Polymer-supported selenium reagents for organic synthesis

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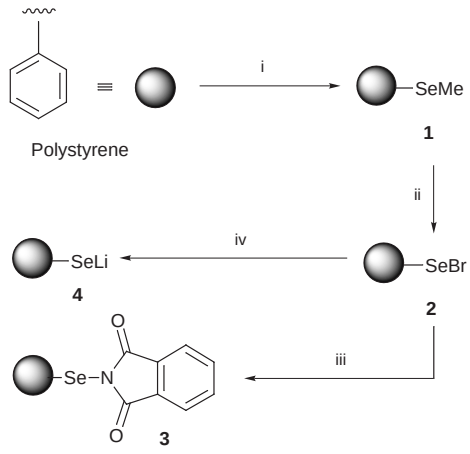
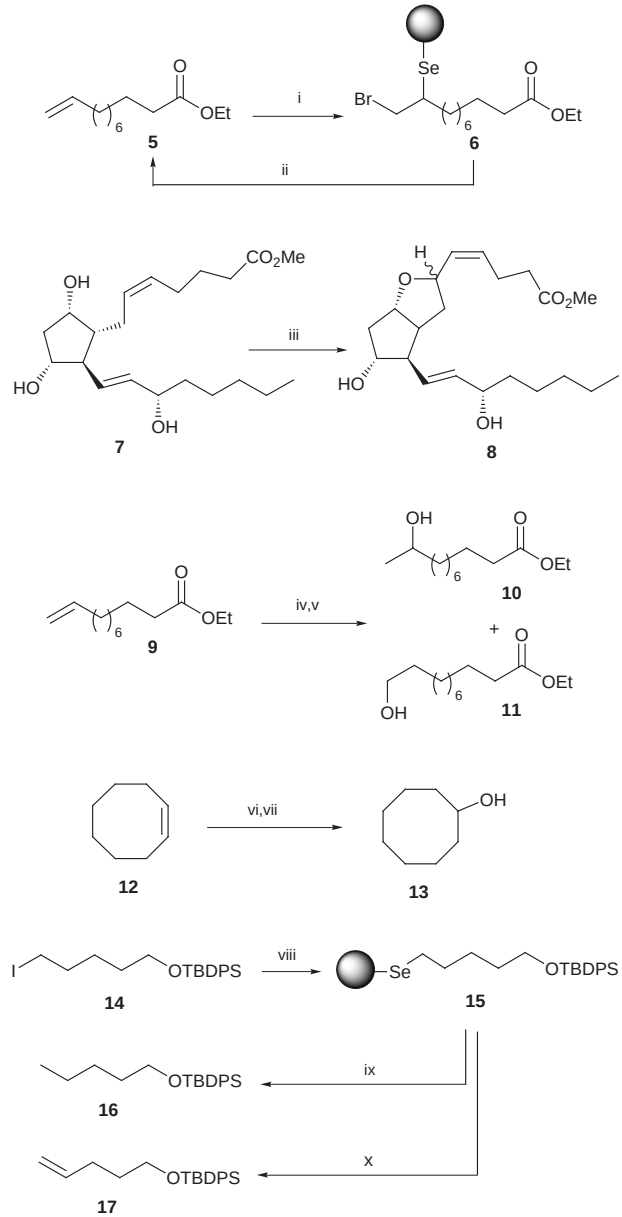
Organoselenium resins 1–4 were prepared from polystyrene *via* lithiation and quenching with MeSeSeMe, and shown to react with a variety of substrates, aiding in useful functionalizations.

Combinatorial chemistry and solid phase synthesis have recently emerged as powerful tools for the drug discovery process.[1] The latter technique is particularly useful for combinatorial library construction due to its adaptability to the powerful and elegant split-pool methods[2] and because of the well recognized purification advantages associated with it. The utilization of polymer-bound reagents,[3] in particular, has gained popularity due to the non-requirement for tethering the substrate to the polymer. Here we describe the preparation of a series of solid-supported selenium resins[4,5] **2–4** (Scheme 1) and their application as linkers and reagents for solid phase synthesis. A distinct advantage of the new reagents is the convenience of handling and their totally odorless nature as compared to the non-bound reagents, whose toxicity and foul smell is often problematic.

