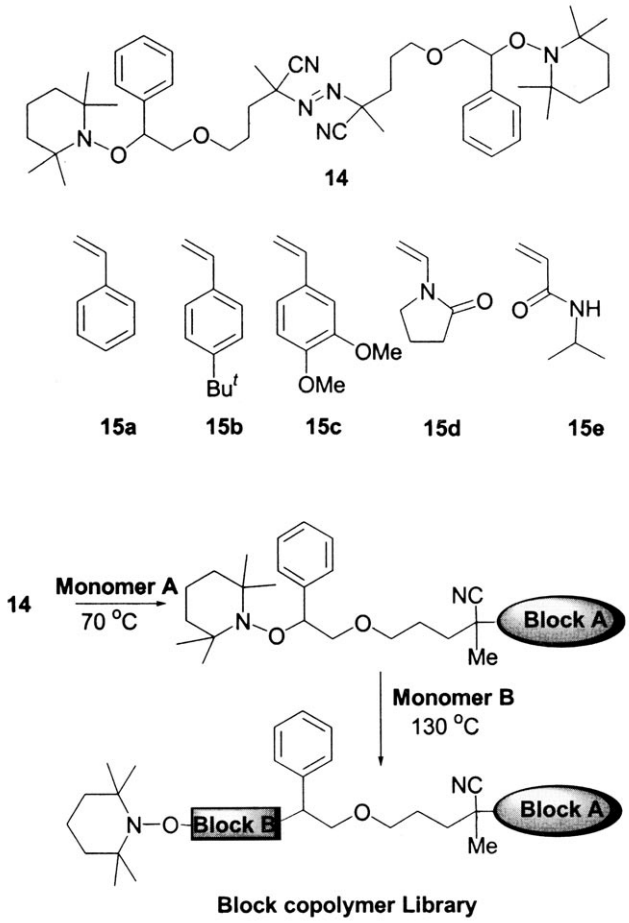
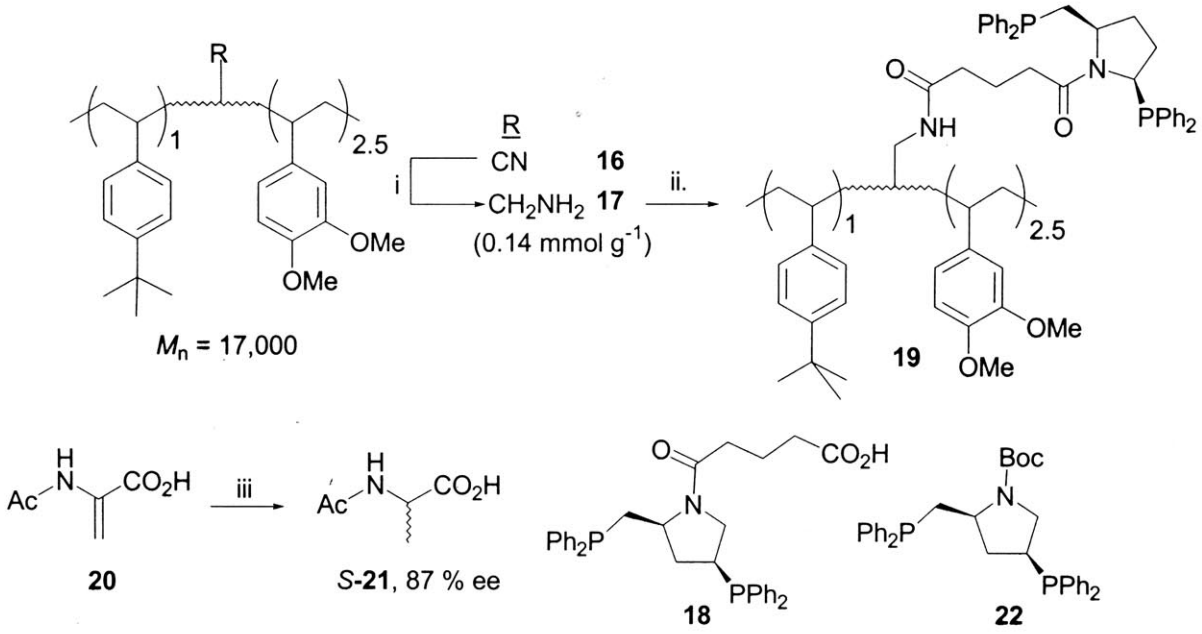
