

## Borohydride Exchange Resin



(chemoselective nucleophilic hydride reducing reagent for aldehydes and ketones, and many other functional groups in the presence of metal salt catalysts)

**Physical Data:** loading 2–3 mmol g<sup>-1</sup> of boron on the polymer (batch dependent).

**Solubility:** cross-linked polystyrene divinylbenzene co-polymers are insoluble in all common solvents.

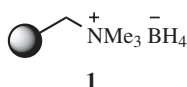
**Form Supplied in:** white microporous or macroreticular solid, available from several large international suppliers.

**Analysis of Reagent Purity:** the loading is usually obtained from elemental analysis.

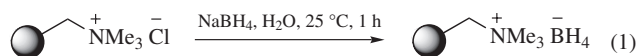
**Purity:** polymer washed using water, then methanol. Drying may be completed in vacuo between 25 °C and 60 °C.

**Handling, Storage, and Precaution:** harmful if inhaled or ingested. Decomposition occurs under acidic conditions to form toxic diborane gas and flammable/explosive hydrogen gas. All reactions should be carried out under a well ventilated fume-hood. Long-term storage should be in a refrigerator under nitrogen.

**Borohydride Exchange Resin (BER).** For many years, insoluble cross-linked polystyrene resins with quaternary ammonium termini have been used as supports for anionic reagents in organic synthesis.<sup>1–14</sup> Polymer bound borohydride was first reported by two independent groups in 1961,<sup>15,16</sup> with the first published reports of borohydride supported on ion-exchange polymer **1** appearing over a decade later.<sup>6,17</sup>



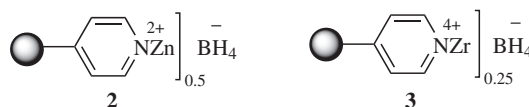
Borohydride exchange resin is available from several commercial suppliers.<sup>18</sup> It can also be prepared by the chemical modification of cross-linked polystyrene-based quaternary ammonium ion exchange polymers. The chloride forms of Amberlyst A-26, Amberlite IRA-400 or Amberlite IRA-900<sup>19</sup> are suspended in an aqueous solution of sodium borohydride for 1 h. The resin is then filtered and washed with distilled water and then methanol before drying under vacuum for several hours (eq 1).<sup>17</sup> After use, the polymeric reagent can easily be regenerated by washing with aqueous hydrochloric acid and water before refunctionalizing as above.



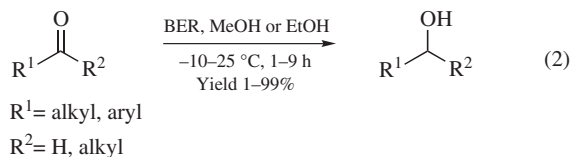
An important modification of reactions with borohydride exchange resin is its use in conjunction with catalytic metal salts which enhance its reducing power.<sup>14</sup>

Supported zinc<sup>20,21</sup> (**2**) and zirconium<sup>22</sup> (**3**) borohydrides have also been prepared on cross-linked poly(4-vinylpyridine). The un-

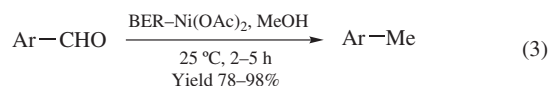
supported forms of these reagents are unstable and require careful storage and use. However, the polymeric versions offer not only greater ease of handling, but can also be stored for several months at room temperature. Furthermore, these poly(4-vinylpyridine)-supported reagents have loadings which are approximately three times higher (~10 mmol g<sup>-1</sup>) than the equivalent polystyrene-based polymers.



