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Solid-supported reagents composed of a copolymer possessing 2-*O*-sulfonyl mannosides and phase-transfer catalysts for the synthesis of 2-fluoroglucose

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ABSTRACT

We described the synthesis of a solid-supported co-polymer possessing mannosides and phase-transfer catalysts and synthesis of 2-fluoroglucoside from it. We first prepared a soluble copolymer from two allene monomers possessing a precursor for the synthesis of 2-fluoroglycose and a crown ether. The copolymerization of the monomers via the π-ally nickel-catalyst smoothly proceeded at room temperature to provide a desired copolymer without decomposition of the sulfonate esters. The copolymer exhibited high reactivity towards fluorination in comparison with a conventional precursor. We next synthesized the solid-supported copolymer by using the solid-supported initiator attached with TentaGel® resins. TentaGel® enabled polymerization under stirring with stirring bar without decomposition. The solid-supported copolymer exhibited comparable reactivity towards fluorination in comparison with the soluble copolymer. In addition, it can be easily separated from the reaction vessel by filtration.

Positron emission tomography (PET) is used to visualize the target cells and organs via radioactive tracers that possess a suitable radionucleotide. The process is used in the clinics and in small animal researches to noninvasively study the molecular basis of disease and to guide the development of novel molecular-based treatments.[1–3] [^{18}F]Fluoride is a useful radionucleotide for PET imaging due to a relatively long half-life time (105 min).[4] Nucleophilic substitution with [^{18}F]fluoride ion is an effective to synthesize [^{18}F]fluorides for use as PET probes with high specific activity because carrier-free [^{18}F]fluorides are adaptable. The yield of the radioactive tracers largely depends not only on the efficiency of the labeling reaction with [^{18}F]fluoride, but also on total manipulation time due to the half-life time of [^{18}F]fluoride. However, the nucleophilicity of the fluoride ion is very low. In addition, purification of the [^{18}F]tracer involves the separation of picomolar to nanomolar amounts of a radioisotope-labeled tracer from the large excess of non-radioactive precursors. The containing precursors should act as competitors against the tracers. To overcome the problems, the phase tag-assisted synthesis of [^{18}F]fluoride-labeled tracers has emerged as an effective method for simplification of the purification protocol (Scheme 1).[5,6] With this process, the precursors are linked to a phase tag through a sulfonate ester[7,8] and are release the fluorinated product by nucleophilic attack with the activated [^{18}F]potassium fluoride via a phase transfer catalyst. The remaining tagged precursors were easily separated from the fluorinated products based on the guidance of the tag. Omitting the HPLC purification process simplifies the manipulation for the purification and shortens the time required for purification to improve the yield of the [^{18}F]PET tracers.[3] Use of a polymer-support as a phase-tag enabled purification of the [^{18}F]PET tracers by filtration.[9,10] Brown and co-workers reported on the synthesis of [^{18}F]2-deoxy-2-fluoroglucose (2-FDG) from the solid-supported precursor. However, immobilization of the reagents on a solid-support frequently reduces the reactivity against the soluble reagents due to an enhanced steric hindrance and their reduced mobility. Application of fluorous-tag technology[11] to the synthesis of the [^{18}F]PET tracers allowed removal of the precursor attached to a fluorous tag by solid-phase extraction with fluorous column chromatography with a minimum unfavourable effect of the tag.[12,13] In these methodology, activation of the fluoride ion was achieved by addition of crown ethers such as Kriptfix[2.2.2]. The crown ethers should be carefully removed for the process of [^{18}F] PET probes due to their toxicity.

