

## Simple and efficient reduction of azides to amines using recyclable polymer-supported formate and zinc

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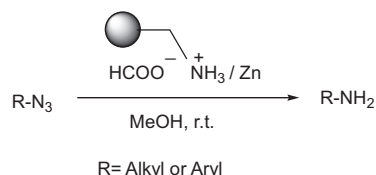
Polymer supported formate in conjunction with commercial zinc dust provides a mild and efficient procedure for the reduction of organic azides to corresponding amines. A variety of alkyl and aryl azides were selectively reduced in high yield and purity at room temperature.

**Keywords:** polymer supported formate, zinc, azides, recyclable, catalytic transfer hydrogenation

In recent years, functionalised polymers have been emerged as useful reagents, catalysts and scavengers in the field of solution phase chemistry, catalysis and homologous parallel synthesis.<sup>1,2</sup> One of the important advantages is that if toxic or volatile compounds being used, then by immobilising them on resins they become benign and far easier to handle and can be reused. Further, immobilised reagents are attractive as they allow the piloting of new synthetic pathway by removing the contaminating spent reagents and by-products, in this way (rather than using standard protocols of water-quenching, solvent extraction, drying, evaporation and chromatography at each stage) saves considerable time and materials. However, industrial success of these reagents and catalysts has been limited since they cost more than low molecular mass analogs. But currently the need for solid-supported reagents has been increasing considerably because of the development of robotic systems, reagent stirrer bars and even flow reactor devices for chemical synthesis in many industrial sectors.<sup>3</sup>

During the last decade polymer-supported reagents suitable for reductive transformation in simple one-step process have been developed using borohydride,<sup>4</sup> tin hydride,<sup>5</sup> cyanoborohydride,<sup>6</sup> tributyltin fluoride,<sup>7</sup> and zinc borohydride.<sup>8</sup> On the other hand, in comparison to all reductive processes, catalytic transfer hydrogenation using stable hydrogen donor in conjunction with a metal catalyst have real and potential advantages.<sup>9</sup> Meanwhile, solid supported reagents have been employing in the field of catalytic transfer hydrogenation and there is a pressing need for the proper exploitation of functionalised polymer supported reagents in organic synthesis. This idea leads to the development of polymer-supported version of formate that is suitable for use as a hydrogen donor. Literature shows that polymer-supported formate (PSF) in conjunction with the suitable catalyst have been used in reduction of various functionalities<sup>10</sup> and also deprotection of amino acids<sup>11</sup> over the past few years.

The reduction of azide to amine is exceedingly important transformation in synthetic organic chemistry, especially for the preparation of nitrogen containing heterocycles,<sup>12</sup> carbohydrates<sup>13</sup> and in nucleoside chemistry. Currently, there are few good methods including  $\text{NaBH}_4$ ,<sup>14a,b</sup>  $\text{LiAlH}_4$ ,<sup>14c</sup> sodium hydrogen telluride,<sup>14d</sup> triphenylphosphine,<sup>14e</sup>  $\text{Zn}/\text{NH}_4\text{Cl}$ ,<sup>14f</sup> and catalytic hydrogenation<sup>14g</sup> have been recently developed for the conversion of azides to amines. Most of them have their own limitations with regard to general applicability, toxicity, selectivity, and operational inconvenience. With our genuine interest in the synthesis of amines by catalytic transfer hydrogenation of various functionalities, recently we demonstrated zinc catalysed transfer hydrogenation of azide to amine using ammonium formate.<sup>15</sup> Now our interest is to develop an environmentally benign and stable hydrogen donor anchored on solid surface. Here we disclose our results



**Scheme 1**

illustrating the synthetic utility of PSF in zinc-catalysed reduction of azides to amines with good to excellent yield.

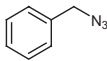
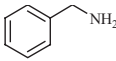
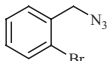
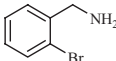
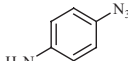
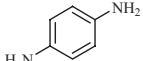
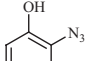
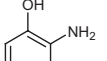
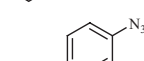
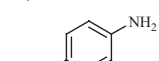
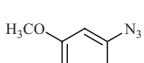
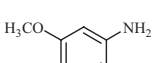
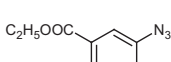
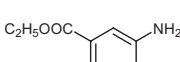
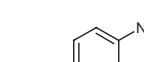
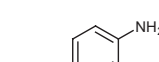
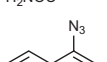
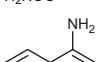
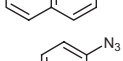
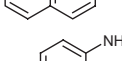
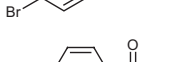
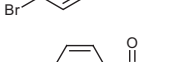
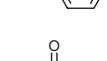
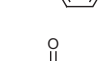
It was anticipated that the polymer-support would not only remove the problems often observed due to sublimation of ammonium formate but also would facilitate the isolation and purification of the water soluble products and the opportunity to use an excess of the reagent to force the reaction to complete without causing workup problems. The new method (Scheme 1) is simple, safe, highly selective, and proceeds under ambient condition of temperature and pressure. It reduces a variety of aliphatic and aromatic azides to corresponding amines in presence of various sensitive functional groups such as halogens, carbonyl, ester, amide, methoxy, carboxyl, phenol and hydroxyl, which are compatible with the present system.

