Borohydride Exchange Resins (BER) – a Group of Versatile and Powerful Polymer-Supported Reductants

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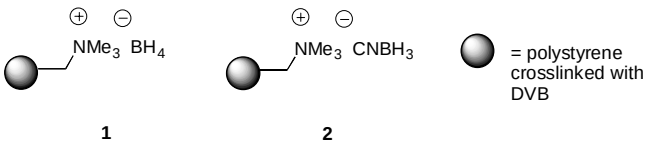
Polymer-supported reagents have seen a renewed interest lately [1]. The dramatic developments in the need for compound library preparation in pharmaceutical and agrochemical industries has moved functionalized polymers from an academic curiosity into a widely recognized synthetic technique. The intrinsic advantage of this hybrid solid/solution phase technique lies in the simple purification typically associated with solid-phase organic synthesis which is combined with the flexibility of solution-phase chemistry. These reagents are typically employed in excess in order to drive the reaction to completion. Furthermore, they may be adapted to continuous flow processes and hence used in automated synthesis.

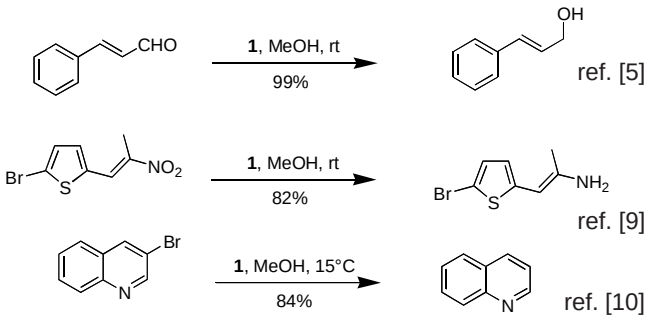
In numerous examples it has been demonstrated that polymeric supports are ideally suited for anchoring reductants. The chemical modification of quaternary ammonium type resins with $NaBH_4$ (**1**) [2] and $NaCNBH_3$ (**2**) furnishes highly efficient and chemoselective reducing agents [3]. These functionalized polymers are simply prepared by passing an aqueous solution of the corresponding sodium salts over a column of macroporous amberlyst A26 or amberlyte IRA 900 (Cls-form) followed by washing with distilled water, methanol and drying *in vacuo* for several hours.



1 **2**

1. Synthetic Applications of Polymer-supported Borohydride

Borohydride containing resins have been utilized in many organic transformations including the reduction of aldehydes and ketones [4], α,β-unsaturated carbonyl-compounds [5], benzyl- and primary alkyl halides [6] and aliphatic acid chlorides [7]. Resin **1** shows remarkable chemoselectivity. *E.g.* in the presence of polymer-bound borohydride, benzaldehyde is exclusively reduced to benzyl alcohol in ethanol while acetophenone remains intact in solution [4]. Their properties have successfully been extended to the selective reduction of α,β-unsaturated cyanoacetates [8] and nitroalkenes [9]. Some selected examples are presented in Scheme 1, giving an indication of the reducing power and the chemoselectivity of reagent **1**.

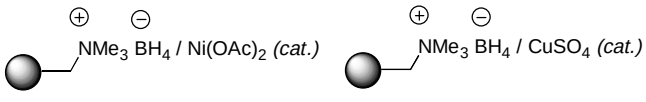


Scheme 1

Furthermore, a special application of these functionalized polymers is the reduction of aryl azides and arylsulfonyl azides to the corresponding aromatic amines and aryl-sulfonamides, respectively, in up to 98% yield [11].

2. Metal-modified Borohydride Exchange Resins

A very important modification of the borohydride exchange resins (BER) is their combination with transition metal salts. Cross-linked poly(4-vinylpyridine)-supported zinc borohydride was used to reduce aldehydes in the presence of ketones in high yields [12]. Likewise, unstable $Zr(BH_4)_4$ could be stabilized on polyvinylpyridine and used as an efficient and regenerable polymer-supported transition metal borohydride reagent [13].



3 **4**

The addition of a catalytic amount of nickel(II) acetate or nickel(II) chloride affords the powerful and highly chemose-

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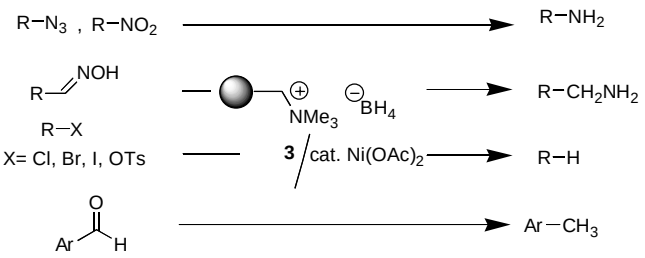
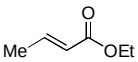
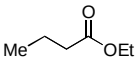
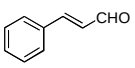
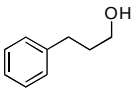
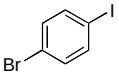
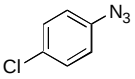
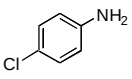
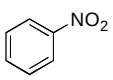
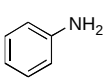
lective functionalized polymer **3** [14] which allows reduction of nitro [15] and azido [16] groups as well as aryloximes [17] to the corresponding primary amines. Alkyl and aryl halides [10, 18], tosylates [18] and remarkably also benzaldehydes [19] are converted into alkanes in moderate to excellent yields.