In this Letter, we planed to prepare the solid-supported copolymer **1** possessing 2-*O*-sulfonyl mannosides and phase-transfer

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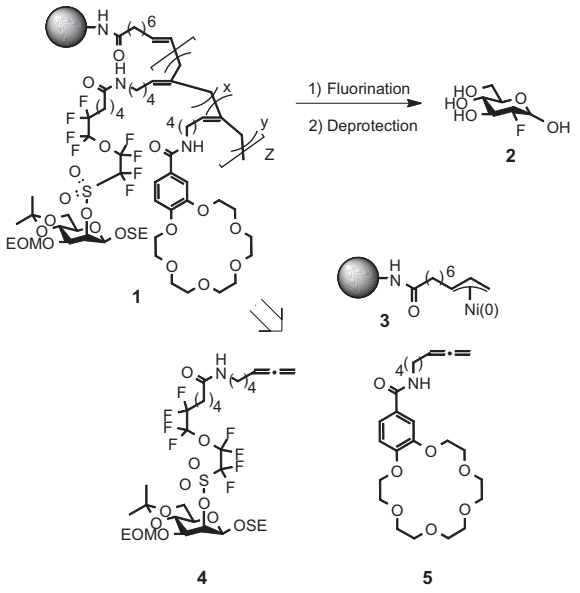
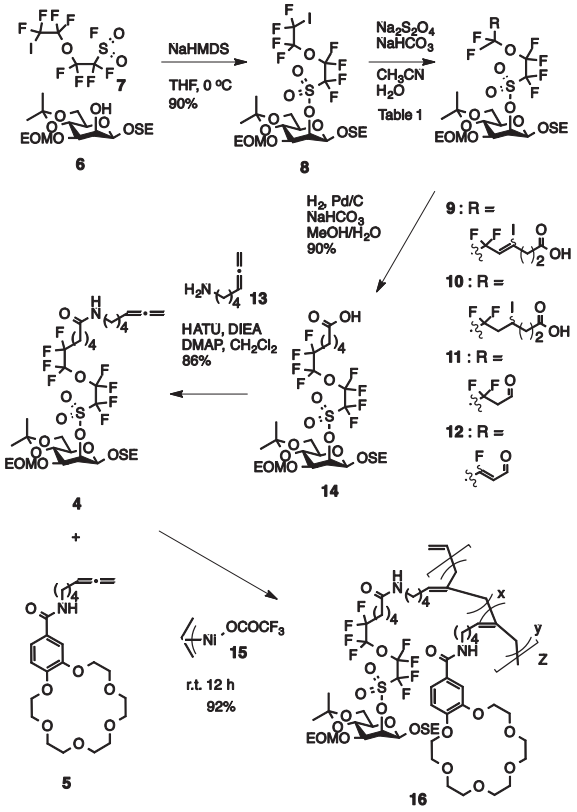


Scheme 1. Synthesis of the 2-fluoroglucose **2** from the solid-supported copolymer **1**.

catalysts as a solid-supported reagent for the synthesis of 2-FDG (Scheme 1). The cyclic protection minimizes β-elimination of the sulfonate ester during fluorination.[7a] The 18-crown-6 was selected as a phase-transfer catalyst. Treatment of the copolymer **1** with potassium fluoride results in activation of fluoride ion with the crown ether. Subsequent fluorination with the activated fluoride releases the fluorinated product. The copolymer **1** can be separated from the products by filtration. The copolymerization of the precursor **4** and the phase-transfer catalyst **5** could enhance the reactivity of the precursor towards fluorination.[14] The solid-supported copolymer **1** was prepared by π-allyl nickel-catalyzed coordinating copolymerization of the allene monomers **4** and **5** with the solid-supported π-allyl nickel-catalyst **3**. The polymerization was compatible with various polar functional groups involved in biologically active compounds and proceeded under ambient temperature without decomposition of the sulfonate linker.[15]