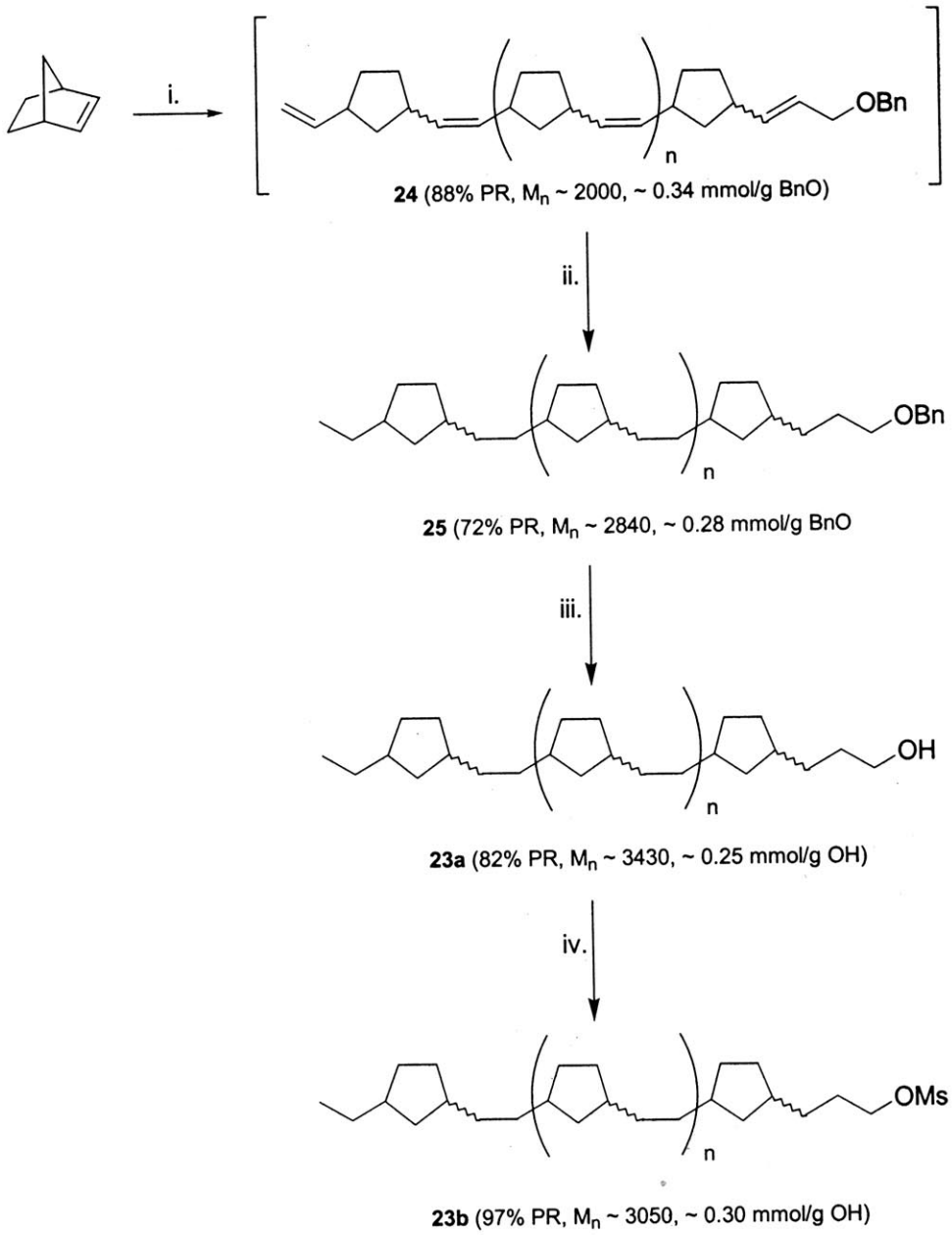


