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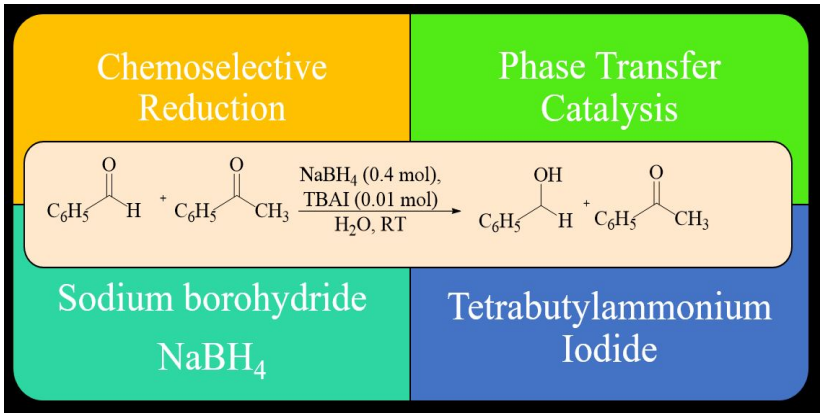
Solid-Liquid Phase Transfer Catalyzed Selective Reduction of Bifunctional Moieties

Monika Verma, Renu Sharma, and Ruchi Bharti*

In this article, a chemoselective reduction process of various aldehydes to their corresponding alcohols is described. An aqueous solution of various aromatic and allylic aldehydes was treated with $NaBH_4$ and tetrabutylammonium iodide as a phase transfer catalyst by choosing appropriate concentrations to give their respective alcohols in good to moderate yield. This methodology offered several advantages, including simple environmentally benign experimental procedure, good yields, short reaction time, and no toxic by-product.

Graphical abstract



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1. Introduction

One of the essential strategic executions in organic synthesis is functional group transformation, especially chemoselective functional transformation, synthesizing the desired products with minor redox manipulation [1]. The Carbonyl group is one of the most ubiquitous and essential functional groups in the repertoire of organic chemistry. Reducing carbonyl groups to alcohols is one of the most basic chemical transformations that have become a trivial reaction in organic synthesis [2]. However, limitations in chemo-selectivity still exist, and in complex settings, such as the selective reduction of aldehydes in ketones and other functional groups, can present a difficult challenge in many scenarios [3].

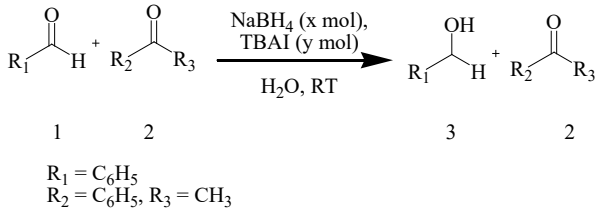
Keeping this in mind, several strategies have been developed to address this problem. Among those, phase transfer catalysts (PTC) have been recently emerged as a firmly established technique that is an alternative to the many traditional biocatalysts and transition-metal catalytic systems in synthetic organic chemistry. Particularly, phase transfer catalysis (PTC) is an arising practical methodology [4]. Economically and ecologically nonthreatening reagents and solvents, mild reaction conditions, simple experimental procedures, and the opportunity of large-scale steering provisions are some of the advantages of this method. During the last few years, various liquid-liquid and solid-liquid phase transfer catalyzed reactions have been intensified. However, the solid-liquid phase transfer catalyst (PTC) is one of the well-popularized techniques used in organic synthesis. In SLPTC, the elimination of the aqueous phase lowers the degree of hydration of the ion pair, leading to an increase in

Department of chemistry, University Institute of Science, Chandigarh University, Gharuan Mohali-140413, Punjab, India. *Corresponding author. E-mail: **ruchi.uis@cumail.in**