We first prepared the soluble copolymer **16** possessing mannosides and crown ethers by using initiator **15** (Scheme 2). Treatment of mannoside **6** possessing a free hydroxy group at the C2 position with the sulfonyl fluoride **7** in the presence of sodium hexamethyldisilazide (NaHMDS) provided the sulfonyl ester **8** in 90% yield. We next examined the incorporation of a carboxylic acid to **8** via the radical coupling reaction of the terminal iodide (Table 1). According to the reported method[7a], the treatment of iodide **8** and ethylvinyl ether with $Na_2S_2O_3$ provided a mixture of the aldehyde **11** and the enal **12** in 59% yield. The reaction of **8** with 4-pentenoic acid under the same conditions provided the alkyl iodide **10** in 58% yield. Although the reaction clearly proceeded, the starting material did not disappeared. On the other hand, use of 4-pentynoic acid as a radical acceptor resulted in a 86% yield of the vinyl iodide **9** as a stereomixture. Subsequent hydrogenolysis of the vinyl iodide **9** provided the carboxylic acid **14** in 90% yield. Amidation of the carboxylic acid **14** with 5-amino-1,2-heptadiene (**13**) in the presence of 1-[Bis (dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate (HATU), diisopropylethylamine (DIEA) and dimethylaminopyridine (DMAP) yielded the allene monomer **4** in 86% yield. Next, copolymerization of the allene monomers **4** and **5** was examined. The 1.0:1.0 mixture of the allene monomers **4** and **5** was reacted by 5 mol % π-ally nickel



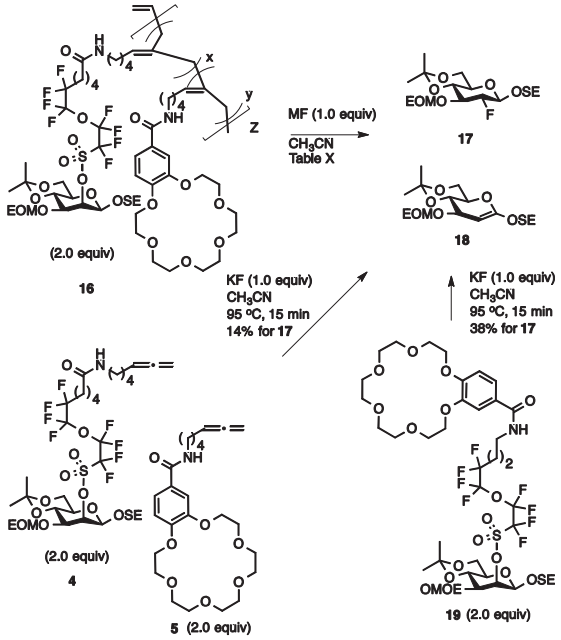
Scheme 2. Synthesis of the allene monomer **4** and copolymer **16**.

Table 1
Radical coupling of **8**

Entry	Reagents	Product	Yield (%)
1	4-Pentynoic acid	**9**	86
2	4-Pentenoic acid	**10**	58
3	Ethylvinyl ether	**11** and **12**	59

catalyst **15** for 12 h at room temperature to provide copolymer **16** in 92%. ^{1}H NMR analysis of **16** revealed that the ratio of the incorporated monomers **4** and **5** in the copolymer **16** was 1.0:1.0 (**4**:**5**). The molecular weight and poly disparity index of the polymer **16** was estimated by a size-exclusive chromatography to be 2.2×10^4 (M_w/M_n = 1.1).

Fluorination of the polymer-supported precursor **16** was examined (Scheme 3 and Table 2). A mixture of potassium fluoride and two equivalents of the polymer-supported precursor **16** in CH_3CN was heated at 95 °C for 15 min to provide the fluorinated product **17** in 74% yield along with glycal **18** in 22% yield. On the other hand, reaction of 1:1 mixture of the monomers **4** and **5** under the same reaction conditions provided the fluorinated product **17** in a dramatically reduced yield (14%). The precursor **19** connected with a phase-transfer catalyst provided the fluorinated product **17** in a moderate yield (38%). These results clearly indicate that the copolymerization of the precursor **4** and the phase-transfer catalyst **5** improved the reactivity of the precursor towards fluorination. The reaction mixture using the copolymer **16** could involve higher local concentration area than **19**. Fluorination of the polymer-supported precursor **16** at 95 °C for 5 min resulted in the reduced yield (36%) of the fluorinated product **17**. However, fluorination of **16** at 50 °C provided the fluorinated compound **17** in a comparable yield (67%). We further examined the effect of the counter cation of fluoride ion on fluorination. Sodium fluoride did not provide the fluorinated compound **17**. Cesium fluoride