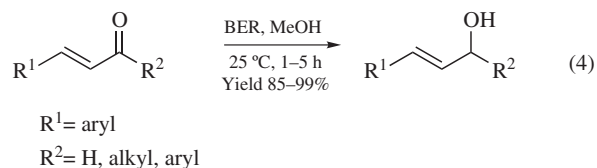
**Reduction of Aldehydes and Ketones.** Borohydride exchange resin readily reduces aldehydes and a variety of ketones to their respective alcohols without affecting esters (except aryl acetates)<sup>23</sup> or amides (eq 2). Reactions can be performed in either methanol or ethanol, but rates of reaction are much higher in methanol. Aldehydes are more reactive towards borohydride exchange resin than ketones and a high level of chemoselectivity has also been observed within these groups.<sup>24</sup>



Enhanced rates of reaction and chemoselectivity have been seen using BER (borohydride exchange resin) with **Lithium Chloride** or **Lithium Nitrate** to reduce carbonyl groups in the presence of other reducible functionalities such as alkenes, amides, halides, nitriles, and nitro groups.<sup>25</sup> Improved rates of reduction also occur when BER is used in conjunction with Ni(OAc)<sub>2</sub> or CuSO<sub>4</sub>. Additionally, nickel catalysis has also been seen to further reduce aromatic aldehydes<sup>26,27</sup> to methyl arenes (eq 3).



When BER reacts with  $\alpha,\beta$ -unsaturated aldehydes and ketones, selective formation of the  $\alpha,\beta$ -unsaturated alcohols occurs with no reduction of the double bond (eq 4).<sup>19,28,29</sup> This is in contrast to sodium borohydride, where conjugate reduction is found to be a substantial competing process.

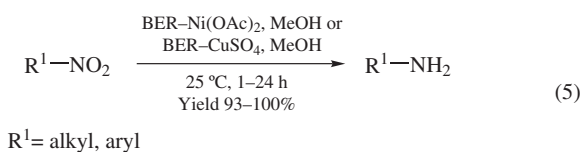


For a comparison, **Amberlyst A-26**, **Amberlyst IRA-400**, and **Sodium Borohydride** on alumina were all tested. The A-26 was more reactive than IRA-400, but both showed similar selectivity. The alumina-supported material reacted fastest but showed reduced selectivity. The importance of the choice of supporting material is also highlighted in an alternative report, where the support used was Seralite-SRA-400. Here a complete reversal of selectivity was reported in which unsaturated ketones are reduced

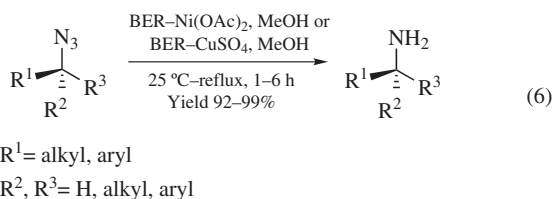
to saturated ketones and  $\alpha,\beta$ -unsaturated aldehydes are reduced to saturated alcohols.<sup>30</sup> Also, if BER is used in conjunction with copper sulfate, most  $\alpha,\beta$ -unsaturated ketones and aldehydes are reduced to the corresponding saturated alcohols.<sup>31</sup>

Poly(4-vinylpyridine)-supported zirconium borohydride is another reliable reagent for reduction of aldehydes or ketones and is reported to leave conjugated double bonds intact.<sup>22</sup> Zinc borohydride on poly- $\eta$ -(pyrazine)<sup>32</sup> can be used as an alternative. However, for absolute selectivity for aldehydes over ketones, zinc borohydride on poly(4-vinylpyridine)<sup>20</sup> can be applied.