Scheme 1 summarizes the preparation of the new resins **2–4** from readily available starting materials. Thus, polystyrene beads suspended in cyclohexane were treated with Bu^nLi–TMEDA[6] and the lithiated species was quenched with MeSeSeMe,[7] furnishing selenium reagent **1** as a pale yellow resin (the loading of selenium was controlled by addition of MeSeSeMe in substoichiometric amounts to the lithiated polystyrene). Exposure of **1** to bromine resulted in quantitative conversion[8] to the polymer-supported selenenyl bromide **2**, which was isolated after filtration and washing as a deep red resin. The selenium

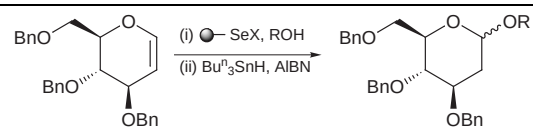


Scheme 1 *Reagents and conditions*: i, Bu^nLi (2.5 M in hexanes, 24 equiv.), TMEDA, cyclohexane, 65 °C, 4 h, then filtration and washing with THF, then dimethyl diselenide (2.0 mmol g^{-1} of polystyrene), THF, 0 °C, 30 min, 100%; ii, Br_2 (0.9 equiv.), $CHCl_3$, 0 °C, 10 min, 100% (based on consumption of Br_2), then filtration and washing, then EtOH, 70 °C, 1 h, > 95%; iii, potassium phthalimide (1.5 equiv.), 18-crown-6 (1.5 equiv.), benzene, 23 °C, 5 h, > 95% yield; iv, $LiBH_4$ (2.0 M in THF, 2.0 equiv.), THF, 23 °C, 1 h, > 95%

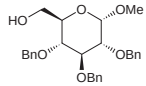
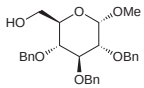
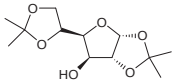


Scheme 2 *Reagents and conditions*: i, **2** (1 equiv.), CH_2Cl_2, 23 °C, 30 min; ii, Bu^n_3SnH (4 equiv.), AIBN (0.01 equiv.), PhMe, 110 °C, 6 h, 92% (2 steps); iii, **2** (1.5 equiv), THF, −78 °C, 30 min, then H_2O_2 (30%, 2 equiv.), −78 → 23 °C, 20 h, 94% (2 steps); iv, **3** (0.5 equiv.), H_2O (1 equiv.), CSA (0.05 equiv.), CH_2Cl_2, 24 h; v, Bu^n_3SnH (2 equiv.), AIBN (0.005 equiv.), PhMe, 110 °C, 6 h, 82% (2 steps), **10** : **11** = 2 : 1; vi, **3** (0.5 equiv.), H_2O (1 equiv.), CSA (0.05 equiv.), CH_2Cl_2, 24 h; vii, Bu^n_3SnH (2 equiv.), AIBN (0.005 equiv.), PhMe, 110 °C, 6 h, 80% (two steps); viii, **4** (0.5 equiv.), THF, 23 °C, 12 h; ix, Bu^n_3SnH (2 equiv.), AIBN (0.005 equiv.), PhMe, 110 °C, 6 h, 89% (2 steps); x, H_2O_2 (30%, 1 equiv), THF, 23 °C, 12 h, 78% (2 steps)

Table 1 Polymer-bound selenium promoted synthesis of 2-deoxyglycosides[a]



18 **19**

Entry	ROH	Reagent	Solvent	*t*/h	Yield (%)	Ratio α : β
1	BnOH	**2**	CH_2Cl_2	24	87	2 : 1
2	BnOH	**2**	PhMe	24	96	2 : 1
3	BnOH	**2**	MeCN–CH_2Cl_2 (2 : 1)	24	86	5 : 1
4	BnOH	**3**	CH_2Cl_2	48	68	1 : 5
5	BnOH	**3**	PhMe	48	72	1 : 5
6	BnOH	**3**	MeCN–CH_2Cl_2 (2 : 1)	48	23	1 : 1
7		**2**	MeCN–CH_2Cl_2 (2 : 1)	24	61	8 : 1
8		**3**	PhMe	48	45	1 : 1
9		**2**	MeCN–CH_2Cl_2 (2 : 1)	96	50	20 : 1

