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REDUCTION OF ALIPHATIC, AROMATIC AND HETEROAROMATIC CARBOXYLIC ACID DERIVATIVES TO ALCOHOL PROMOTED BY TRITYL RESIN UNDER PRESENCE OF COPPER SULPHATE AND SODIUM BOROHYDRIDE CATALYTIC SYSTEM

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ABSTRACT: An efficient, eco-friendly, mild protocol for the acid-alcohol transformation is developed. Varied aliphatic, aromatic and heteroaromatic carboxylic acid derivatives loaded on to the 2-chloro trityl chloride resin under perseverance of DIPEA base followed by subsequent reduction into corresponding alcohol using $CuSO_4$- $NaBH_4$ catalytic system have been achieved in excellent yield with easy product isolation technique. Facile recycling of the recovered resin is also associated to this methodology. All the products were characterized by ^1H NMR and ^{13}CNMR spectral analysis.

KEYWORDS: $CuSO_4$-$NaBH_4$ system, 2-chlorotrityl chloride resin, Carboxylic acids reduction

INTRODUCTION:

The reduction of carboxylic acids to corresponding alcohols is a substantial transformation in the field of synthetic organic chemistry [i-ii]. In traditional practice the corresponding alcohols are obtained from the reduction of aldehyde and ketones, as the carboxylic acid derivatives possess reluctant potency towards this acid-to-alcohol catalytic transformations. Hitherto methodologies utilizing variety of metal hydrides reagents such as $LiAlH_4$ [iii], AlH_3 [iv], DIBAL-H [v], $NaAlH_2(O\text{-}CH_2\text{-}CH_2\text{-}OCH_3)_2$ [vi] etc. Borane reagent systems BH_3-THF [vii], BF_3-Et_2O [viii] etc. have been employed for this model conversion. Plethora of protocols applying $NaBH_4$ in surrogacy of Br_2 [ix], I_2 [x-xii], H_2SO_4 [xiii], Diglyme [xiv], Catechol-TFA [xv], $ZnCl_2$ [xvi], $ZrCl_4$ [xvii], $TiCl_4$ [xviii], TCT-PPh_3-K_2CO_3 [xix], PNT-NMM [xx], T_3P-DIPEA [xxi], BOP reagent [xxii], Cyanuric chloride [xxiii] etc. has also been reported in the literature. In addition to this, some well-designed modified procedures for the reduction of carboxylic acids routing to representative alcohol *via* prior conversion to ester has also been achieved by applying $NaBH_4$ [xxiv-xxv]. However, some of these protocols suffer from constraints including drastic reaction condition, long reaction time, high temperature requirement, use of toxic and expensive reagents, tedious work up procedure which limits its regular practical implementations. Nonetheless, for ever-growing exploration

over synthetic organic chemistry and green chemistry, such reduction methodologies including facile, mild, cost-effective features that dodge the application of expensive and hazardous reagents/catalysts, is still highly desirable and subject of attention too.

2-chlorotrityl chloride resin (CTCR) has led by a huge attention for solid phase synthesis of C-terminal peptides. This resin is often utilized in former context and efficiently binds with carboxylic acids [xxvi-xxx], alcohols [xxxi], phenols [xxxii], amines [xxxiii-xxxv], imidazoles [xxxvi] and hydroxylamines [xxxvii-xxxviii] by stable linkage for the subsequent chemical transformation. Moreover, owing to higher stability of trityl cations, the linkage of CTCR is easily cleaved under mild acidic condition (1% TFA in dichloromethane) [xxxix]. The advantages of CTCR includes easy work up procedure i.e., excess soluble reagents and by-products could be removed by easy filtration and washing only [xl], hence it would be extremely advantageous to introduce CTCR as a solid support in organic synthesis for the reduction of carboxylic acid derivatives to corresponding alcohols.