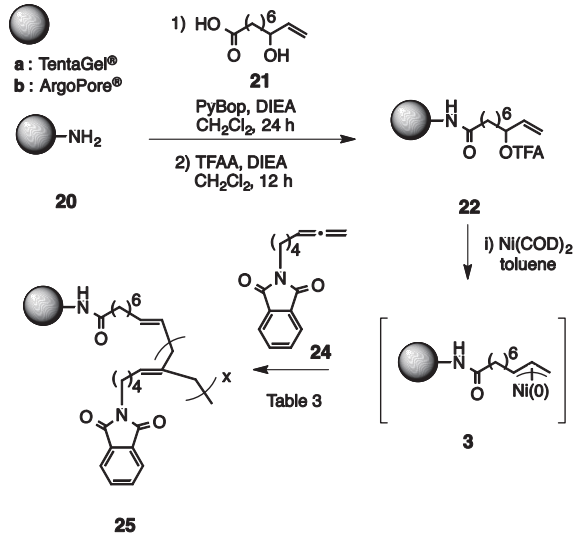
Scheme 3. Flurorination of the copolymer **16**.

Table 2
Fluorination of the copolymer **16**

Entry	*M*	Time (min)	Temp (°C)	Yield of **17** (%)	Yield of **18** (%)
1	K	15	95	74	22
2	K	5	95	36	Trace
3	K	15	50	67	20
4	Na	15	95	0	0
5	Cs	15	95	44	12

resulted in the reduced yield of **17** (44%). Forming a 1:2 complex of cesium ion and the 18-crown ether might promote fluorination.[16]

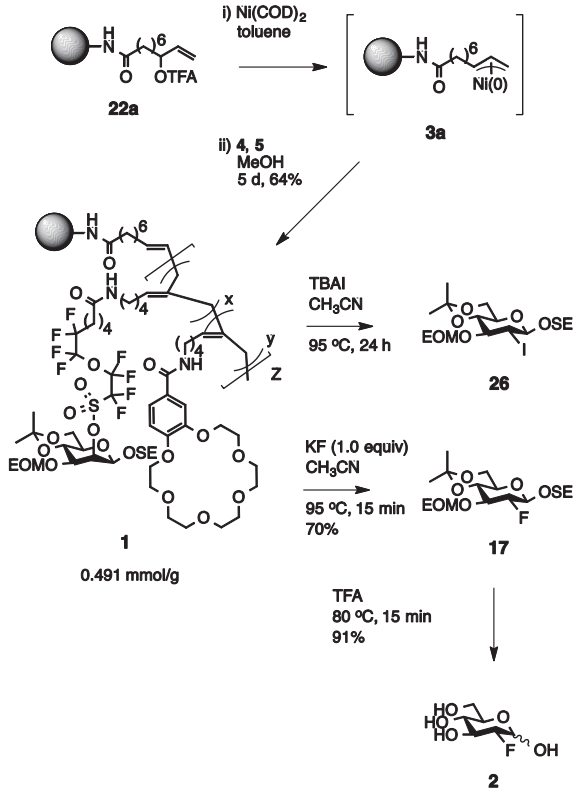
Next the synthesis of the solid-supported copolymer **1** by using the solid-supported π-ally nickel initiator **3** was achieved. We first tested polymerization of polymer-supported initiators **3a** and **3b** attached at two different resins (TentaGel® and ArgoPore®) (Scheme 4 and Table 3). TentaGel® resins are a poly(styrene-oxyethylene) graft copolymers and are swelling with polar solvents. ArgoPore® are macroporous polystyrene resins. Treatment of the amino-functional resins **20a** and **20b** with the carboxylic acid **21** and PyBrop in the presence of DIEA at room temperature till the amino groups were disappeared based on Kaizer Test. Subsequent acylation of the alcohol with TFAA provided the solid-supported allyl trifluoroacetate **22a** and **22b**. Polymerization of allenes **24** by the solid-supported initiator **3a** and **3b** was examined. The solid-supported TFA ester **22a** and **22b** was treated with Ni $(COD)_2$ in toluene at room temperature under nitrogen atmosphere for 20 min. After the resin was washed with toluene by three times, a solution of allene **24** were added at room temperature. The TentaGel®-bound initiator **3a** with monomer **24** were stirring for 18 h at room temperature. On the other hand, ArgoPore®-bound resins **3b** was shaking with monomer **24** under the same reaction conditions because ArgoPore® is mechanically destroyed by stirring with a stirring bar. The yield of the resin-supported polymer **25a** and **25b** was estimated based on the increasing weight of the resin. Use of TentaGel®-bound initiator **3a** in MeOH provided the resin-supported polymer **25a** in the best yield (95%). On the other hand, the ArgoPore®-bound initiator **3b** did not worked in MeOH Stirring should be important for polymerization from the solid-supported initiator **3a**.