Fig. (2). Bifunctional initiator **14** and monomers **15a-e** utilized in a parallel format for block copolymer library production.

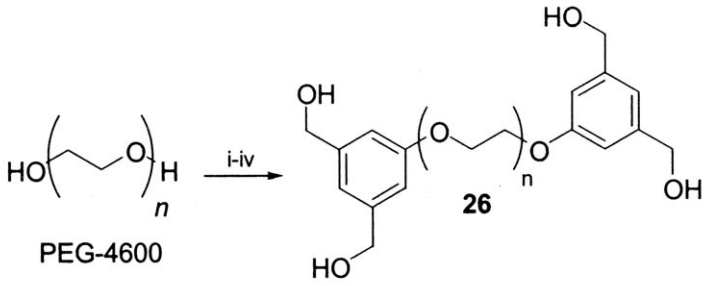


Scheme 2 *Reagents and conditions*: i. $LiAlH_4$ (76 equiv), THF, reflux, 2 h (quantitative); ii. **18** (4 equiv), DMAP (6 equiv), EDC (8 equiv), THF, rt, 4 h (quantitative); iii. **19** (0.04 equiv), μ-dichloro-bis(1,5-cyclooctadiene)dirhodium(I) (0.02 equiv), THF, rt, 4 h; **20** (1.0 equiv), H_2 (20 psi), THF, 2 days.



Scheme 3 *Reagents and conditions*: i. allylbenzyl ether (0.1 equiv.), Grubbs' catalyst (0.0005 equiv.), toluene, r.t. 24h; ii. 840 psi H_2, Grubbs' catalyst (0.0005 equiv.), toluene, 130 °C, 15 h; iii. 110 psi H_2, 10% Pd/C, chloro-form, 60 °C, 15 h; iv. MsCl (8 equiv.), DIPEA (16 equiv.), chloroform, 60 °C, 18 h.

Initial ROMP polymerization of norbornene with allylbenzyl ether and benzylidene-bis(tricyclohexylphosphine)-dichlororuthenium as catalyst furnished the benzyloxy poly(norbornylene) **24** in 88 % yield, based on recovered material. The molecular weight of **24** was routinely determined by integration of the NMR signals of the 3-benzyloxypropenyl & vinyl end groups and the olefinic protons of the backbone which gave M_n = 2000. Reduction of **24** with hydrogen in an autoclave (840 psi) at 130°C for 15 h furnished the benzyloxy poly(dihydronorbornylene) **24**. Catalytic reduction (10 % Pd/C) of **24** with hydrogen, in an autoclave (110 psi) at 60°C for 15 h gave the hydroxy-functionalized poly(dihydronorbornylene) **23a**. Poor ionization prevented routine mass-spectral analysis of **23a**, however the M_n was determined by integration of the NMR signals of the 3-hydroxypropyl & ethyl end groups and the protons of the backbone: n = 35.7; M_n = 3430. This is equivalent to a loading of ~ 0.3 mmol/g that compares favorably with commercially available PEG. Polymer **23a** does not dissolve significantly in any solvent at room temperature. However, good solubility (up to 5 %w/v) is observed in warm (> 50 °C) toluene, chloroform, and 1,2-dichloroethane. After cooling to room temperature the polymer precipitates and is easily collected by filtration (polymer recovery: > 95%). This solubility profile offers the exciting prospect of generating temperature-dependent polymer-supported catalysts and/or reagents that would be activated when solubilized. To investigate the accessibility



Scheme 4 *Reagents and conditions*: i. methanesulfonyl chloride; ii. dimethyl 5-hydroxyisophthalate (3 equiv), Cs_2CO_3 (3 equiv), DMF, 50 ^oC, 15 h (95 %); iii KOH (aq. 2M, rt, 15 h, (70 %); iv diisobutylaluminium hydride (10 equiv), toluene, reflux, 15 h (60 %).

of the hydroxyl-terminus could for organic synthesis we formed the methanesulfonate ester derivative **23b**. Treatment of **23a** with methanesulfonyl chloride (8 eq.) for 16 h furnishes mesylate **23b** that could be isolated by simple precipitation in (> 88 % yield).