its reactivity. Therefore, higher selectivity and yields are obtained by operating PTC in solid-liquid mode compared to liquid-liquid mode [5]. Nowadays, in several areas of carbon-based chemistry, it appears to be a most important synthetic method, it also have a large industrial applications [6-8], in epoxidation[9], Michael addition [10-11], Barbier reaction of carbonyl compounds [12], aldol and related reactions [13], Horner-Wadsworth-Emmons reaction [14], Darzens reaction [15], Witting and Wittig-Horner reactions [16], cyclopropanation [17], asymmetric Weitz-Scheffer epoxidation [18], fluorination [19-21], aziridination [22-23], cyanation [24-25], reduction [26], alkylation [27], Strecker reaction of aldimines [28], oxidation [29], transesterification [30]. PTC itself has both organic and aqueous functional sites to get both systems and transfer substances from one system to another. It is usually a salt of quaternary ammonium, phosphonium compound, and crown ether, etc. [31]. By using a simple phase-transfer (PT) catalyst, a diversity of liquid-liquid and liquid-solid reactions such as quats, Crown ethers, ionic liquids [35], polyethylene glycol-400 [32-35] etc. have been intensified and selective, permitting ionic species to be transmitted from aqueous part to organic part.

In synthetic organic chemistry, the development of methodology for the efficient generation of relative reducing agents is the subject of significant importance. Researches in these eco-conscious days have been increasingly devoted to the development of environmentally benign synthetic procedures. Our investigation is principally ardent to finding new measures using low-priced and green reagents [36-39] for chemoselective reduction of carbon-based functionalities.

Here, we report a non-traditional approach to the highly selective and facile reduction of bifunctional carbonyl moieties. $NaBH_4$ with tetra butyl ammonium iodide (TBAI) is trustworthy, harmless, and comparatively cheap reduction processes, amendable both to laboratory production and extensive procedures (Scheme 1).



$R_1 = C_6H_5$
$R_2 = C_6H_5$, $R_3 = CH_3$

Scheme 1. Selective reduction of carbonyl compounds into alcohols.

2. Results and Discussion

In our early studies, we reduced benzaldehyde in the presence of acetophenone with $NaBH_4$ and TBAI in 1: 0.5: 0.5 ratios. It took only 5 minutes to get clean spots on the TLC, but both the carbonyl moieties got reduced. To achieve the chemoselectivity in the reaction, the reaction conditions were optimized by reducing the molar ratio of reagents. During optimization, it was found that the concentration of PTC and reducing agent both affected the reaction to a considerable extent. A high concentration of reducing agents and PTC promoted reduction but without chemoselectivity. Optimization revealed that the phase transfer catalyst was required in a minimal amount to facilitate the reaction. It was found that PTC Chemoselectivity in good yield and reasonable time was obtained by optimizing $NaBH_4$ to 0.4 and TBAI 0.01 (Table 1, Entry 7).

Table 1. Optimization Table.[a]

Entry	R_1CHO (mol)	R_2COR_3 (mol)	$NaBH_4$ (mol)	TBAI (mol)	Yield	Time	Chemoselectivity
1	1	1	0.5	0.5	100%	5 min.	No
2	1	1	0.25	0.5	30%	30 min	Yes
3	1	1	0.4	0.5	80%	10 min	No
4	1	1	0.4	0.05	88%	10-15 min	yes
5	1	1	0.4	0.3	100%	5 min.	No
6	1	1	0.4	0.2	92 %	7 min.	No
7	**1**	**1**	**0.4**	**0.01**	**89%**	**10-15 min**	**Yes**
8	1	1	0.4	0.1	90 %	7 min.	No

[a] Isolated yield

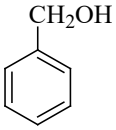
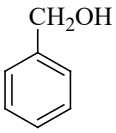
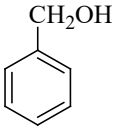
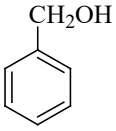
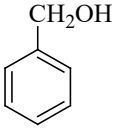
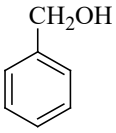
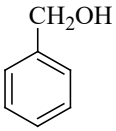
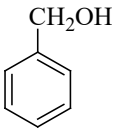
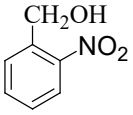
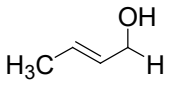
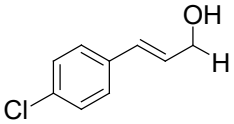
Then a variety of aldehydes and ketones were treated with $NaBH_4$ and tetrabutylammonium iodide (PTC) in aqueous media by choosing appropriate concentrations, which resulted in selective reduction of aldehyde. This ecologically benevolent road offers improved yields of products in 10-20 minutes at room temperature compared to prevailing conventional procedures. The results are shown in Table 2 (Entry 1-8).