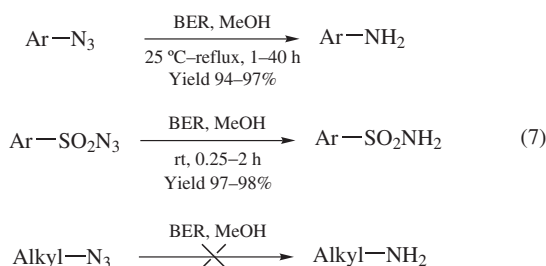
**Reduction of Nitro Compounds.** Uncatalyzed BER reacts with nitroalkenes which are reduced to the respective nitroalkanes.<sup>33</sup> However, it is unable to reduce aliphatic or aromatic nitro groups unless it is employed in conjunction with a transition metal catalyst such as Ni(OAc)<sub>2</sub>,<sup>27</sup> NiCl<sub>2</sub>·6H<sub>2</sub>O,<sup>34</sup> PdCl<sub>2</sub>,<sup>35,36</sup> CuCl,<sup>35</sup> Cu(OAc)<sub>2</sub>·4H<sub>2</sub>O,<sup>35</sup> CuSO<sub>4</sub>,<sup>37</sup> or Ni<sub>2</sub>B.<sup>37</sup> These systems give successful reduction of both aliphatic and aromatic nitro groups to the corresponding amines in excellent yields (eq 5).



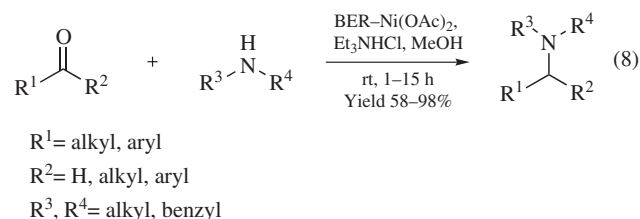
**Reduction of Azides.** For the general reduction of aliphatic and aromatic azides, catalytic nickel acetate<sup>38</sup> or copper sulfate<sup>37</sup> are usually employed, although poly(4-vinylpyridine)-supported Zr(BH<sub>4</sub>)<sub>2</sub> has also been reported to facilitate these reactions (eq 6).<sup>22</sup>



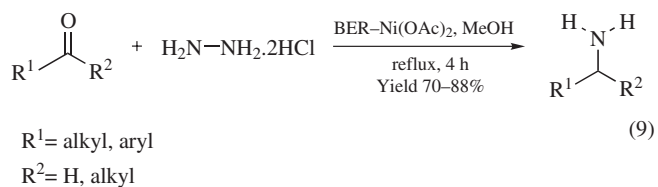
Borohydride exchange resin itself only reduces aryl azides and sulfonyl azides to the corresponding aryl amines and sulfonamides respectively.<sup>39</sup> Aryl azides with electron-withdrawing substituents are readily reduced at room temperature, whereas unactivated phenylic and benzylic azides require reflux for long periods. Aliphatic azides do not react under these conditions (eq 7).



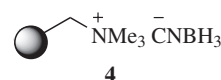
**Reduction of Imines.** BER is useful in the reductive amination of aldehydes and ketones in acidified methanol or ethanol.<sup>40–43</sup> Secondary or tertiary amines are produced in high yield from the reaction between aldehydes and primary or secondary amines (eq 8). Ketones react well when coupled with less hindered aliphatic amines, but low yields are obtained with aromatic amines.



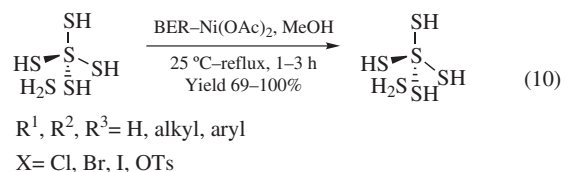
Although secondary and tertiary amines are prepared in good yield using these methods, yields of primary amines are moderate to poor. However, reductive amination of aldehydes and ketones with hydrazine has been found to be a good alternative (eq 9). The intermediate hydrazones undergo N–N cleavage with BER–Ni(OAc)<sub>2</sub> in refluxing methanol to afford the resultant primary amines in good yield.<sup>44</sup>



An alternative reducing reagent for reductive amination is supported cyanoborohydride **4**, which is commercially available or can be prepared in a similar manner to BER using sodium cyanoborohydride and the chloride form of the polymer.<sup>45</sup>