One of the main criticisms levelled at soluble polymer supports for organic synthesis is their low loading. The limiting factor when developing high-loading supports is the compromise between loading and solubility profile. Cozzi and coworkers [35] linked dendrimer and PEG chemistry to 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} **26** with a loading capacity of 0.86 mmol g^{-1} (Scheme 4). This high-loading PEG-derivative was then utilised in a synthetic scheme to generate β-lactams. All of the intermediates were purified by precipitation into diethyl ether with excellent polymer recovery, showing that the solubility profile of PEG_{4600} is not modified by the higher terminal substitution.

Our efforts to improve the loading of PEG-based polymers while maintaining their solubility profiles has led to the development of PEG-star polymers (**27a-c**) containing a cyclotriphosphazene core (Fig. **3**) [36]. The first stage in the process necessitated the development of a routine synthesis of monobenzyl-protected poly(ethylene glycol) which was achieved with KH/2-benzyloxyethanol initiated anionic polymerization of ethylene oxide. This method gave almost quantitative amounts (95-99%) of pure monobenzyl PEG[37].

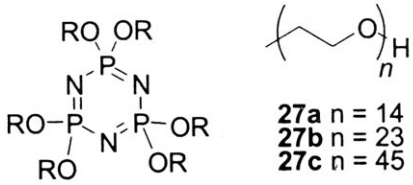


Fig. (3). Stealth star PEG-polymers **27a-c**.

Monobenzyl PEG of varying molecular weight reacted smoothly with $N_3P_3Cl_6$ to give the star polymers **27a-c**. This allowed the production of PEG with loading capacity of 1 mmol/g. The cyclotriphosphazene core is invisible to NMR and so does not complicate the analysis of any polymer-bound intermediates. For this reason these derivatives have been dubbed 'stealth star' polymers.

The past five years has seen an explosion in the utility of soluble polymers as supports in combinatorial and organic chemistry [5,6,38]. Their unique properties that facilitate purification and easy analysis are making them increasingly useful to academicians 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.

METHODS

General Remarks for NMR Spectra

cm = centered multiplet, higher order multiplets that were interpreted by 1st order rules are marked with apostrophes (e.g. 'q'), signals assigned to the polymer backbone are underlined.

Benzyloxy-Functionalized Poly(norbornylene) (24)

A solution of norbornene (9.41 g, 100 mmol) and allyl-benzylether (1.54 mL, 1.48 g, 10 mmol, 0.1 equiv.) in dry toluene (70 mL) was degassed by passing a moderate stream of argon through the solution for 15 min. Then, a solution of benzylidene-bis(tricyclohexylphosphine)-dichlororuthenium (41 mg, 50 μmol, 0.0005 equiv.) in dry dichloromethane (1 mL) was injected in one portion. After a short period of time the color of the solution changed from purple to burgundy, a slight exotherm was observed and the solution became viscous. Stirring was continued at room temperature over night under argon. 20 mL of the dark orange colored viscous reaction mixture was slowly added to vigorously stirred methanol (200 mL) the remaining 50 mL were directly hydrogenated under homogeneous conditions (*vide infra*).The precipitated polymer was isolated by filtration and resuspended in fresh methanol (200 mL). After stirring at room temperature for 2h the polymer was collected by suction filtration and air-dried. High vacuum drying over night at room temperature gave a light gray coarse powder (2.38 g, 88% polymer recovery).

^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.05 (cm, 1H), 1.35 (cm, 2H), 1.75-2.00 (m, 3H), 2.42 (cm, 2H, C*H*-O- *trans*-isomer), 2.77 (cm, 2H, CH-O- *cis*-isomer), 3.96 (d, 2H,

J=6.2 Hz, OCH_2 *trans*-isomer), 4.08 (d, 2H, *J*=5.5 Hz, OCH_2 *cis*-isomer), 4.49 (s, 2H, OCH_2Ph *trans*-isomer), 4.50 (s, 2H, OCH_2Ph *cis*-isomer), 4.86 (ddd, 1H, *J*=10.3, 2.2, 1.1 Hz, CH=CH_2, H-*cis*), 4.97 (ddd, 1H, J=17.2, 1.8, 1.1 Hz, CH=CH_2, H-*trans*), 5.21 (cm, 2H, -C*H*=C*H*-, *cis*-isomer), 5.34 (cm, 2H, -C*H*=C*H*-, *trans*-isomer), 5.48-5.75 (m, 2H, -C*H*=C*H*CH2O), 5.80 (cm, 1H, C*H*=CH_2), 7.30-7.50 (m, 5H, Ph).