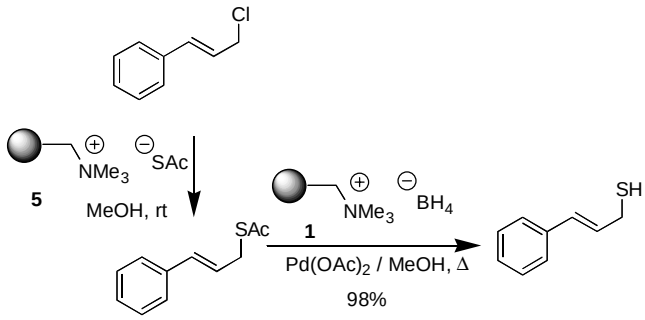
Scheme 2

When borohydride is attached to Amberlite IRA 400 and treated with a catalytic amount of $CuSO_4$, a functionalized polymer **4** with strong reducing properties towards different functional groups is obtained. Some selected examples are listed in table 1 [20]. Reagent **4** is particular useful for the reduction of alkyl halides including aryl iodides as well as azides, aldehydes and ketones. Some functional groups like nitriles and particularly esters as well as amides are poor substrates. Alkenic double bonds when in conjugation with aryl or carbonyl groups are readily hydrogenated.

Table 1 Reductive properties of BER treated with $CuSO_4$ (cat).

Starting material	Conditions	Product	Yield %
	**4**, MeOH 1h, rt		>99
	**4**, MeOH 0.5h, rt		>99
	**4**, MeOH 1h, rt		>99
	**4**, MeOH 1h, rt		97
	**4**, MeOH 6h, rt		94
	**4**, MeOH 3h, rt		98

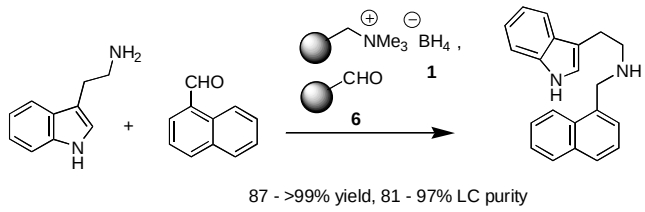
The synthesis of thiols from alkyl halides *via* thioacetates has been achieved with two functionalized polymers (Scheme 3). In the presence of reagent **1**, palladium-catalyzed methanolysis of thioacetates furnishes thiols [21]. Prior to this step, alkyl halides were converted into the thioacetates using the appropriately loaded ion-exchange resin **5**.



Scheme 3

3. Reductive Amination of Carbonyl Compounds

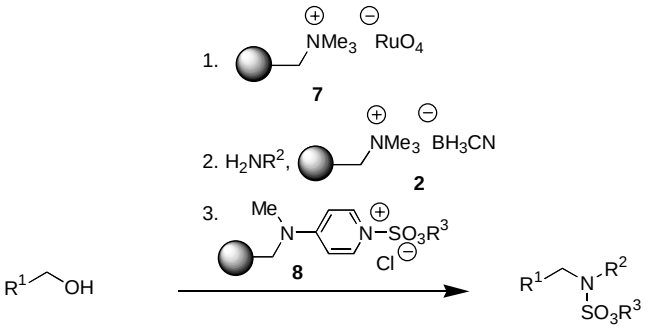
Borohydride-exchange-resin **1** and **2** are ideally suited for use in the reductive amination of carbonyl compounds because workup is highly simplified [22, 23]. The reaction can be driven to completion if the amine is employed in excess and finally removed by addition of polymer-supported carboxaldehyde **6**. By this sequence, a small group of secondary amines was generated (Scheme 4) [24].



Scheme 4

In analogy to these results, libraries of amines and sulfonamides were prepared in a three-step process fully controlled by polymer-supported reagents (Scheme 5) [25]. A set of benzyl alcohols was oxidized to the corresponding aldehydes followed by reductive amination in the usual way using reagents **2** and **7**. Finally, the secondary amines were further functionalized using sulfonated amino pyridine polymers **8** which promote sulfonation to sulfonamides. By using this technique, the preparation of a medium sized compound library was achieved. It should be noted, that polymer-supported synthetic sequences of this kind can be conducted with the same technical equipment for parallization that is used in combinatorial synthesis.