[a] All reactions were carried out under an atmosphere of argon in the presence of 4 Å molecular sieves. *Reagents and conditions*: i, (for reagent **2)** ROH (1 equiv.), 2,6-di-*tert*-butyl-4-methylpyridine (1 equiv.), **2** (0.5 equiv.); (for reagent **3)** ROH (1 equiv.), CSA (1 equiv.) and **3** (0.5 equiv.); solvent and time as shown in Table; ii, Bu$^n_3$SnH (2 equiv.), AIBN (0.005 equiv.), PhMe, 110 °C, 8 h.

phthalimide reagent **3** was obtained as a yellow resin from **2** by displacement with potassium phthalimide in the presence of 18-crown-6 (> 95% yield),[9] while the lithium selenide **4** (a pale yellow resin) was prepared by $LiBH_4$ reduction of **2** (95% yield). All new reagents appeared to be quite stable in the air at ambient temperature (inert atmosphere is recommended, however, for their storage and use).

Scheme 2 displays chemistry demonstrating the use of resins **2–4** both as solid phase linkers and polymer-bound reagents. Thus, olefin **5** was quantitatively loaded onto the polymer by treatment with the polymer-bound selenium bromide resin **2** and, subsequently, released reductively under the influence of Bu$^n_3$SnH–AIBN (cat.) to recover the starting olefin **5** in 92% overall yield. The polymer-bound selenium bromide **2** was also shown to be as effective as phenylselenium bromide for the known two-step transformation[10] of $PGF_{2\alpha}$ methyl ester **7** to the PGI_2 analogues **8** (94% yield, *ca.* 2 : 1 ratio of C-6 epimers, Scheme 2). Hydration of an olefin was demonstrated to proceed smoothly with the selenium phthalimide resin **3**.[9] Thus, terminal olefin **9** was converted to the regioisomeric alcohols **10** and **11** in 82% overall yield (**10** : **11** *ca.* 2 : 1 ratio) by the action of reagent **3** and CSA in the presence of H_2O, followed by reductive cleavage from the solid support with Bu$^n_3$SnH–AIBN. Furthermore, cyclic olefin **12** was converted to alcohol **13** in 80% overall yield by the same two-step procedure. The use of the resin **4** was demonstrated as follows. Alkyl iodide **14** was efficiently loaded onto the polymer through mild alkylation conditions in THF. The substrate was then released from the polymer (**15**) by either free radical chemistry to obtain the corresponding alkyl compound **16** (89% overall yield) or oxidative conditions leading to olefinic product **17** (78% overall yield).

Table 1 summarizes applications of polymer-bound selenium bromide **2** and selenium phthalimide[11] **3** to the synthesis of 2-deoxyglycosides.[12] Most noteworthy is the inverse glycosidation stereoselectivity obtained under different reaction conditions. Thus, glycosidation of tri-*O*-benzylglucal **18** with BnOH using the polymer-bound selenenyl bromide reagent **2** (X = Br) followed by Bu$^n_3$SnH–AIBN (cat.) cleavage of the newly formed selenium–carbon bond released the 2-deoxy glycosylated product **19** in 86% yield with 5 : 1 selectivity in favor of the α-anomer (entry 3), whereas the same transformation carried out with the polymer-bound selenenyl phthalimide reagent **2** yielded the product in 72% with a 5 : 1 selectivity in favor of the β-anomer (entry 5).

In conclusion, we have successfully prepared a series of polymer-bound selenium reagents/linkers and demonstrated a number of their uses in organic synthesis. These reagents should find useful applications in solid phase and combinatorial synthesis due to their versatility and ease of handling.

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