Microstructure: cis/trans ratio of the backbone: 1:4.5; cis/trans ratio of the 3-benzyloxypropenyl terminus: 1:1.3. Ratio of benzyloxy to vinyl terminus: 1:1.9.

Molecular weight: Determined by integration of the NMR signals of the 3-benzyloxypropenyl & vinyl end groups and the olefinic protons of the backbone: n = 21.3; M_n = 2000.

Loading: 0.34 mmol/g benzyloxy functionality, 0.66 mmol/g vinyl functionality

Benzyloxy-Functionalized Poly(dihydronorbornylene) (25)

An aliquot (50 mL) of the crude reaction mixture mentioned from the previous experiment was transferred into a steel autoclave (Parr, 200 mL capacity) equipped with a glass liner and magnetic stir bar. The autoclave was pressurized with hydrogen (840 psi at room temperature) placed into an preheated oil bath (130 °C) and stirred for 15h. During this time the hydrogen pressure fell to 770 psi. The autoclave was removed from the oil bath and after reaching room temperature the polymer suspension formed was filtered. The filter cake was washed with cold toluene, suspended in methanol (200 mL) and stirred for 2 h at room temperature. The polymer was filtered off and air dried. High vacuum drying gave an off white powder (4.93 g, 72% polymer recovery).

^{1}H-NMR (600 MHz, $CDCl_3$, t=50°C) δ 0.62 ('q', 1H, *J*=10.7 Hz), 0.87 (t, 3H, *J*=7.3, -CH_2CH_3), 1.13 (br s, 2H), 1.26 (br s, 4H), 1.29-1.40 (m), 1.57-1.66 (m), 1.71 (cm, 4H), 1.90 (cm, 1H), 3.45 (t, 2H, *J*=6.6 Hz, CH_2OCH_2Ph), 4.50 (s, 2H, CH_2OCH_2Ph), 7.26-7.40 (m, 5H, Ph).

^{13}C-NMR (150 MHz, $CDCl_3$, t=50°C) δ 13.0 (CH_3CH_2), 28.9, 29.4, 31.3, 31.6, 31.7, 33.0, 33.1, 35.8, 39.0, 40.0, 40.4, 40.7, 40.8, 42.0, 70.8 (OCH_2), 72.8 (OCH_2Ph), 127.4 (Ph-*C*4), 127.6 (Ph-*C*3,5), 128.3 (Ph-*C*2,6), 138.7 (Ph-*C*1).

MALDI-TOF: no signal, polymer does not ionize:

Microstructure: Ratio of benzyloxy to ethyl terminus: 1:1.5.

Mol. Wt.: Determined by integration of the NMR signals of the 3-benzyloxypropyl & ethyl end groups and the protons of the backbone: n = 29.5; M_n = 2840.

Loading: 0.28 mmol/g benzyloxy functionality, 0.42 mmol/g ethyl functionality. From the filtrate a second polymer fraction with lower molecular weight could be obtained. The filtrate was concentrated to about 10 mL *in vacuo* and the polymer was precipitated by adding the solution to vigorously stirred cold methanol (150 mL). After stirring for 1 h the polymer was filtered off, washed with fresh cold methanol (2x 25 mL), air dried, and high vacuum dried to give an off white powder (1.25 g, 18% polymer recovery).

MALDI-TOF: no signal, polymer does not ionize

Microstructure: Ratio of benzyloxy to ethyl terminus: 1:1

Molecular weight: Determined by integration of the NMR signals of the 3-benzyloxypropyl & ethyl end groups and the protons of the backbone: n = 7.2; M_n = 692.

Loading: 1.45 mmol/g hydroxy functionality, 1.45 mmol/g ethyl functionality

Hydroxy-Functionalized Poly(dihydronorbornylene) (23a)

A Parr steel autoclave equipped with glass liner and stir bar (200 mL capacity) was charged with a suspension of polymer **25** (2.00 g, fraction 1, M_n = 2840) in freshly distilled chloroform (100 mL). Then, 10% Pd on carbon (500 mg) was added and the autoclave was pressurized with hydrogen (110 psi). The hydrogenation was conducted for 15 h at 60 °C oil bath temperature with stirring. After reaching room temperature the suspension was filtered and the collected polymer was resuspended in methanol (100 mL). The colorless suspension was stirred for 1h at room temperature. Suction filtration, followed by washing with methanol (2x 25 mL), air dry, and high vacuum dry afforded polymer **23a** as a colorless powder (1.64 g, 82% polymer recovery).