In view of above, for the very first time an effort was made by Sung-eun Yoo group, reporting $CuSO_4$-$NaBH_4$ system aided reduction protocol for variety of functional groups. Although, carboxylic acids, amides, anilides and aromatic esters (i.e., carbonyl group of ester functionality directly attached to phenyl ring) was not susceptible for the reduction [xli]. Similarly, our recent report on scrutinizing the potencies of Cu(II) salts:$NaBH_4$ catalytic system-based hydrogenation of varied Nitro, Azo, Azoxy, N-aryl hydroxylamine, Nitroso, Acid halide, Ester and Azide functionalities were documented [xlii]. Unfortunately, the system could not be able to facilitate the reduction of the substrate with appended acid functionality. This led us to further investigate the hydrogenation of such substrates using our delight catalytic system. Following our studies on Cu(II) salts, herein we intend to report an efficient approach for the reduction of carboxylic acids into corresponding alcohols using 2-chlorotrityl chloride resin (CTCR) and $CuSO_4$-$NaBH_4$ system operational under mild reaction condition, atmospheric pressure and prompted time.

EXPERIMENTAL:

MATERIALS AND METHODS:

2-chlorotrityl chloride resin (CTCR, 200-400 mesh size, 1% DVB crosslinked, -Cl loading 1.0-1.5 mmol/g, polystyrene bounded, Sigma Aldrich), *N*,*N*-diisopropylethylamine (DIPEA, 99%, Spectrochem, Vadodara, India), copper sulphate ($CuSO_4$, 99%, anhydrous, Himedia, Mumbai, India) and sodium borohydride ($NaBH_4$, 99%, Sigma Aldrich) and other chemicals were used as received. Dichloromethane (DCM, HPLC grade, Spectrochem, Vadodara, India) was freshly distilled over calcium hydride (CaH) prior to utilization, and other solvents (HPLC grade) were used as received. Double distilled water (DD water) was used throughout for all experimental studies.

Thin-layer chromatography (TLC, on aluminum plates precoated with silica gel, 60F, 0.25 mm thickness, Merck, Darmstadt, Germany) was used for monitoring the progress the reactions. The melting points were determined by an open-tube capillary method and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded by Bruker Advance 400F (MHz) spectrometer at 400 MHz and 100 MHz respectively.

GENERAL PROCEDURE:

GENERAL PROCEDURE OF SWELLING OF CTCR AND ANCHORING OF CARBOXYLIC ACID DERIVATIVES ON CTCR:

General procedure for the swelling and anchoring of carboxylic acid derivatives on CTCR is as follows. For swelling, the four-necked round bottom flask equipped with a

mechanical stirrer, thermopocket and Teflon coated condenser, containing 2-chlorotrityl chloride resin (1g) in dichloromethane (5 mL, pre-dried on CaH) was stirred at 25-30 ^{o}C for 30 min under N_2 environment. Subsequently, for anchoring, diisopropylethylamine (3 mmol) and carboxylic acid derivative (1 mmol) pre-dissolved in dry dichloromethane was added and further stir for 60 min at 25-30 ^{o}C under N_2 environment. The progress of reaction (i.e., absence of carboxylic acid in reaction mass) was monitored and evidenced by TLC. After reaction completion, the anchored CTCR resin was isolated upon filtration prior twice successive washing with 5 mL DCM solvent, so that the unreacted part of carboxylic acid derivatives and other soluble impurities are washed away. Eventually, >99 % of anchoring efficacy was achieved.

GENERAL PROCEDURE OF CAPPING OF UNUSED ACTIVE SITES OF CTCR AND REDUCTION OF CARBOXYLIC ACID DERIVATIVES:

The three-necked round bottom flask equipped with a mechanical stirrer, thermopocket and Teflon coated condenser, containing the above wet anchored CTCR in methanol (5 mL) was stirred at 25-30 ^{o}C for 10 min for complete capping of unused active sites of CTCR.