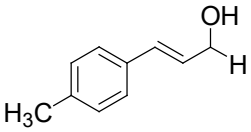
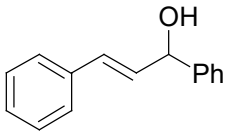
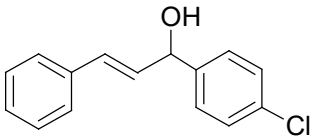
To explore the reaction scope, 2-nitrobenzaldehyde was reduced under the same reaction condition, and very encouraging results were obtained where only carbonyl moiety was reduced, and the nitro group remained intact. A good yield of desired product was obtained (Table 2, Entry 9).

The applicability of the optimized conditions was further explored with the selective reduction α,β-unsaturated carbonyl compounds, where promising results were obtained. Double bond at α,β position was not affected by reducing agent although carbonyl group got reduced nicely (Table 2, Entry 10-15).

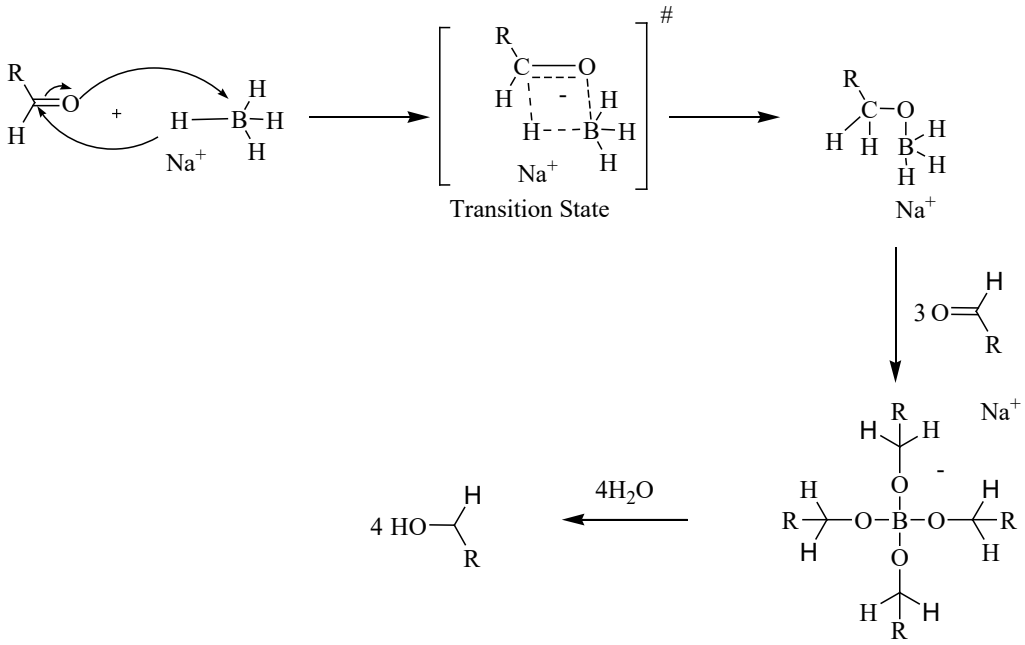
The possible mechanism for the above chemoselective reduction has been illustrated in Scheme 2. Reduction of carbonyl moiety of aldehyde by using sodium borohydride involves two steps. First of all, the H detaches from BH_4 and attacks on the carbon of carbonyl moiety, as a result of which bond between carbon and oxygen breaks, and BH_3 also combines oxygen. All this happens through a transition state where a four-membered cyclic structure is observed. This process is repeated again and again until all the hydrogens of BH_4 are replaced by aldehydes. Hydrolysis by water, at last, gives the desired alcohol.

Table 2. Selective reduction of carbonyl compounds with $NaBH_4$ – TBAI.

