

Free Radical Allyl Transfers Utilizing Soluble Non-Cross-Linked Polystyrene and Carbohydrate Scaffold Supports

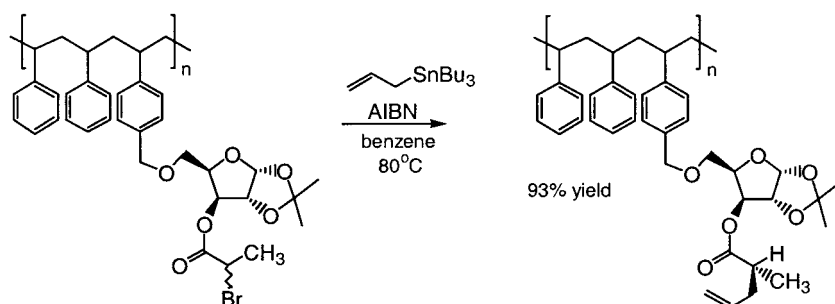
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ABSTRACT



Free radical allylations were studied using (1) soluble non-cross-linked polystyrene supports, (2) carbohydrate scaffolds, and (3) a combination of both synthetic motifs. Allylations on these custom designer supports provide easily purified products, free of tin residues. A D-xylose carbohydrate scaffold bearing a bromoester was used for a diastereoselective allyl tin transfer thermally at 80 °C and with Lewis acids. This is the first example of a diastereoselective radical reaction directed by a removable polymer-supported carbohydrate auxiliary.

Combinatorial chemistry and solid-phase reactions have become important recent developments in organic synthesis, representing a new approach to the preparation of libraries of compounds, pharmaceuticals, and new organic materials.¹ We have recently begun a study of liquid-phase organic chemistry (LPOC) using soluble non-cross-linked polystyrene-supported (NCPS) reactions and reagents.^{2,3} This soluble polymer support differs markedly from the standard Merrifield 2–3% divinylbenzene cross-linked polystyrene polymers currently used extensively.¹

We now report that free radical reactions with allyltributyltin have great synthetic potential with these designer soluble supports (*vide infra*). Compared to the wide spectrum of thousands of reactions now being studied and prepared

for solid-phase work, free radical reactions as a class are very poorly developed in this respect.⁴ As shown in Figure 1, we will initially use the NCPS protocol in two ways: (general approach 1) soluble polymer-supported free radical

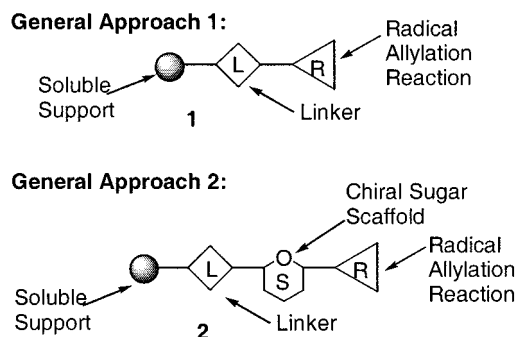


Figure 1. Two approaches to radical reactions on soluble support.

(1) (a) Mendonca, A. J.; Xiao, X. Y. *Med. Res. Rev.* **1999**, *19*, 451–462. (b) Gordon, K.; Balasubramanian, J. *J. Chem. Technol. Biotech.* **1999**, *74*, 835–851 (c) Brown, A. R.; Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. C. *Synlett* **1998**, 817–820.

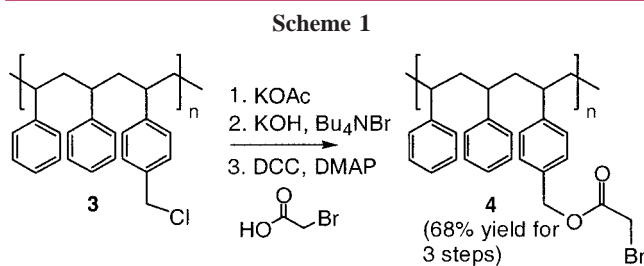
(2) Enholm, E. J.; Gallagher, M. E.; Lombardi, J. S.; Moran, K. M. Schulte, J. P., II. *Org. Lett.* **1999**, *1*, 689–691.