^{1}H-NMR (600 MHz, $CDCl_3$, t=50°C) δ 0.65 ('q', 1H, *J*=10.1 Hz), 0.88 (t, 3H, *J*=7.5, -CH_2CH_3), 1.16 (br s, 2H), 1.29 (br s, 4H), 1.29-1.40 (m), 1.57-1.66 (m), 1.73 (cm, 4H), 1.91 (cm, 1H), 3.63 (br dt, 2H, *J*=7.0, 4.4 Hz, CH_2OH).

ATR-IR (neat): 3385 (OH), 2933, 2903, 2858, 2841, 1465, 1450, 1358, 1322, 1262, 1223, 1109, 947, 753 cm^{-1}.

Microstructure: Ratio of hydroxy to ethyl terminus: 1:1.3

Molecular weight: Determined by integration of the NMR signals of the 3-hydroxypropyl & ethyl end groups and the protons of the backbone: n = 35.7; M_n = 3430.

Loading: 0.30 mmol/g hydroxy functionality, 0.33 mmol/g ethyl functionality

Methanesulfonate-Functionalized Poly(dihydronorbornylene) (23b)

To a suspension of polymer **23a** (1 g, 0.25 mmol free OH) in dry chloroform (25 mL) was added ethyldiisopropylamine (0.7 mL, 517 mg, 4 mmol, 16 equiv.) and methanesulfonyl chloride (0.15 mL, 229 mg, 2 mmol, 8 equiv.). The reaction mixture was stirred for 18 h at 60 °C

under argon. It was then cooled to room temperature and poured into methanol (200 mL) with stirring. The precipitated polymer was collected by filtration, resuspended in fresh methanol (100 mL) and stirred for further 2h at room temperature. Then, the polymer was filtered off, washed with methanol (2x 25 mL), air died, and vacuum dried to afford polymer **23b** as a colorless powder (970 mg, 97% polymer recovery).

^{1}H-NMR (600 MHz, $CDCl_3$, t=50°C) δ 0.64 ('q', 1H, *J*=10.1 Hz), 0.88 (t, 3H, *J*=7.4, $-CH_2CH_3$), 1.15 (br s, 2H), 1.28 (br s, 4H), 1.29-1.40 (m), 1.72 (cm, 4H), 1.91 (cm, 1H), 2.99 (s, 3H, H_3CSO_2O), 4.21 (t, 2H, *J*=6.6 Hz, CH_2OMs).

ATR-IR (neat): 2934, 2903, 2858, 2841, 1465, 1450, 1358, 1263, 1222, 1179, 947, 754, 634 cm^{-1}.

Microstructure: Ratio of hydroxy to ethyl terminus: 1:1.2

Molecular weight: Determined by integration of the NMR signals of the methanesulfonate & ethyl end groups and the protons of the backbone: n = 31.7; M_n = 3050.

Loading: 0.30 mmol/g methanesulfonate functionality, 0.36 mmol/g ethyl functionality

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REFERENCES

[1] Fruchtel, J. S.; Jung, G. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 17.

[2] Thompson, L. A.; Ellman, J. A. *Chem. Rev.* **1996**, *96*, 555.

[3] Yan, B. *Acc. Chem. Res.* **1998**, *31*, 621.

[4] Han, H.; Wolfe, M. M.; Brenner, S.; Janda, K. D. *Proc. Natl. Acad. Sci. U.S.A.* **1995**, *92*, 6419.

[5] Wentworth Jr., P.; Janda, K. D. *Chem. Commun.* **1999**, 1917.

[6] Gravert, D. J.; Janda, K. D. *Chem. Rev.* **1997**, *97*, 489.

[7] Han, H.; Janda, K. D. *J. Am. Chem. Soc.* **1996**, *118*, 2539.

[8] Lopéz-Pelegrín, J. A.; Janda, K. D. *Chem. Eur. J.* **2000**, *6*, 1917.