Entry	R_1	R_2	R_3	Product	Time (minutes)	Yield (%)[a]	M.p./ B.P. (°C) Found	M.P./B.P. (°C) Reported
1	C_6H_5	C_6H_5	CH_3	 **3a**	12	88	203-205	204-206 [36]
2	C_6H_5	C_6H_5	C_6H_5	 **3b**	12	87	203-205	204-206 [36]
3	C_6H_5	4-Cl, C_6H_4	CH_3	 **3c**	12	85	203-205	204-206 [36]
4	C_6H_5	4-OMe, C_6H_4	CH_3	 **3d**	12	83	203-205	204-206 [36]
5	C_6H_5	4-OH, C_6H_4	CH_3	 **3e**	12	89	203-205	204-206 [36]
6	C_6H_5	C_6H_5	$-OC_2H_5$	 **3f**	12	88	203-205	204-206 [36]
7	C_6H_5	C_6H_5	$-NH_2$	 **3g**	12	89	203-205	204-206 [36]
8	C_6H_5	C_6H_4NH	CH_3	 **3h**	12	87	203-205	204-206 [36]
9	2-NO_2, C_6H_4	-	-	 **3i**	5	92	70-72	70-71 [40]
10	C_6H_5CH=CH-	-	-	C_6H_5CH=CH-CH_2OH **3j**	10	80	249-250	-
11	CH_3CH=CH-	-	-	 **3k**	30	72	120-122	-
12	4-Cl, C_6H_4CH=CH-	-	-	 **3l**	30	83	58-60	-

13	4-CH_3, C_6H_4CH=CH-	-	-	 **3m**	30	80	278-280	-
14	-	C_6H_5CH=CH-	C_6H_5	 **3n**	30	89	55-57	-
15	-	C_6H_5CH=CH-	4-Cl, C_6H_4	 **3o**	30	87	98-100	-

[a] Isolated yield



Scheme 2. A possible approach for the chemoselective reduction of bifunctional moieties.

3. Material and Methods

3.1 General procedure for chemoselective reduction of bifunctional carbonyl moieties with $NaBH_4$/TBAI in aqueous conditions

Equimolar (0.009) mixture of aldehyde and ketone is mixed with 0.0009 moles of TBAI, and 0.0036 moles of $NaBH_4$ in 10 mL distilled water. The reaction mixture is stirred at room temperature. Quenching of reaction was done using a saturated sodium chloride solution, and extraction was done with chloroform. Na_2SO_4 was used for drying the organic layer. Evaporation of the organic solvent afforded the crude product, which was further purified by column chromatography using ethyl acetate and hexane over silica gel. Progress of the reaction was observed with TLC, and the product was identified using IR and NMR.

3.2 General procedure for chemoselective reduction of α,β-unsaturated carbonyl compound with $NaBH_4$/TBAI

Aqueous $NaBH_4$ (3.95 mmol) and tetrabutylammonium iodide (0.87 g, 2.3 mmol, in one lot) were introduced to a stirred solution of α,β-unsaturated carbonyl compound (7.9 mmol) in ethanol (10 mL). The mixture was stirred at room temperature. ethanol was removed by distillation. Extraction of the aqueous layer was performed by diethyl ether (3.25 mL) which was further dried (anhyd. Na_2SO_4), and concentrated. Column chromatography was used to purify the crude product by involving a solvent mixture of ethyl acetate and hexane over silica gel. The reaction was examined with TLC, and the product was recognized by IR and NMR. Spectroscopic data of all reduction product molecules are explained below.

Phenylmethanol (3a-3h): IR (υ, cm^{-1}): 3363, 2873, 1953, 1874, 1652, 1604, 1495, 1452, 1206, 1016, 1010, 965, 848, 765. ^1H NMR (400 MHz, $CDCl_3$): 4.07 (s, 1H, OH), 4.40 (s, 2H, CH2), 7.15-7.23 (m, 5H, ArH) ppm.

2-Nitro Phenylmethanol (3i): IR (υ, cm^{-1}): 3287, 2961, 2420, 1610, 1522, 1338, 1186, 1035,856. ^1H NMR (400 MHz, $CDCl_3$): 3.41 (s, 1H, OH), 4.93 (s, 2H, CH2), 7.41-7.45 (t, 1H, ArH),

7.61-7.65 (t, 1H, ArH), 7.72-7.74 (d, 1H, ArH), 8.02-8.05 (d, 1H, ArH) ppm.

