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PS-COD and PS-9-BBN: Polymer-Supported Reagents for Solution-Phase Parallel Synthesis[†]

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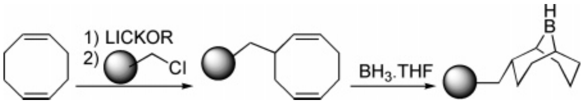
ABSTRACT



1,5-Cyclooctadiene was deprotonated under LICKOR conditions and reacted with Merrifield resin to afford an immobilized cyclooctadiene in high yield. This polymer is effective as a halogen scavenger, while hydroboration leads to a supported 9-BBN analogue. The latter exhibits similar regioselectivity to 9-BBN in olefin hydroboration.

Phase separation methods are central[1] to the implementation of high-throughput organic chemistry. Solid-phase synthesis facilitates the use of large reagent excesses to drive reactions forward, as workup is achieved by simple filtration. Nevertheless, the method has other limitations, and hybrid technologies have evolved to combine the desirable features of solution- and solid-phase synthesis. One attractive option[2] involves the immobilization of reagents or scavengers for reaction workup, rather than the compound being made. The Ley group in particular has devised numerous multistep routes[3] that rely solely on such processes.

Despite the many reported as well as commercially available immobilized reagents and scavengers, significant gaps exist in our armamentarium. For example, among reducing agents, borane was coordinated[4] to a Lewis basic polymer or immobilized with a chiral ligand[5] as pioneered by Itsuno for enantioselective reductions. Meanwhile, immobilized alkylboranes are unprecedented in the literature. Our objective was a polymer-supported version of the reducing agent 9-borabicyclo[3.3.1]nonane (9-BBN). Due to its ease[6] of preparation, high stability in air, and exceptional regioselectivity[7] in hydroboration, 9-BBN is a popular[8]

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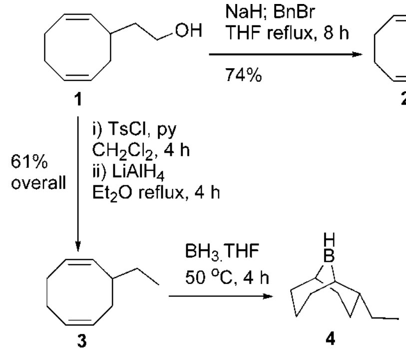
reducing agent as well as a precursor to other synthetically useful boron reagents.

9-BBN is synthesized by the hydroboration of 1,5-cyclooctadiene. For immobilization, a means for attaching 1,5-cyclooctadiene to polystyrene resins needs to be developed. Recently, we have shown[9] that the anion generated by deprotonation of 1,5-cyclooctadiene under "LICKOR" (BuLi/KO*t*-Bu) superbase conditions is cleanly alkylated at the allylic position. Thus, reaction with ethylene oxide yielded[9] hydroxyethyl cyclooctadiene **1** (Scheme 1). Conversion to the benzyl ether **2** provided a solution-phase model for the attachment of **1** to chloromethyl polystyrene. Reaction of **2** with borane gave a white solid, which, however, did not behave as a hydroborating agent. While the reasons for this failure are not fully understood, the presence of the oxygen functionality in **2** is a likely complication. Instead, **1** was reduced in two steps to ethylcyclooctadiene **3**, which upon hydroboration and removal of volatile species afforded **4** as a colorless glass. This was immediately reacted with 4-vinyl-1-cyclohexene. Upon oxidative workup, the desired 4-(1-hydroxyethyl)-cyclohexene was isolated in 67% yield, together with ethyl cyclooctanediol (91%) arising from **4**. Hydroboration of the internal olefin in 4-vinyl-1-cyclohexene was not observed, confirming that the hydroboration was due to a 9-BBN-like species and not adventitious borane.

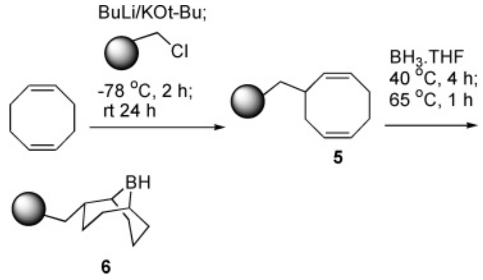
Scheme 1. Solution-Phase Models for Immobilized 9-BBN



Buoyed by this success, we set out to attach **1** via a nonheteroatom linker to polystyrene. The alcohol was converted to the corresponding bromide (PBr$_3$, 66%), which was then added to lithiated polystyrene resin, prepared either by the direct deprotonation[10] of polystyrene or the lithium−halogen exchange[11] of bromopolystyrene. Subsequent reaction with BH$_3$ presumably generated an immobilized 9-BBN analogue. However, alkene hydroboration/oxidation using these resins was poor (∼10%) due to poor yields in the alkylation step. Although lithiated polystyrene reacts well with some electrophiles, we are unaware of examples with unactivated alkyl halides.