The general procedure of reduction of carboxylic acid derivative involves, further rise in temperature of the reaction mass to 60-65 ^{o}C, followed by subsequent addition of the copper sulphate (3 mol % respective to carboxylic acids) catalyst. Immediately, the sodium borohydride (2.5 mmol) was added portion wise (portion should not more than 0.25 mmol) in 20 min at 60-65 ^{o}C. The progress of reaction monitored by preparative TLC. Upon reaction completion, the reaction mass was filtered and washed of the used resin with methanol (5ml x 2). In case of solid products, DD water was directly added to the collected filtrate to isolate the precipitate of solid product at 10-15 ^{o}C and then dried under *vacuo* till continuous weight of crude product is observed, whereas in case of liquid products upon addition of DD water, the aqueous layer was extracted by ethyl acetate, then distilled and degassed to obtained crude product sequentially. Without any involvement of hectic column or flash chromatographic separation 95% Crude yield and >99% purity by ^{1}H NMR was obtained for the isolated crude product.

GENERAL PROCEDURE OF RECYCLING OF USED CTCR:

After every run the isolated used wet CTCR was collected and washed with 10% dilute HCl solution (10 ml x 2) for complete removal of copper metal, followed by DD water and methanol (10 ml x 2 each) wash, followed by suction drying under vacuum for 20 min for complete removal of methanol with subsequent washing of DCM (10 ml x 2). Thus, obtained wet resin in DCM (5 mL) was charged into the three-necked round bottom flask equipped with a mechanical stirrer, addition funnel and thermopocket under N_2 environment. Further for complete activation of CTCR resin, the reaction mass was cooled up to 5-10 ^{o}C with gradual addition of acetyl chloride (3 M in DCM) within 10 min with continuous stirring by maintaining the temperature at 5-10 ^{o}C for 20 min. The activated resin was filtered upon washing with DCM (10 ml x 2), so that the excess quantity of acetyl chloride is removed. Finally, the isolated activated resin was exposed to suction drying for 10 min under N_2 environment and then immediately packed into airtight bottle or reused for consecutive runs. It should be noted that pre-dried DCM is required in entire experiment.

2-chloroethan-1-ol (Table-4, Entry-1) [xliii]

B.P.:128-130 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.10 (br s, 1H, -OH), 3.61 (td, *J*=6.6 Hz, 2H), 3.86 (td, *J*=6.6 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 46.77, 63.88 ppm

octadecan-1-ol (Table-4, Entry-2) [xliv]

M.P.: 56-59 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.858 (t, *J*=7.2 Hz, 3H), 1.11-1.46 (m, 30H), 1.11-1.46 (br s, 1H, -OH), 1.68-1.77 (m, 2H), 3.60 (t, *J*=7.2 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.56, 22.91, 25.74, 29.23, 30.63, 31.61, 61.76 ppm

phenylmethanol (Table-4, Entry-3) [xlv]

B.P.: 204-206 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.37 (br s, 1H, -OH), 4.62 (s, 2H), 7.31-7.41 (m, 5H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 64.10, 126.19, 126.70, 127.66, 140.03 ppm

naphthalen-1-ylmethanol (Table-4, Entry-4) [xlvi]

M.P.:61-63 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.90 (br s, 1H, -OH), 5.27 (s, 2H), 7.47-7.62 (m, 4H), 7.84-7.94 (m, 2H), 8.28 (dd, *J*=8 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 62.47, 124.21, 124.94, 125.64, 125.81, 126.05, 126.49, 127.83, 131.65, 133.55, 137.20 ppm

p-tolylmethanol (Table-4, Entry-5) [xlvii]

M.P.: 59-61 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.24 (s, 3H), 2.52 (br s, 1H, -OH), 4.54 (s, 2H), 7.15 (dd, *J*=8 Hz, 2H), 7.24 (dd, *J*=7.8 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.89, 64.66, 121.46, 123.77, 137.27, 139.54 ppm