[9] Wentworth Jr., P.; Vandersteen, A. M.; Janda, K. D. *Chem. Commun.* **1997**, 759.

[10] Sieber, F.; Wentworth Jr., P.; Toker, J. D.; Wentworth, A. D.; Metz, W. A.; Reed, N. N.; Janda, K. D. *J. Org. Chem.* **1999**, *64*, 5188.

[11] Wentworth, A. D.; Wentworth Jr., P.; Mansoor, U. F.; Janda, K. D. *Org. Letters* **2000**, *2*.

[12] Han, H.; Janda, K. D. *J. Am. Chem. Soc.* **1996**, *118*, 7632.

[13] Han, H.; Janda, K. D. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1731.

[14] Hori, M.; Janda, K. D. *J. Org. Chem.* **1998**, *63*, 889.

[15] Chen, S.; Janda, K. D. *J. Am. Chem. Soc.* **1997**, *119*, 8724.

[16] Chen, S.; Janda, K. D. *Tetrahedron Lett.* **1998**, *39*, 3943.

[17] Lopéz-Pelegrín, J. A.; Wentworth Jr., P.; Sieber, F.; Metz, W. A.; Janda, K. D. *J. Org. Chem.* **2000**, *65*, 8527.

[18] Merrifield, R. B. *J. Am. Chem. Soc.* **1963**, *85*, 2149.

[19] Mutter, M.; Hagenmaier, H.; Bayer, E. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 811.

[20] Bergbreiter, D. E. *ACS Symp. Ser.* **1986**, *308*, 17.

[21] Bayer, E. A*ngew. Chem., Int. Ed. Engl.* **1991**, *30*, 113.

[22] Rapp, W. E. In *Combinatorial Chemistry Synthesis and Applications*; Wilson, S. R., Czarnik, A. W., Eds.; John Wiley & Sons, Inc.: New York, **1997**, p 65.

[23] Rademann, J.; Grøtli, M.; Meldal, M.; Bock, K. *J. Am. Chem. Soc.* **1999**, *121*, 5459.

[24] Renil, M.; Meldal, M. *Tetrahedron Lett.* **1996**, *37*, 6185.

[25] Toy, P. H.; Reger, T. S.; Janda, K. D. *Aldrichimica Acta* **2000**, *33*, 87.

[26] Toy, P. H.; Reger, T. S.; Garibay, P.; Garno, J. C.; Malikayil, J. A.; Liu, G.-Y.; Janda, K. D. *J. Comb. Chem.* **2001**, *3*, 117.

[27] Bergbreiter, D. E.; Case, B. L.; Liu, Y.-S.; Caraway, J. W. *Macromolecules* **1998**, *31*, 6053.

[28] Zhao, X.-Y.; Metz, W. A.; Sieber, F.; Janda, K. D. *Tetrahedron Lett.* **1998**, *39*, 8433.

[29] Narita, M. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 1477.

[30] Ellman, J. A.; Thompson, L. A. *Tetrahedron Lett.* **1994**, *35*, 9333.

[31] Gravert, D. J.; Datta, A.; Wentworth Jr., P.; Janda, K. D. *J. Am. Chem. Soc.* **1998**, *120*, 9481.

[32] Pinazzi, C. P.; Campistron, I.; Croissandeau, M. C.; Reyx, D. *J. Mol. Catal.* **1980**, *8*, 325.

[33] Hillmyer, M. A.; Grubbs, R. H. *Macromolecules* **1995**, *28*, 8662.

[34] Fraser, C.; Hillmyer, M. A.; Guttierrez, E.; Grubbs, R. H. *Macromolecules* **1995**, *28*, 7256.

[35] Benaglia, M.; Annunziata, R.; Cinquini, M.; Cozzi, F.; Ressel, S. *J. Org. Chem.* **1998**, *63*, 8628.

[36] Reed, N. N.; Janda, K. D. *Org. Letters* **2000**, *2*, 1311.

[37] Reed, N. N.; Janda, K. D. *J. Org. Chem.* **2000**, *65*, 5843.

[38] Toy, P. H.; Janda, K. D. *Acc. Chem. Res.* **2000**, *33*, 546.

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