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Novel Polymer-Bound Chiral Selenium Electrophiles

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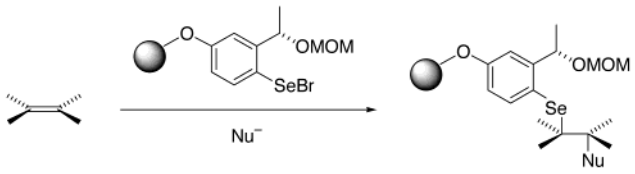
ABSTRACT



Polymer-bound chiral electrophilic selenium reagents have been developed and applied to stereoselective selenenylation reactions of various alkenes. Different cleavage protocols allow further functionalization of the addition products leading to improvements in selenium-based solid-phase chemistry.

Polymer-supported reagents have attracted growing interest because they can provide attractive and practical methods for combinatorial chemistry and solid-phase synthesis.[1] The demand of a fast access to complex structures has led to a large improvement of this methodology during the past years. Although polymers with selenium functionalities have been known for a long time,[2] there is a high interest in this kind of solid-phase organic chemistry. Recently, selenium-based approaches for solid-phase chemistry have been reported from different research groups.[3] New linking strategies with various loading and cleavage protocols now make use of the selenium moiety for further functionalizations of the product molecules. The development of chiral selenium electrophiles has already established a very efficient tool for the highly stereoselective synthesis of various molecules.[4] We have already reported first applications of this chemistry to solid-phase synthesis[3l] and describe herein more efficient polymer-bound reagents leading to further improvements in selenium-based solid-phase chemistry.

It is known that the counterion of the selenium electrophile plays an important but still not well understood role in the addition reactions. Our solution-phase studies revealed that chiral selenenyltriflates lead to highest selectivities and yields.[5] Their preparation is, however, accompanied with the formation of colloidal silverbromide, and if applied to the polymer-bound reagents, they were found to be no longer reactive in subsequent reactions with alkenes. Therefore, it

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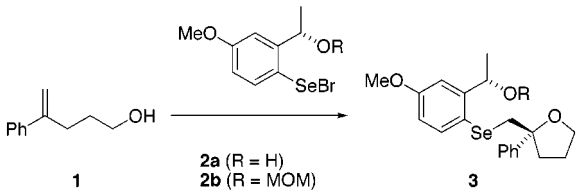
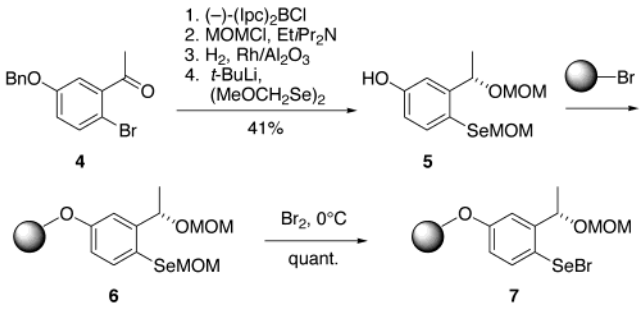
was first necessary to optimize the conditions for additions with selenenylbromides in solution-phase reactions. The unsaturated alcohol **1** has been cyclized with selenenylbromides **2** leading to the products with 57% de (**3a**, R = H) and 75% de (**3b**, R = MOM), respectively, showing again the advantage of a protected chiral side chain with a MOM substituent.[3l]

Scheme 1. Solution-Phase Selenenylations with Chiral Selenenyl Bromides



After these promising results, we prepared the corresponding selenenylbromide on solid support as shown in Scheme 2. Because the cleavage of selenomethyl ethers to the

Scheme 2. Synthesis of Reagent **7** on Solid Support

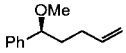
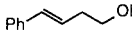
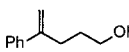
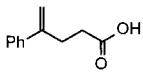
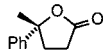
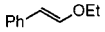
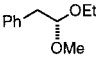


corresponding selenenylbromides failed,[3c,l,6] we again took advantage of the mixed acetal moiety, which was recently introduced by us as a very versatile precursor to generate selenenyl bromides on solid support under mild reaction conditions.[3l] Phenol **5** was prepared from **4**[7] and attached to either polystyrene, TentaGel, or mesoporous silica[8] as a solid support, yielding compounds of type **6**. Although the handling of mesoporous silica is simple because the material has a rigid structure, does not swell in solvents, and can be used at low temperatures, the loading achieved was quite low (between 0.12 mmol/g and 0.3 mmol/g as determined by elemental analysis).