[1,1'-biphenyl]-4-ylmethanol (Table-4, Entry-6) [xlviii]

M.P.: 97-99 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.52 (s, 2H), 5.31 (br s, 1H, -OH), 7.48-7.67 (m, 7H), 7.73-7.76 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 64.37, 127.50, 127.54, 128.47, 128.53, 129.54, 137.61, 139.88, 143.24 ppm

(2-chlorophenyl)methanol (Table-4, Entry-7) [xlix]

M.P.: 69-72 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.59 (br s, 1H, -OH), 4.76 (s, 2H), 7.14-7.24 (m, 2H), 7.26 (dd, *J*=7.9 Hz, 1H), 7.50 (dd, *J*=7.9 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 61.95, 124.65, 127.79, 128.05, 129.21, 133.16, 138.18 ppm

(3-chlorophenyl)methanol (Table-4, Entry-8) [l]

B.P.: 236-238 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.91 (br s, 1H, -OH), 4.50 (s, 2H), 7.22-7.34 (m, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 65.84, 124.83, 125.81, 126.31, 128.56, 134.42, 142.02 ppm

(4-chlorophenyl)methanol (Table-4, Entry-9) [xlv]

M.P.: 68-71 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.25 (br s, 1H, -OH), 4.65 (s, 2H), 7.29 (d, *J*=8.4 Hz, 2H), 7.34 (d, *J*=8.4 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 64.87, 128.68, 129.06, 133.74, 139.64 ppm

(2,4-dichlorophenyl)methanol (Table-4, Entry-10) [li]

M.P.: 55-58 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.69 (br s, 1H, -OH), 4.78 (s, 2H), 7.19 (dd, *J*=8.2 Hz, 1H), 7.48-7.56 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 62.54, 126.48, 128.60, 129.10, 132.64, 134.08, 137.21 ppm

(4-fluorophenyl)methanol (Table-4, Entry-11) [lii]

B.P.: 205-210 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.13 (br s, 1H, -OH), 4.56 (s, 2H), 2.69 (br s, 1H, -OH), 7.02 (t, *J*=8.6 Hz, 2H), 7.28 (t, *J*=5.36, 7.2 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 64.24, 115.16, 115.37, 128.68, 128.76, 136.59, 136.62, 161.03, 163.47 ppm

(4-methoxyphenyl)methanol (Table-4, Entry-12) [xlv]

B.P.: 257-262 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.95 (br s, 1H, -OH), 3.89 (s, 3H), 4.64 (s, 2H), 6.97 (d, *J*=8.4 Hz, 2H), 7.35 (d, *J*=8.4 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.08, 64.46, 113.71, 128.43, 133.06, 158.88 ppm

(2,4-dimethoxyphenyl)methanol (Table-4, Entry-13) [liii]

M.P.: 38-40 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.41 (br s, 1H, -OH), 3.80 (s, 2H), 3.82 (s, 2H), 4.57 (s, 2H), 6.54 (d, *J*=7.2 Hz, 1H), 6.82 (s, 1H), 7.18 (d, *J*=8.4 Hz, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 53.57, 62.91, 98.08, 104.07, 122.46, 130.22, 158.66, 162.45 ppm

