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New Sulfur- and Selenium-Based Traceless Linkers—More than just Linkers?

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Linkers that enable the release of unfunctionalized hydrocarbons (alkanes, alkenes, arenes) from insoluble supports are attracting considerable interest.[1] Such "traceless" linkers can give access to compound libraries devoid of a common functional group that was required for covalent attachment of the intermediates to the support. The production of highly diverse libraries by solid-phase synthesis should, therefore, be possible with such linkers. Herein some new strategies for traceless linking based on the cleavage of C-S or C-Se bonds are presented.

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Sulfur-Based Linkers

The carbon – sulfur bond in thioethers can be cleaved by photolysis[2] or with reducing agents such as Raney nickel or tin hydrides.[3] These cleavage conditions are not easily adapted to parallel synthesis, and only a few examples of thioether-based traceless linking have been reported.[2, 3] Sulfones, available by oxidation of thioethers with *m*-chloroperbenzoic acid (MCPBA), are generally too stable to undergo homolytic or heterolytic C–S bond cleavage under suitably mild conditions to yield unfunctionalized hydrocarbons.[4] More reactive than thioethers or sulfones, however, are trialkylsulfonium salts, which can be prepared on cross-linked polystyrene by the S-alkylation of thioethers with trialkyloxonium salts. Polystyrene-bound trialkylsulfonium salts have recently been introduced by Wagner and Mioskowski et al.[5] as new traceless linkers for the preparation of

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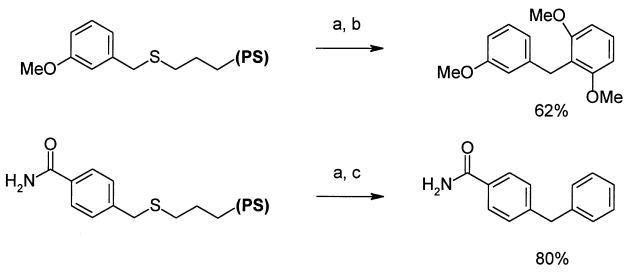
diarylmethanes (Scheme 1). These salts undergo reaction with soft nucleophiles such as iodide,[6] or, upon catalysis by palladium(0), with arylboronic acids.[5]

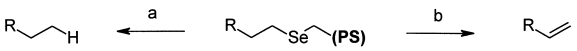


Scheme 1. Synthesis of diarylmethanes from benzyl thioethers. a) Et_3OBF_4 (5 equiv), CH_2Cl_2, 0–20 °C, 8 h; b) 2,6-dimethoxyphenylboronic acid (1–2 equiv), [Pd(dppf)Cl_2] (0.2 equiv), K_2CO_3 (3 equiv), THF, 60 °C, 14 h; c) phenylboronic acid (1–2 equiv), [Pd(dppf)Cl_2] (0.2 equiv), K_2CO_3 (3 equiv), THF, 60 °C, 14 h. (PS) = cross-linked polystyrene; dppf = 1,1′-diphenylphosphanylferrocene.

Unfortunately, this new linking strategy is hampered by some problems. These include the formation of biaryls by homocoupling of the arylboronic acid and the contamination of the crude products with nonvolatile byproducts (various salts, excess boronic acid). Furthermore, it remains to be evaluated which functional groups will undergo irreversible alkylation during treatment with the trialkyloxonium salt. The concept of using a thioether as a linker is, however, highly attractive because thioethers are chemically inert under a broad selection of reaction conditions. If the S-alkylation required for activating the linker proceeds with high chemoselectivity, further nucleophiles or cleavage strategies based on trialkylsulfonium salts might offer interesting possibilities.

Selenium-Based Linkers

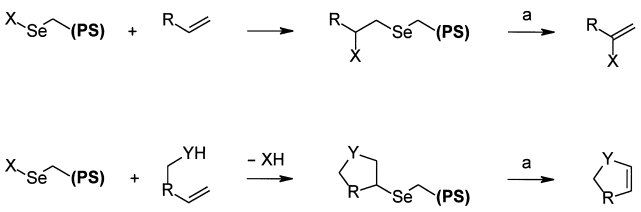
Polystyrene-bound selenides have proven to be versatile traceless linkers, which give access to alkanes by homolytic C–Se bond cleavage, and to alkenes by oxidation followed by β-elimination (Scheme 2).[7] Oxidative cleavage of selenides



Scheme 2. Selenides as linkers for alkanes and alkenes. a) Bu_3SnH, AIBN, heat; b) oxidant, heat. (PS) = cross-linked polystyrene; AIBN = azobisisobutyronitrile.