It was shown that the reagents bound to mesoporous silica are little superior to polystyrene, whereas the reagent with TentaGel as a solid support was much less successful in the subsequent selenenylation reactions. All following reactions have been carried out with polystyrene (loading about 2 mmol/g) or with mesoporous silica (loading 0.12−0.3 mmol/g) as the solid support. Because of the low loading of the reagents bound to mesoporous silica, yields have not been determined in selenenylation reactions with this reagent, although the selectivities were found to be a little bit more efficient than with the polystyrene-based reagent. By treating **6** with bromine at 0 °C, **7** is obtained quantitatively.

Various addition reactions to alkenes with the polymer-bound selenium electrophile **7** have been performed. The products **9** obtained after subsequent cleavage from the solid support are summarized in Table 1. Up to 80% ee in the

Table 1. Selenenylation of Different Alkenes with Reagent **7** and Subsequent Cleavage from the Solid Support Using Different Methods

entry	alkene	product **9**[a]	yield (**9**)[b]	e.r. product
1			n.d. 60%	4:1 (61% *ee*)[c] 3:1 (51% *ee*)[d]
2[e]			44%	3:1 (52% *ee*)[d]
3			n.d. 54%	4:1 (60% *ee*)[c] 3:1 (53% *ee*)[d]
4			n.d. 58%	9:1 (80% *ee*)[c] 6:1 (71% *ee*)[d]
5			n.d. 72%	8:1 (78% *ee*)[c] 5:1 (69% *ee*)[d]
6			70%	3:1 (46% *ee*)[d]
7[f]			56%	3:1 (48% *ee*)[d]

[a] Major enantiomer is shown. [b] Yields determined by GC with an internal standard (naphthalene); n.d., not determined. [c] Reaction carried out using mesoporous silica bound reagent **7** (Et_2O, −100 °C). [d] Reaction carried out using polystyrene-bound reagent **7** (Et_2O, −78 °C). [e] Allyltributyltin used instead of tributyltin hydride for the radical cleavage reaction. [f] Cleavage by oxidative elimination with hydrogen peroxide.

products can be obtained in the selenenylation reactions, making the reagent **7** on solid support almost equally attractive for organic synthesis as their soluble counterparts with respect to the stereoselectivities. For ease of handling, they are much more convenient because the workup of these reactions is only filtration and washing of the resin. Usually the radical cleavage of the product is performed by treating the resin with 5 equiv of tributyltin hydride and AIBN in refluxing benzene for 3 h (Table 1, entries 1, 3−6). Other reactions such as radical cyclizations[3f] or elimination

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reactions[3d,g−i] can be used as alternative cleavage methods to simultaneously functionalize the products. Using 10 equiv of allyltributyltin instead of tributyltin hydride transfers an allyl moiety to the product as shown in Table 1 (entry 2). Because the tin reagents are very difficult to separate from the quite volatile product molecules **9**, a product purity was not determined for these reactions. Cleavage by oxidative elimination via the selenoxide leads to chiral allylic ethers (Table 1, entry 7). The selenoxide is generated by adding 10 equiv of hydrogen peroxide in THF to the polymer and stirring for 3 h at room temperature. The purity in this case was determined to be >95%.

Although selenenylation of enolethers has been known for a long time[9] and is an established concept for glycosylation in carbohydrate chemistry,[10] we employed (*E*)-*β*-ethoxystyrene in the methoxyselenenylation, and after radical cleavage the acetal (Table 1, entry 6), with the acetal-carbon being the only chiral atom in the molecule, was obtained.[11] The absolute stereochemistry of this compound was assigned by reduction of an addition product obtained in a homogeneous reaction and comparison to a known compound as described in the Supporting Information.

The selenium-containing molecule is removed completely by filtration, and the reagent can be regenerated by treatment with CsF and MOMCl via the MOM-derivative **6**.[12] This procedure was, however, applied successfully only for the TentaGel-based polymer **6**.

In conclusion, we have synthesized efficient chiral selenium electrophiles on solid support. These reagents have successfully been used to add to various alkenes with reasonable stereoselectivities. They should find useful applications in solid-phase synthesis and probably also in combinatorial chemistry as a result of their versatility and ease of handling. In the future we would like to extend these polymer-bound selenium-containing reagents toward natural product synthesis, as well as toward catalytic applications for various reactions.[13]

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

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