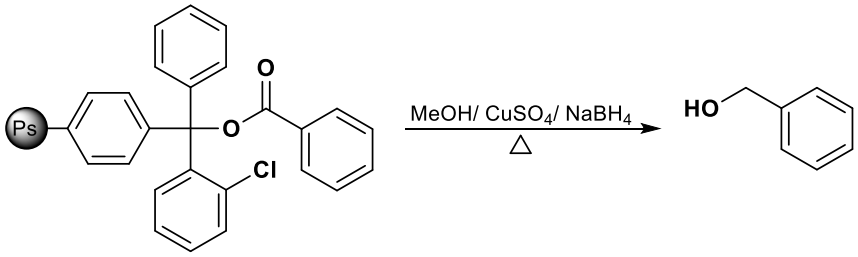
4-(hydroxymethyl)benzonitrile (Table-4, Entry-14) [liv]
M.P.: 39-43 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.37 (br s, 1H, -OH), 4.31 (s, 2H), 7.39 (dd, *J*=6.4 Hz, 2H), 7.77 (dd, *J*=6.4 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 64.02, 110.64, 117.93, 127.99, 132.62, 139.24 ppm
furan-2-ylmethanol (Table-4, Entry-15) [lv]
B.P.: 170-172 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.63 (br s, 1H, -OH), 4.50 (s, 2H), 6.24 (d, 1H, *J*=3.2 Hz), 6.31 (dd, *J*=3.1 Hz, 1H), 7.36 (dd, *J*=1.7 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 56.91, 107.64, 110.33, 142.40, 154.17 ppm
thiophen-2-ylmethanol (Table-4, Entry-16) [lvi]
B.P.: 206-208 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.94 (br s, 1H, -OH), 4.89 (s, 2H), 6.85-6.95 (m, 2H), 7.30 (dd, *J*=7.6 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 59.55, 124.85, 125.23, 127.30, 142.40 ppm
pyridin-3-ylmethanol (Table-4, Entry-17) [lvii]
B.P.: 153-155ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.60 (br s, 1H, -OH), 5.84 (s, 2H), 7.04-7.07 (m, 1H), 7.13-7.16 (m, 1H), 8.09 (dd, *J*=3 Hz, 1H), 8.18 (d, *J*=3 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 61.99, 123.77, 137.27, 139.54, 147.88, 148.04 ppm
(1-ethyl-1H-indol-3-yl)methanol (Table-4, Entry-18) [lviii]
M.P.: 61-63 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.30 (t, *J*=6.8 Hz, 3H), 8.18 (q, *J*=6.8 Hz, 2H), 4.64 (s, 2H), 4.74 (br s, 1H, -OH), 7.30-7.36 (m, 2H), 7.66 (d, *J*=8 Hz, 1H), 8.14 (d, *J*=8 Hz, 1H), 8.36 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.33, 40.30, 56.32, 111.67, 117.22, 121.11, 122.61, 123.21, 124.48, 136.47, 140.21 ppm
(2-chloroquinolin-3-yl)methanol (Table-4, Entry-20) [lix]
M.P.: 155-158 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.14 (br s, 1H, -OH), 5.25 (s, 2H), 7.45-7.52 (m, 2H), 7.63-7.67 (m, 2H), 7.97-8.02 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 60.62, 124.32, 126.28, 127.74, 128.52, 129.55, 130.87, 146.59, 150.89 ppm

RESULTS AND DISCUSSION:

The commonly used 2-chlorotrityl chloride resin (CTCR) is generally a polystyrene crosslinked divinylbenzene beads. Primarily, mesh size of CTCR is very important factor for the selection of resin. Commercially, two variants of resin with 100-200 and 200-400 mesh size are available. The resin with 100-200 mess size is larger in size but possesses fewer reaction sites, eventually much resin quantity is required. Whereas, in case of latter 200-400 mesh size resin, they are smaller in size with more reactive sites available for linkage, due to large surface area this resin exhibits faster reaction rate with greater loading efficacy. Subsequently, the crosslinking of divinylbenzene (DVB) also affects the anchoring efficacy of resin. The 1% DVB crosslinked CTCR shows 2-4 times swelling in dichloromethane (DCM) and it is sufficient for our experiment. The selected CTCR possesses 1.0-1.5 mmol/g active sites (-Cl loading), therefore considering lower limit basis it is advisable to take 1 mmol of carboxylic acid per gram of resin.