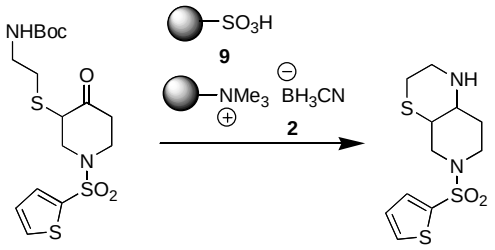
Ley and coworkers developed a route to piperidino-thiomorpholines using a series of polymer-anchored reagents



intermediate amines: 88 examples, 35 - 92% LC purity
sulfonamides: 7 examples, >82% yield, > 90% LC purity.

Scheme 5

(Scheme 6) [26]. During the course of the multistep sequence ion-exchange-mediated removal of a *N*-Boc-protection using acidic reagent **9** allowed for intramolecular imine formation which was followed by polymer-supported reduction with cyanoborohydride (**2**).

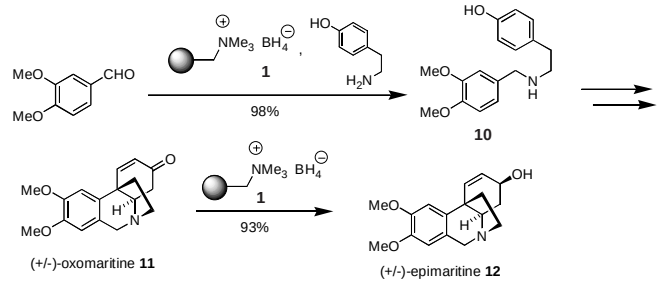


Scheme 6

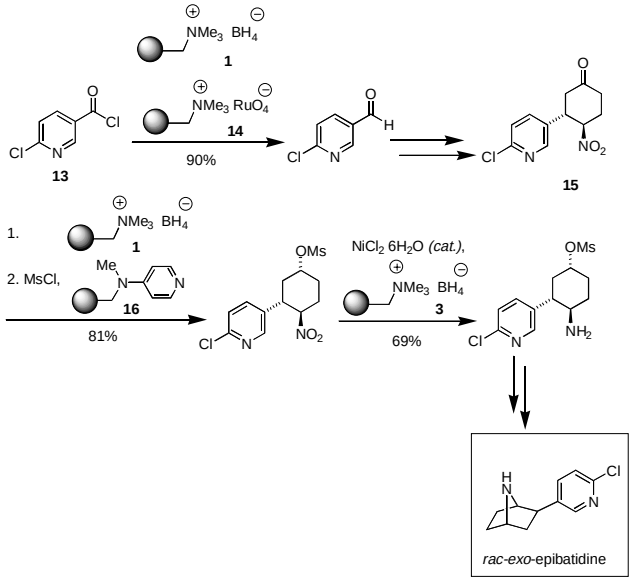
4. Natural Product Synthesis

Reductive amination of aldehydes promoted by functionalized polymers have proven to be important preparative steps in the synthesis of various alkaloids. Thus, a concise synthesis of (+/–)-oxomaritidine (**11**) and (+/–)-epimaritidine (**12**) was achieved by a sequence of five- and six, respectively, consecutive polymer-supported steps (Scheme 7) [27]. The synthesis is initiated by a reductive amination step leading to secondary amine **10**. Further modification of the amino group set the stage for an intramolecular phenolic oxidative cyclization which after a spontaneous intramolecular 1,4-addition of the intermediate amine afforded (+/–)-oxomaritidine **11**. The sequence was terminated by reduction of the keto group to provide (+/–)-epimaritidine (**12**).

For the synthesis of the potent analgesic compound (+/–)-epibatidine, isolated from the Ecuadorian poison frog *Epipedobates tricolor* Ley and coworkers designed an even longer synthetic sequence [28] mainly based on polymer-supported reagents (Scheme 8). Three of these steps involved the use of borohydride exchange resins. Thus, acid chloride **13** was converted into the corresponding aldehyde by a reduction/oxidation protocol using polymer-supported reagents **1** and **14**. Polymer-promoted Henry reaction and elimination followed by thermal Diels–Alder reaction in an undried, sealed vial initially provided *trans*-configured cyclohexanone **15**. The synthesis was continued by polymer-supported reduction of the ketone and mesylation using functionalized polymers **1** and **16**. The amino group was then elaborated by reduction of the nitro group using the nickel-modified BER-reagent **3**. The authors note that polymer-supported borohydride with $NiCl_2$ $6H_2O$ is superior to $NaBH_4$ $6H_2O$. Unlike other hydrogenation methods (H_2 and Rh/Al_2O_3, Pd/C or PtO_2) or transfer hydrogenation protocols (HCO_2NH_4, Pd/C) the polymer-supported reducing agent **3** does not attack the labile chloro substituent of the pyridyl ring. The synthesis of (+/–)-epibatidine was finally terminated by transannular cyclization and epimerization.



Scheme 7



Scheme 8

It is noteworthy that the synthesis was achieved without chromatographic purification, with excellent yields for most steps and importantly with minimum optimization, a clear advantage of functionalized polymers, including BER-reagents.

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