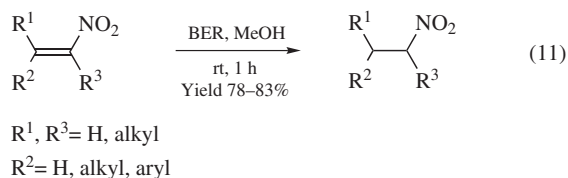
**Reductions of Alkyl and Aryl Halides and Tosylates.** Borohydride exchange resin alone is able to react with only certain halides.<sup>46</sup> However, in the presence of Ni(OAc)<sub>2</sub> most aliphatic or aromatic halides and tosylates are successfully reduced (eq 10).<sup>47,48</sup>



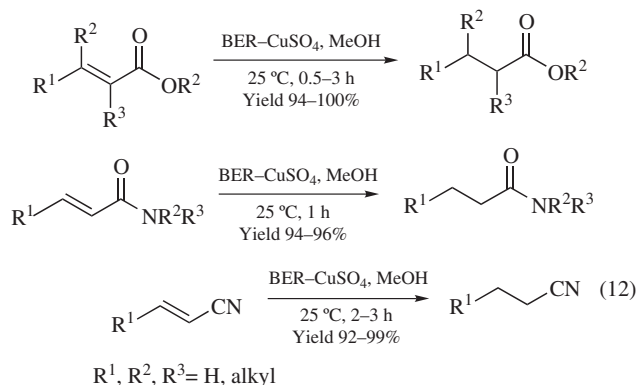
Borohydride exchange resin used in conjunction with CuSO<sub>4</sub> and BER–nickel boride (Ni<sub>2</sub>B) has been successfully employed in the reduction of bromides and iodides or benzylic chlorides.<sup>37</sup>

A BER–Ni<sub>2</sub>B system prepared in situ from BER–Ni(OAc)<sub>2</sub> in methanol has been used for a novel C–C bond formation via radical addition or radical cyclization of alkyl halides with electron deficient alkenes of  $\alpha,\beta$ -unsaturated esters, ketones and nitriles.<sup>49,50</sup>

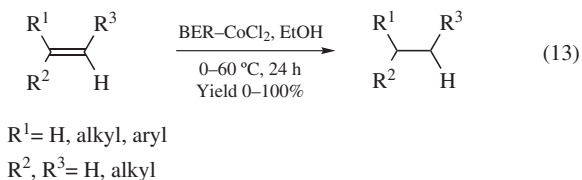
**Reduction of Alkenes.** Although most double bonds are unreactive to BER, an exception to this is conjugated nitroalkenes which can be efficiently reduced to saturated nitroalkanes (eq 11).<sup>33</sup>



The reductions of  $\alpha,\beta$ -unsaturated amides, esters, and nitriles using BER require a catalyst. When BER-CuSO<sub>4</sub> is used, the saturated species are formed with no concurrent reduction of the amide, ester, or nitrile functionalities (eq 12).<sup>51</sup>

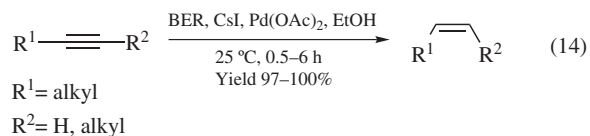


When catalyzed by cobalt, nickel, or copper, BER has been shown to reduce a wide variety of isolated double bonds (eq 13).<sup>52,53</sup> Mono- and di-substituted alkenes are successfully reduced. Less hindered alkenes and those attached to electron-withdrawing substituents show enhanced rates, whereas hindered and trisubstituted olefins are not reduced.