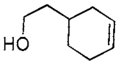
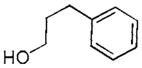
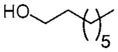
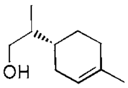
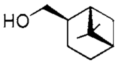
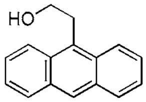
These difficulties led us to explore direct alkylation of deprotonated 1,5-cyclooctadiene (under LICKOR conditions) by high-loading Merrifield chloromethyl polystyrene resin (Novabiochem, 4.55 mmol/g by chloride microanalysis, Scheme 2). After alkylation, a significant increase in mass was noted for the dried resin. On the basis of residual chloride microanalysis (0.45 mmol/g), resin **5** (PS-COD) has a loading of 3.85 mmol/g. Hydroboration of **5** afforded PS-9-BBN **6**, with a loading of 3.24 mmol/g by boron microanalysis. Gel-phase ^{11}B NMR of **6** shows two peaks at δ 28.0 and 19.8 ppm relative to BF$_3$·OEt$_2$. The smaller peak at 28.0 is similar to that of commercially available 9-BBN, known to exist as a dimer. We attribute the larger resin peak to the monomeric form, dimerization presumably being inhibited by the resin environment.

Scheme 2. Synthesis of PS-COD and PS-9-BBN



Hydroboration of limonene with resin **6** (PS-9-BBN) resulted in an immobilized trialkylborane. Several conditions were investigated for oxidative release to *p*-menth-1en-9-ol: (i) aq H$_2$O$_2$ and methanolic Bu$_4$NOH in THF (66%); (ii) aq H$_2$O$_2$ and NaOH in THF (59%); (iii) Me$_3$NO (66%); (iv) NaBO$_3$ in aq THF (0%). On the basis of these results, H$_2$O$_2$/Bu$_4$NOH was selected as the method of choice, and a set of alkenes was subjected to hydroboration/oxidation by PS-9-

Table 1. Alkene Hydroboration−Oxidation with PS-9-BBN

alkene	product[a]	yield[b]
4-vinyl-1- cyclohexene		60
allylbenzene		53
1-octene		56
(+)-limonene		66
β-pinene		59
9-vinylanthracene		35

[a] Reaction conditions: (1) PS-9-BBN, 3 equiv of alkene, THF, 40 °C, 24 h. (2) 3 equiv of Bu$_4$NOH (1 M in MeOH), 5 equiv of aq H$_2$O$_2$ (35%), THF, rt 1 h; 50 °C, 3 h. [b] Percentage yield of isolated product.

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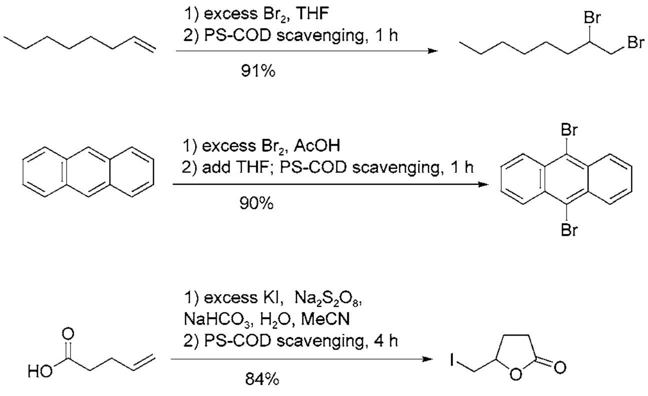
BBN (Table 1). Reaction workup consisted simply of concentrating the supernatant and passage through a short silica plug (1:9 EtOAc/hexanes eluent). Solvent removal provided the alcohol products in excellent purity, as determined by NMR comparison with authentic standards.

In the above hydroborations, PS-9-BBN was treated as the limiting reagent and the alkene added in excess. For applications with precious alkenes, higher conversions can be achieved by using the resin in excess. Thus, when a 5-fold excess of PS-9-BBN was used, the hydroboration/oxidation of 1-octene and limonene proceeded in 86 and 89% yields, respectively.

The precursor to PS-9-BBN, PS-COD (**5**), is an interesting resin in its own right, as it is a high-loading resin with close to 8 mmol/g of alkene functionality. Both bromine and iodine add rapidly to PS-COD, and we have exploited this reactivity by using PS-COD as a halogen-scavenging resin (Scheme 3). In the bromination of 1-octene and anthracence, excess bromine was quenched after the reaction by the addition of a 2-fold excess of PS-COD. The anthracene reaction involved acetic acid as a solvent and quenching in this polar medium by the polstyrene-based resin is sluggish. However, addition of THF as a cosolvent resulted in fast scavenging. The other example shown illustrates the removal of excess iodine from an iodolactonization reaction.

Scheme 3. Halogen Scavenging by PS-COD Resin



In summary, we report the synthesis of two new polymer-supported reagents containing novel functionality (1,5-diene for PS-COD, dialkylborane for PS-9-BBN). We show that PS-COD is useful as a halogen scavenger, and it is likely to have additional applications as a diene ligand for organometallic complexes. PS-9-BBN functions as a hydroborating reagent in the same way as its solution-phase counterpart. Both resins feature high loadings (>3 mmol/g) and are readily prepared in large scale by a simple and concise route from inexpensive reagents.

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Supporting Information Available: Experimental procedures for the preparation of PS-COD and PS-9-BBN and their use in halogen scavenging and hydroboration/oxidation, respectively. This material is available free of charge via the Internet at http://pubs.acs.org.

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