The best optimized reaction condition for our protocol were established by investigating the hydrogenation of CTCR bound benzoic acid as a model reaction (Scheme-1), where varied reaction parameters including solvents, $NaBH_4$ and $CuSO_4$ concentration were screened. Primarily, we screened the influence of different solvents on the hydrogenation of benzoic acid promoted by CTCR-$CuSO_4$ system with $NaBH_4$ surrogate as a model reaction (Table-1). It was observed that the hydrogenation conditions were favored under habitancy of polar solvents rather than non-polar solvents. In comparison to other solvents (Table-1, Entry 4-7) the best results were obtained under vicinity of water and methanol solvent in prompt time with high conversion and yield. Nevertheless, the conversion was much pleasing under methanol than

water. Under manifestation of other solvents, the elevated temperature could not be able to promote effectual conversion with substantial yield (Table-1, Entry 1, 4-7).



Scheme-1 Reduction of benzoic acid

Table -1 Effect of solvent on reduction of Benzoic acid [a]

Entry	Solvent	Time (min.)	Temperature (°C)	Conversion (%) [b]	Yield (%) [c]
1	DCM	120	40	<05	<01
2	Water	35	70	>92	86
3	**Methanol**	**20**	**65**	**>99**	**97**
4	Ethanol	120	75	22	15
5	n-propanol	120	85	15	<05
6	2-propanol	120	75	21	16
7	n-butanol	120	90	13	<05

[a] Reaction condition: 10 mmol of benzoic acid as a substrate, 2.5 equivalent of $NaBH_4$ to the substrate, 3 mol % of $CuSO_4$ catalyst to the substrate, 5 mL of solvent, [b] Conversion (%) determined by ^1H NMR, [c] isolated crude yield.

Further we ought to screen the appropriate concentration of hydrogen source $NaBH_4$ required for the efficient reduction of model reaction. Initially at lower equivalent of $NaBH_4$ (Table-2, entry 1-4) lower to moderate conversion were achieved. 2.5 equivalent (Table-2, entry 5) resulted in >99 % conversion to benzyl alcohol. Similarly, the screening results of appropriate $CuSO_4$ catalyst concentration revealed that 3 mol % of $CuSO_4$ was sufficient to tune the acid-alcohol transformation efficiently in 20 min (table-3, entry -6). The consequences of further increase in the $NaBH_4$ and $CuSO_4$ concentration up to 3.5 equivalents (Table-2, entry 6-7) and 4 mol % (Table-3, entry 7-8) respectively could not significantly modify the obtained results anymore.

Table -2 Effect of $NaBH_4$ concentration on reduction of Benzoic acid [a]

Entry	$NaBH_4$ (equivalent)	Conversion (%) [b]	Yield (%) [c]
1	0.5	19	<10
2	1.0	42	30
3	1.5	61	51
4	2.0	84	76
5	**2.5**	**>99**	**97**
6	3.0	>99	97
7	3.5	>99	97

[a] Reaction condition: 65 °C, 20 min., 10 mmol of benzoic acid as a substrate, 3 mol % of $CuSO_4$ catalyst to the substrate, 5 mL of methanol, [b] Conversion (%) determined by ^1H NMR, [c] isolated crude yield.

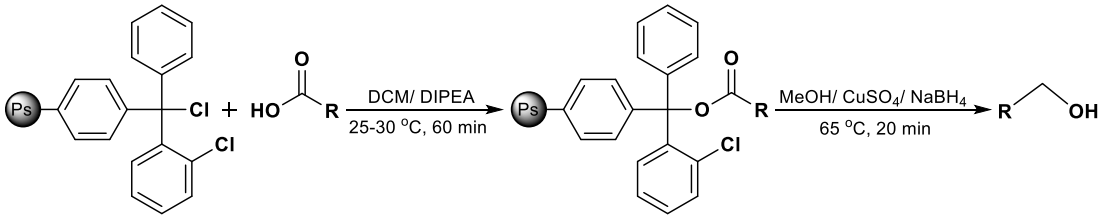
Table -3 Effect of $CuSO_4$ catalyst concentration on reduction of Benzoic acid [a]