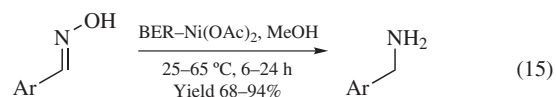


**Nickel Boride** (Ni<sub>2</sub>B) also catalyses the selective borohydride exchange resin-mediated hydrogenation of mono- and di-substituted olefins. Monosubstituted alkenes are quantitatively hydrogenated in 1 h at 0 °C in the presence of di-substituted alkenes and trisubstituted  $\alpha,\beta$ -unsaturated acid derivatives. Disubstituted double bonds are hydrogenated at reflux in 1 h without affecting trisubstituted olefins, benzenes, or heteroaromatics.<sup>54</sup>

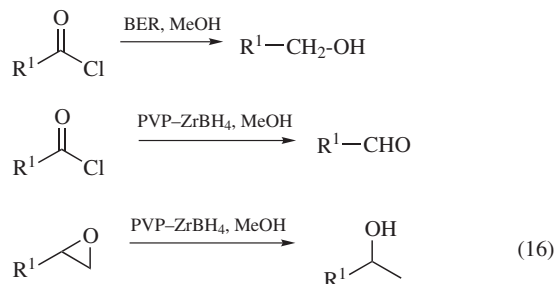
**Reduction of Alkynes.** It was reported that Pd(OAc)<sub>2</sub>-doped BER in the presence of cesium iodide promotes hydrogenation of alkynes to give *cis*-alkenes (eq 14).<sup>55</sup> This method was excellent for the semihydrogenation of terminal and internal alkynes.



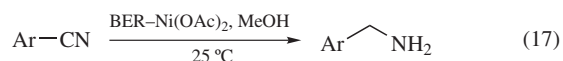
**Reduction of Oximes.** Oximes are resistant to reduction by BER, but aromatic oximes can be transformed to primary benzylamines using BER-Ni(OAc)<sub>2</sub> (eq 15).<sup>56</sup> Aryl aldoximes with electron-withdrawing substituents such as nitro and chloro are readily reduced, but simultaneous reduction of the nitro and chloro groups also occurs. Reduction of aryl aldoximes with electron-donating substituents is slow, but they can be successfully reduced using higher temperatures and longer reaction times.



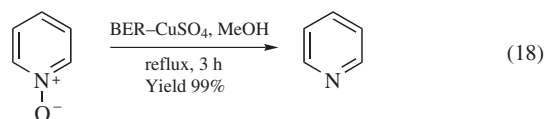
**Reduction of Acid Chlorides and Epoxides.** BER successfully reduces acid chlorides to alcohols.<sup>34,57</sup> Poly(4-vinylpyridine)-supported Zr(BH<sub>4</sub>)<sub>4</sub> converts acid chlorides to aldehydes and epoxides to the more substituted alcohols (eq 16).<sup>22</sup> AlCl<sub>2</sub>(BH<sub>4</sub>) supported on poly(4-vinylpyridine) has also been used to open epoxides in a similar manner.<sup>58</sup>



**Reduction of Nitriles.** Generally, nitriles are inert to BER and copper-catalyzed BER although benzonitriles can be converted to benzylamines using BER-Ni(OAc)<sub>2</sub> (eq 17).<sup>27</sup>

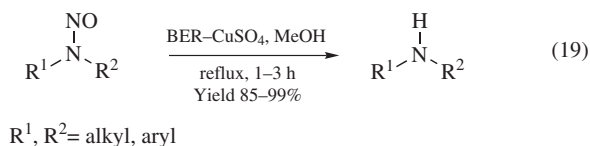


**Deoxygenation of Amine N-Oxides.** Under copper catalysis, BER quantitatively deoxygenates both tertiary amine *N*-oxides and heteroatomic *N*-oxides. For example, BER-CuSO<sub>4</sub> is able to cleanly reduce pyridine-*N*-oxide to pyridine in 99% yield in refluxing methanol (eq 18).<sup>37,59</sup>

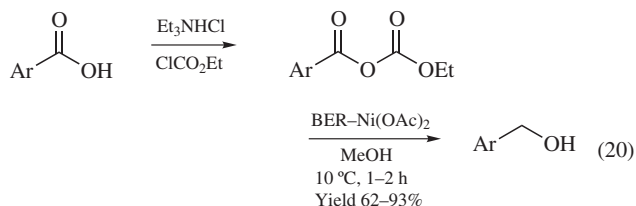


**Reduction of Nitrosoamines.** Nitrosoamines have been used for the introduction of alkyl groups at the  $\alpha$ -position. BER-CuSO<sub>4</sub>