(3) Enholm, E. J.; Schulte, J. P., II. *Org. Lett.* **1999**, *1*, 1275–1277.

reactions and linking agents, and (general approach 2) soluble polymer-supported asymmetric radical reactions using embedded carbohydrates as chiral scaffolds. This reaction represents the first example of diastereoselective radical reaction on soluble support. We hope these two approaches will lead to useful studies in the new and promising field of free radical reactions on soluble support.

Although showing some success, cross-linked resin supports for the current state-of-the-art solid-phase organic chemistry (SPOC) still have many drawbacks to address. Soluble supports for free radical reactions avoid many of these difficulties and have several distinct advantages.⁵ These include (1) complete organic solubility (EtOAc, benzene, CHCl₃, CH₂Cl₂, and THF) of compounds, (2) more reactive sites on the polymer, providing a substantial 2- to 3-fold increase, (3) ability to stir reactions with a standard stir-bar, (4) convenient monitoring of radical reactions by standard ¹H NMR spectroscopy without cleavage from polymer support, and (5) virtually quantitative yield of allylated products after the radical reaction, obtained as tin-free white crystalline-like solids from cold methanol.^{2,3}

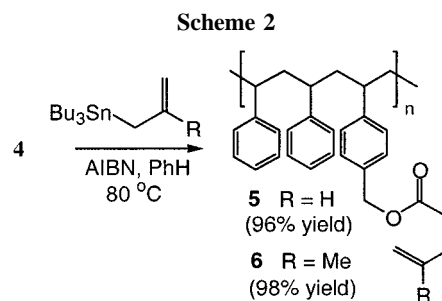
Benzyl chloride NCPS polymer **3**, prepared by radical polymerization of styrene (2 equiv) and *p*-chloromethylstyrene (1 equiv) was converted to a benzyl alcohol via an ester displacement followed by a saponification, as shown in Scheme 1. Bromoester **4** was then prepared by a coupling



reaction with DCC and bromoacetic acid (68% for three steps). Treatment of **4** with allyltributyltin and methallyltributyltin under free radical conditions, shown in Scheme 2, provided two allylated products **5** (96% yield) and **6** (98% yield) with near quantitative recovery of the polymer and complete conversion as determined by ¹H NMR. The