Scheme 4. Synthesis of the solid-supported polymer **25**.

Table 3
Polymerization of the allene monroe **24** by the initiators **3a** and **3b**

Entry	Initiator	Solvent	Yield (%)
1	**3a**	CH_3OH	95
2	**3a**	CH_2Cl_2	55
3	**3b**	CH_3OH	0
4	**3b**	CH_2Cl_2	43



Scheme 5. Synthesis of the solid-supported copolymer **1**.

Synthesis of the solid-supported copolymer **1** from the allenes **4** and **5** by the solid-supported initiator **3a** was examined (Scheme 5). The solid-supported TFA ester **22a** was treated with Ni$(COD)_2$ in

toluene at room temperature under nitrogen atmosphere for 20 min to provided the solid-supported π-ally nickel initiator **3**. After the resin was washed with toluene by three times, a MeOH solution of the allenes **4** and **5** were added at room temperature. After being stirring for 5 days at room temperature, the solid-supported copolymer **1** was obtained in 64% yield. The yield of the solid-supported copolymer **1** was estimated based on the increasing weight of the resin. The loading amount of the mannoside was calculated based on a weight of the released 2-iodoglucoside **26** by treatment with a large excess amount of tetrabutylammonium iodide (TBAI) to be 0.491 mmol/g.

Preparation of 2-fluoroglucoside **17** from the solid-supported copolymer **1** was examined. Two equivalents of copolymer **1** was treated with an equivalent of KF in CH_3CN for 15 min. HPLC analysis of the reaction solvents based on a evaporative light scattering detector indicated that fluoride **17** were generated with 81% purity. Separation of the resin through a filter paper, followed by purification of the filtrate provided the fluoride **17** in 70% isolated yield. These results indicated that reactivity of selectivity of the solid-supported copolymer **1** toward fluorination would be comparable with those of the soluble copolymer **16**. Finally, removal of the protecting groups of **17** under acidic conditions provided 2-fluoro-glucose **2** in 80% yield.

In conclusion, we described the synthesis of a solid-supported co-polymer **1** possessing both mannosides and phase-transfer catalysts as a solid-supported reagent for the synthesis of 2-fluoroglycose. We first prepared a soluble copolymer **16** from the allene monomers **4** and **5**. The copolymerization of **4** and **5** via the π-ally nickel-catalyst smoothly proceeded to provide copolymer without decomposition of sulfonate esters. The copolymer exhibited high reactivity towards fluorination in comparison with a mixture of the two monomers **4** and **5** and the heterodimer **19** of the precursor and the phase-transfer catalyst. We next synthesized the solid-supported copolymer **1** by using the solid-supported initiators **3a** attached with TentaGel® resins. TentaGel was suitable for immobilization of the initiator because they are swelling under polar solvents and can be stirred with a stirring bar without decomposition. The solid-supported copolymer **1** exhibited comparable reactivity towards fluorination in comparison with the soluble copolymer **16**. In addition, it can be easily separated from the reaction vessel by filtration. The property of the solid-supported copolymer **1** would be suitable for application to radioisotope labeling experiments. Now we plan to apply the solid-supported reagent **1** to the synthesis of [^{18}F]2-deoxy-2-fluoroglucose.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2015.10.068.

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