The polymer-supported formate was prepared by washing (aminomethyl) polystyrene (2 mmol/g) with an excess of 50% solution of formic acid in dichloromethane and washed thoroughly, successively with dichloromethane, ether and dried under vacuum. The resulting (aminomethyl) polystyrene formate is used directly for catalytic reduction. A mixture of azide, (aminomethyl) polystyrene formate and Zn dust in methanol was shaken well at room temperature for about 2–3 hr (Table 1). After completion of the reaction, mixture was filtered and washed thoroughly with methanol, the filtrate was evaporated under vacuum. The crude product isolated, was of good yield and purity for most cases. The water-soluble aromatic amines were produced with excellent yields (entries 1 and 6). (Aminomethyl) polystyrene formate was regenerated and reused for the next set of hydrogenolysis up to ten cycles before there was an appreciable changes in reaction yield and purity (Table 2). All the products were characterised by comparison of their TLC, m.p., IR and NMR with the authentic samples.

In conclusion, we have shown that zinc catalysed transfer hydrogenation can be performed on variety of aliphatic and aromatic azides to amines using aminomethyl polystyrene formate as the source of hydrogen. The method is operationally simple, easiness of separation of the polymer-support and recyclability. The major advantages of this method are clean work up, high yields, environmentally benign conditions and the enhanced chemo-selectivity. The use of aminomethyl polystyrene formate showed some substrate selectivity and the transfer hydrogenation appears to proceed at a slower rate in comparison to that of ammonium formate. Further studies on the mechanistic aspects including the use of other transition

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**Table 1** Zinc catalysed transfer hydrogenation of aliphatic and aromatic azides using polymer-supported formate

Entry	Substrate	Time/h	Product	Yield/% <sup>a</sup>	Melting point/°C	
					Found	Lit.
1		2		96	182–184 <sup>b</sup>	184–185 <sup>16</sup>
2		3		93	109–110 <sup>b</sup>	110–112 <sup>17</sup>
3	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>5</sub> N <sub>3</sub>	2	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>5</sub> NH <sub>2</sub>	84	129–130 <sup>b</sup>	131–132 <sup>16</sup>
4		5		95	144–146	145–147 <sup>16</sup>
5		4		96	172–174	174 <sup>16</sup>
6		4		91	185–186	187 <sup>16</sup>
7		6		94	248–249 <sup>b</sup>	251 <sup>16</sup>
8		4		93	290–292 <sup>b</sup>	290–294 <sup>17</sup>
9		3		94	180–182	183 <sup>17</sup>
10		5		90	49–52	50 <sup>16</sup>
11		5		96	64–65	62–64 <sup>16</sup>
12		1.5		96	136–139	136–138 <sup>17</sup>
13		2		92	86	85–89 <sup>17</sup>

<sup>a</sup>Isolated yields are based on single experiment and yields were not optimised. <sup>b</sup>Boiling point.

**Table 2** Recycling of polymer-supported formate for the reduction of benzyl azide.

Cycles	1	2	3	4	5	6	7	8	9	10
Time/h	2.0	2.0	2.0	2.5	2.5	2.5	3.0	3.0	3.5	4.0
Yield/%	98	96	96	94	93	92	92	92	91	90

metals and new polymer supported hydrogen donors are of major interest.

## Experimental

### Materials

<sup>1</sup>H NMR spectra were recorded on an AMX-400 MHz spectrometer using CDCl<sub>3</sub> as solvent and TMS as internal standard. The IR spectra were recorded on Shimadzu FTIR-8300 spectrometer. The melting points were determined by using Thomas–Hoover melting point apparatus and are uncorrected. Thin-layer chromatography was carried out on silica gel plates obtained from E-Merck (India) Ltd. The substrates were either commercial products and were used as purchased or were prepared according to literature procedures. Aminomethyl polystyrene was purchased from Advanced Chemtech (1% DVB cross-linked, 100–200 mesh, 2 mmol/g). Zinc was purchased from E-Merck (India) Ltd. All of the solvents used were analytical grade or were purified according to standard procedures.

### General procedure for the reduction of azides using PSF/zinc

To a solution of azide (1 mmol) in methanol (15 ml) taken in a horizontal solid phase vessel, (aminomethyl) polystyrene formate (1 g) and zinc dust (1 mmol) were added. The suspension was shaken well for the specified time at room temperature. After consumption of the starting material, as monitored by TLC, the reaction mixture was filtered and washed thoroughly with methanol. The combined washings and filtrate were evaporated under reduced pressure. The crude product was found to be analytically pure in most cases. Where necessary, the crude product was taken into organic layer and washed with saturated sodium chloride.

For recycling purposes, the residue containing (aminomethyl) polystyrene formate and the catalyst was washed thoroughly and successively with DMF, dichloromethane, 50% solution of formic acid in dichloromethane, dichloromethane and ether. Thus activated resin along with the catalyst was dried under vacuum and used as such for further reduction reactions.

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