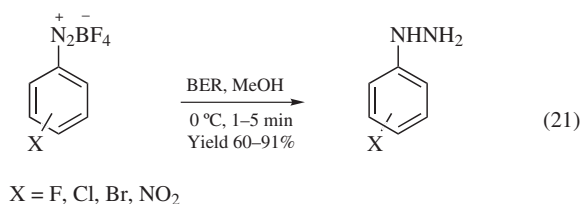
has been successfully utilized in the reduction of nitroso compounds to give the corresponding secondary amines (eq 19).<sup>60</sup>



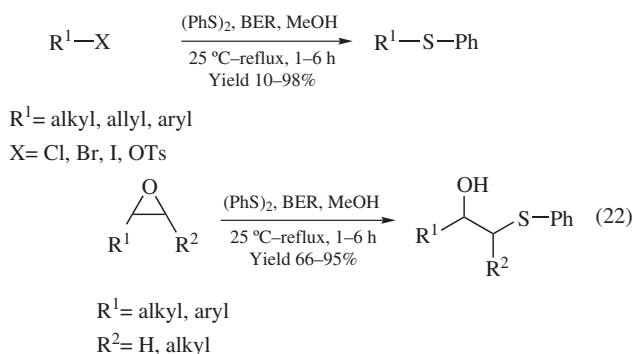
**Reduction of Mixed Anhydrides.** BER-Ni(OAc)<sub>2</sub> converts mixed anhydrides of aromatic carboxylic acids to alcohols (eq 20).<sup>61</sup>



**Reduction of Aryl Diazonium Fluoroborates.** Borohydride exchange resin will reduce substituted aryl diazonium fluoroborates to the corresponding phenylhydrazines under mild conditions (eq 21).<sup>62</sup>

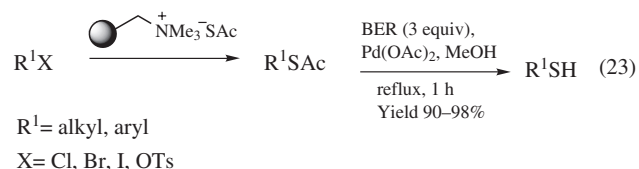


**Formation of Phenyl Sulfides.** Borohydride exchange resin readily reduces phenyl disulfides in methanol under neutral conditions. The resultant mixtures, on reaction with alkyl halides or epoxides, provide convenient and selective reagents for the preparation of phenyl sulfides (eq 22). Filtration of the resin leaves a solution of products which is essentially free from both sulfur- and boron-containing side products.<sup>63</sup>

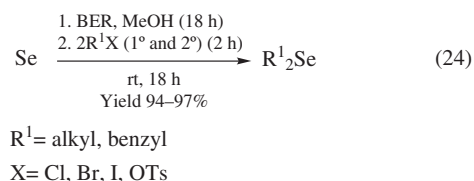


**Formation of Thiols.** After thioacetate formation by the reaction of a variety of halides with a polymer-supported thioacetate, a palladium-catalyzed methanolysis protocol yields thiols selectively in high yield in a one-pot reaction (eq 23).<sup>64</sup> This method,

involving palladium deposited on BER, requires 3 equiv of BER to prevent the formation of disulfide by-products.



**Reduction of Selenium.** Selenium may be reduced by BER to give an immobilized selenide that reacts with alkyl halides or tosylates to form dialkyl selenides in high yields. No release of toxic or malodorous by-products occurs, as these are scavenged from the reaction by the polymer (eq 24).<sup>65</sup>



**Related Reagents.** Sodium Borohydride, Nickel Boride, Sodium Cyanoborohydride.

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Steven V. Ley & R. Ian Storer  
*University Chemical Laboratories, Cambridge, UK*