3-phenylprop-2-en-1-ol (3j): IR (υ, cm^{-1}): 3345, 3030, 2873, 1952, 1873, 1646, 1495, 1453, 1206, 1015, 911, 738. ^{1}H NMR (400 MHz, $CDCl_3$): 4.12 (s, 1H, OH), 4.31-4.33 (d, 2H, CH2), 6.33-6.40 (m, 1H, HC=CH), 6.60-6.64 (d, 1H, CH), 7.22-7.40 (m, 5H, ArH) ppm.

But-2-ene-2-ol (3k): IR (υ, cm^{-1}):3611, 3362, 3056, 3003, 2976, 2814, 2723, 1444, 1393, 1256, 1160, 1043, 970, 723. ^{1}H NMR (400 MHz, $CDCl_3$): 3.25 (s, 1H, OH), 5.14 (s, 1H, CH), 6.39-6.31 (m, J = 6.0 Hz, 2H, HC=CH), 7.35 (d, 2H, CH), 7.36 (D, J = 6.0, 2H, CH), 7.38 (t, J = 6.0, 3H, CH) 7.90 (t, J = 6.0, 2H), 8.06 (t, J = 6.0 Hz, 2H) ppm.

4-(4-chlorophenyl)but-3-en-2-ol (3l): IR (υ, cm^{-1}): 3347, 2873, 1953, 1874, 1810, 1646, 1495, 1453, 1206, 1015, 911, 739, 595.

^{1}H NMR (400 MHz, $CDCl_3$): 2.45 (s, 1H, OH), 4.59 (d, 2H, CH2), 7.22 (s, 1H, HC=CH), 7.26-7.33(m, 5H, CH) ppm.

4-(*p*-tolyl)but-3ene-2ol (3m): ^{1}H NMR (400 MHz, $CDCl_3$): 2.75 (d, 3H, CH_3), 3.76 (s, 1H, OH), 4.44 (d, 2H, CH_2), 6.4 (d, 1H, CH), 6.6 (1H, CH), 7.17 – 7.24 (m, 4H, ArH) ppm.

1,3-phenylprop-2-en-1-ol (3n): IR (υ, cm^{-1}): 3567, 3058, 3033, 2993- 2800, 884, 751. ^{1}H NMR (400 MHz, $CDCl_3$): 3.66 (s, 1H, OH), 5.14 (s, 1H, CH), 6.39-6.31 (m, J = 6.0 Hz, 2H, HC=CH), 7.35 (d, 2H, CH), 7.36 (d, J = 6.0, 2H, CH), 7.38 (t, J = 6.0, 3H, CH) 7.90 (t, J = 6.0, 2H), 8.06 (t, J = 6.0 Hz, 2H) ppm.

1-(4-chlorophenyl)-3-phenylprop-2-ene-1-ol (3o): IR (υ, cm^{-1}):3470, 3278, 3132, 2893- 2864, 889, 755. ^{1}H NMR (400 MHz, $CDCl_3$): 3.95 (s, 1H, OH), 5.11 (s, 1H, CH), 6.36-6.29 (m, J = 6.0 Hz, 2H, HC=CH), 7.30 (d, 2H, CH),7.34 (d, J = 6.0, 2H, CH), 7.39 (t, J = 6.0, 2H, CH), 7.99 (t, J = 6.0, 2H), 8.16 (t, J = 6.0 Hz, 2H) ppm.

4. Conclusions

During our study, we found that tetra butyl ammonium iodide is a proficient catalyst for the chemoselective reduction of aldehydes over ketones using $NaBH_4$ as a reducing agent. In view of extended reaction period, adequate yields, tiresome work up subsequently the reaction in conservative method, a comparatively more adaptable yet streamlined process is professed. Key to the industrial feasibility of the method is the reduction of the large excess reducing agent required to drive the reaction to completion. The present catalytic reaction method proves to be a remarkably simple, green sustainable, less expensive method and has high performance.

Supporting Information

General experimental methods, full characterization data for 3a-3h, and 3i-3o, IR, ^{1}H NMR, ^{13}C NMR spectra of new compounds.

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Author Contributions

Monika Verma: Methodology, Data-curation, Writing Original-Draft preparation, Software, Investigation, Resources. Renu Sharma: Formal Analysis, Validation. Ruchi Bharti: Conceptualization, Supervision, Writing-Reviewing and Editing, Project administration, Validation.

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