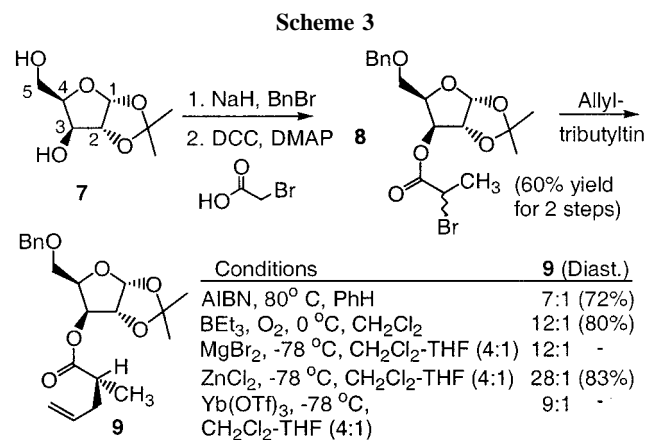
(4) (a) Sibi, M. P.; Chandramouli, S. V. *Tetrahedron Lett.* **1997**, *38*, 8929–8932. (b) Miyabe, H.; Konishi, C.; Naito, T. *Org. Lett.* **2000**, *2*, 1443–1445. (c) Jia, G. F.; Iida, H.; Lown, J. W. *Synlett* **2000**, 603–606. (d) Wendeborn, S.; De Mesmaeker, A.; Brill, W. K. D.; Berteina, S. *Acc. Chem. Res.* **2000**, *215–224*. (e) Jeon, G. H.; Yoon, J. Y.; Kim, S.; Kim, S. S. *Synlett* **2000**, 128–130. (f) Miyabe, H.; Ueda, M.; Yoshioka, N.; Yamakawa, K.; Naito, T. *Tetrahedron* **2000**, *56*, 2413–2420. (g) Miyabe, H.; Tanaka, H.; Naito, T. *Tetrahedron Lett.* **1999**, *40*, 8387–8390. (h) Caddick, S.; Hamza, D.; Wadman, S. N. *Tetrahedron Lett.* **1999**, *40*, 7285–7288. (i) Berteina, S.; De Mesmaeker, A.; Wendeborn, S. *Synlett* **1999**, 1121–1123. (j) Zhu, X. W.; Ganesan, A. *J. Comb. Chem.* **1999**, *1*, 157–162. (k) Yim, A. M.; Vidal, Y.; Viallefont, P.; Martinez, J. *Tetrahedron Lett.* **1999**, *40*, 4535–4538. (l) Miyabe, H.; Fujishima, Y.; Naito, T. *J. Org. Chem.* **2000**, *64*, 2174–2175. (m) Watanabe, Y.; Ishikawa, S.; Takao, G.; Toru, T. *Tetrahedron Lett.* **1999**, *40*, 3411–3414. (n) Berteina, S.; Wendeborn, S.; De Mesmaeker, A. *Synlett* **1998**, 1231–1233.

(5) Wentworth, P.; Janda, K. D. *J. Chem. Soc., Chem. Commun.* **1999**, 1917–1924.



allylated esters **5** and **6** were hydrolyzed to give pentenoic acid and 4-methyl-4-pentenoic acid, respectively. The loading of the soluble polymer **3** was near quantitative as determined by ¹H NMR, or a very high 2.7–3.0 mmol/g.

Once we had established that NCPS polymers functioned well in radical allylations and organotin byproducts could be removed by precipitation of the products, we turned our attention to diastereoselective allylations using the protected *D*-xylose pentose **7** as a means of asymmetric control (Scheme 3).⁶ We reasoned that with a C₁–C₂ acetonide



effectively blocked the α -face oxygens of **7** for chelation. The remaining oxygens at C₃, C₄, and C₅ would be available for a tridentate chelate on the β -face of the ring. An initial concern was that the sugar would be too far from the reacting radical center at the C₃-carbon would exert almost no control in an allyl transfer. A second concern was the effect the polymer backbone would have on the diastereoselectivity of the reaction. A third concern was the potential for cleavage of the sugar from the backbone in the presence of strong Lewis acids.

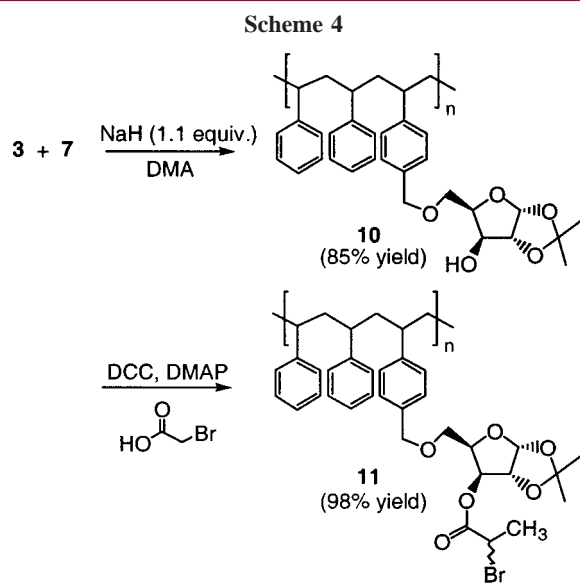
Because carbohydrates have not been studied as removable chiral auxiliaries for radical reactions, this reaction had to be separately investigated off-support, as shown in Scheme 3. Thus, α -bromo ester **8** was prepared from commercially available xylose derivative **7**. Protection of the C₅-hydroxyl in **7** as a benzyl ether, followed by DCC-mediated coupling

(6) Enholm, E. J.; Jiang, S. *J. Org. Chem.* **2000**, *65*, 4756–4758.

of α -bromopropionic acid with the secondary C₃-alcohol afforded compound **8**. Treatment of **8** with allyltributyltin under free radical conditions produced the allylated ester **9**.