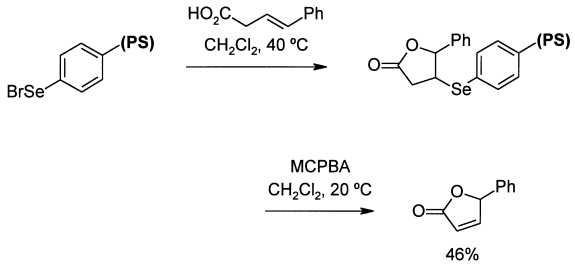
proceeds more readily than the cleavage of sulfoxides or sulfones. Since such oxidative cleavage is feasible with volatile reagents (for example, H_2O_2), it appears to be well suited for parallel synthesis.

Strategies for preparing selenides on insoluble supports include aliphatic nucleophilic substitution with anionic selenium reagents and the oxidative addition of support-bound electrophilic selenium reagents to alkenes.[7] If alkenes containing a nucleophilic functionality are treated with support-bound electrophilic selenium reagents, cyclization can occur during the attachment to the support (Scheme 3).

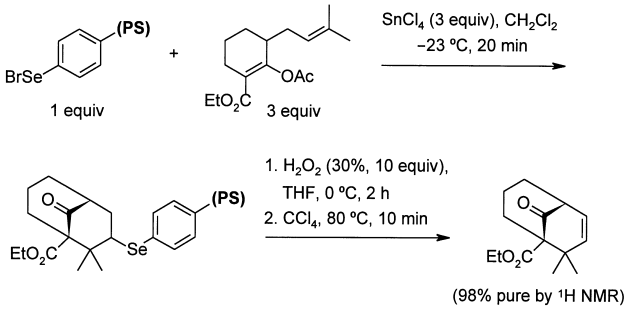


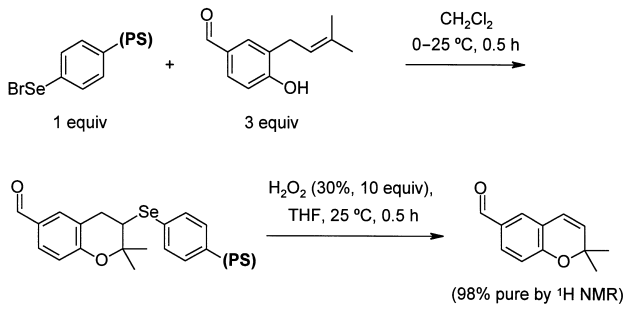
Scheme 3. Electrophilic selenium reagents as linkers for alkenes. a) Oxidant, heat. X = Br, CN, phthalimidyl; (PS) = cross-linked polystyrene.

Some of the few examples reported for oxidative cyclizations with polymer-bound selenium reagents are shown in Schemes 4 and 5. Fujita et al.[8] recently used polystyrene-bound selenyl cyanides and selenyl bromides to prepare γ-lactones (Scheme 4). The selenolactonization of 4-phenyl-3-butenoic acid with selenyl cyanides required high reaction temperatures and catalysis by copper(II) chloride. Selenyl bromides, however, underwent smooth addition in dichloromethane without the need of any catalyst. Cleavage was effected by treatment with MCPBA in dichloromethane.[8]



Scheme 4. Preparation of γ-lactones by selenolactonization with an insoluble selenyl bromide. (PS) = cross-linked polystyrene with a spacer; MCPBA = *m*-chloroperoxybenzoic acid.





Scheme 5. Synthesis of bicyclo[3.3.1]nonan-9-ones and 2,2-dimethyl-2*H*-chromenes by oxidative cyclization with support-bound selenyl bromide. (PS) = cross-linked polystyrene.

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Nicolaou et al. utilized a similar strategy to construct carbon frameworks relevant to the synthesis of natural products on insoluble supports. Treatment of suitable precursors with polystyrene-bound selenyl bromide led to the formation of bicyclo[3.3.1]nonan-9-ones[9] and 2,2-dimethyl-2*H*-chromanes[10] (Scheme 5).

Selenides are inert towards a broad range of reaction conditions, such as the treatment with strong bases, organolithium reagents, and alkylating reagents. Also prolonged heating (for example, 140 °C, 48 h) does not lead to the cleavage of C–Se bonds. This stability was exploited in a multitude of transformations carried out with polystyrene-bound 2,2-dimethyl-2*H*-chromane-derived selenides (Scheme 5).[11]

Conclusion

Chalcogen-based traceless linkers enable the solid-phase synthesis of products which were formerly only accessible by tedious, multistep solution-phase chemistry. Some of the newer linkers can be cleaved with volatile reagents and tolerate a broad range of reaction conditions, which gives the chemist plenty of freedom in the design of new synthetic sequences. Interestingly, support-bound electrophilic selenium reagents can also mediate useful chemical transformations of substrates during their attachment to the support, and thereby function as reagents as well as linkers.

Future developments should further focus on cleavage protocols that yield crude products devoid of nonvolatile by-products. Such cleavage strategies enable the preparation of essentially pure crude products, as required for the parallel synthesis of compound libraries. New traceless linkers cleavable with volatile reagents would be a useful supplement to existing methodologies, and would have the potential of finding widespread application.

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