This reaction was studied using several Lewis acids and temperatures, with the goal of determining what conditions provided the best diastereoselectivity. Diastereomeric ratios for **9** ranged from 7:1 to 12:1 for reactions in which no Lewis acids were added. We assumed that the byproduct tributyltin bromide and/or BEt₃ were functioning as Lewis acids in these reactions. Lower temperature played a role in increasing the diastereoselectivity in these reactions. The best conditions were observed using ZnCl₂ at -78 °C, which gave a gratifying 28:1 diastereomeric ratio (83% yield) for **9**.

The NCPS support **3** was covalently linked via an ether bond to sugar **7** in Scheme 4 with NaH (1.1 equiv), resulting

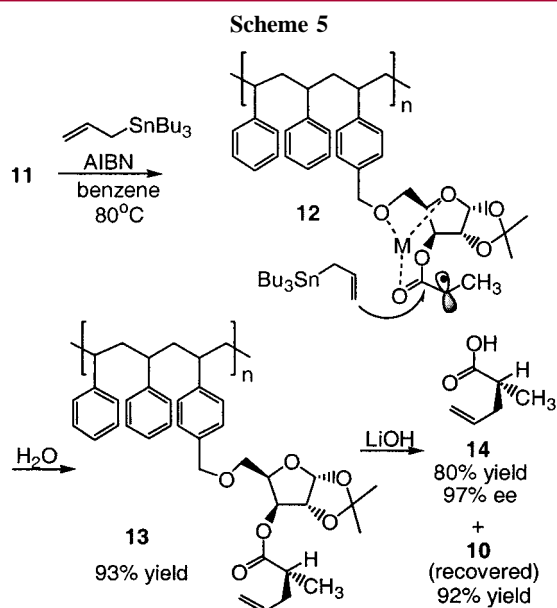


in the polymer-supported carbohydrate **10**. Increased base resulted in a hard polymer by cross-linking. Esterification of the remaining C₃-hydroxyl with bromoacetic acid, as before, constructed **11** in 98% yield. Treatment of **11** with allyltributyltin, under free radical conditions, gave **13** in 93% yield as shown in Scheme 5. All attempts to add Lewis acids

(7) Riley, R. G.; Silverstein, R. M. *Tetrahedron* **1974**, *30*, 1171

(8) Sibi, M. P.; Ji, J. *J. Am. Chem. Soc.* **1996**, *118*, 3063–3064.

(9) This experiment also confirms the stereochemistry of **9**.



resulted in cleavage of the sugar from the polymer backbone at the benzyl ether site. Thermal conditions functioned best presumably with M = ⁿBu₃SnBr, formed during the allylation, as the Lewis acid in **12**.⁸ Although these conditions are usually not conducive to high diastereoselectivity, we were surprised to find the results were excellent here. This was confirmed by base treatment of **13** to give (*R*)-(-)-2-methyl-4-pentenoic acid **14** (97% ee,⁷ 80% yield) and recovered polymer **10** (92% yield) as a white precipitated powder.⁹

In conclusion, free radical allylations were studied using soluble non-cross-linked polystyrene supports and embedded carbohydrate scaffolds. These designer supports provide crystalline-like products, free of tin residues. The first diastereoselective radical reaction directed by a supported carbohydrate auxiliary was also reported.

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Supporting Information Available: Procedures and spectral data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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