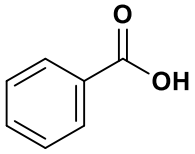
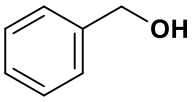
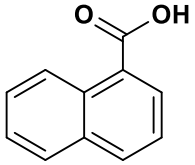
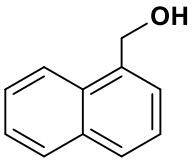
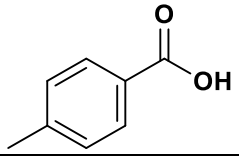
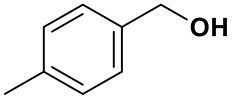
Entry	$CuSO_4$ (mol %)	Conversion (%) [b]	Yield (%) [c]
1	0.5	12	<01
2	1.0	23	<10
3	1.5	54	40
4	2.0	76	63
5	2.5	93	81
6	**3.0**	**>99**	**97**
7	3.5	>99	97
8	4.0	>99	97

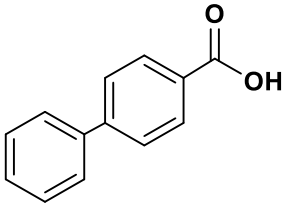
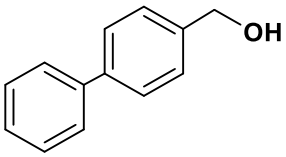
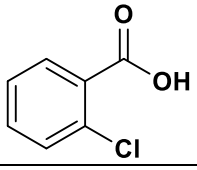
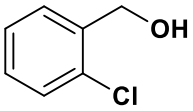
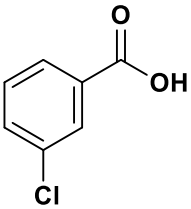
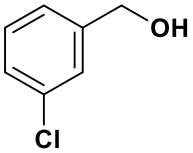
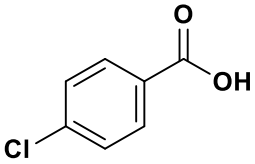
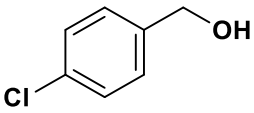
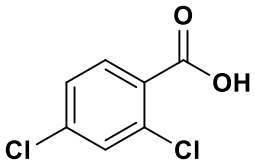
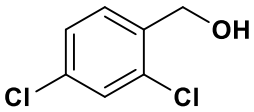
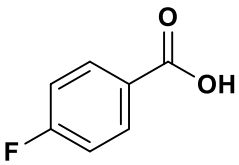
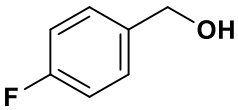
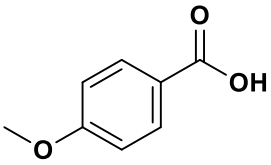
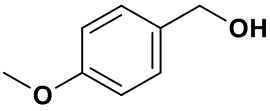
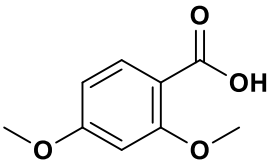
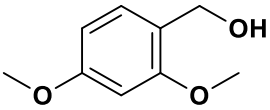
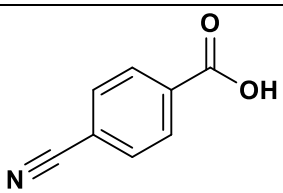
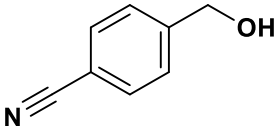
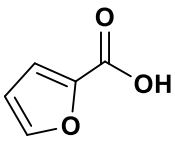
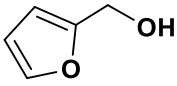
[a] Reaction condition: 65 °C, 20 min., 10 mmol of benzoic acid as a substrate, 2.5 equivalent of $NaBH_4$ to the substrate, 5 mL of methanol, [b] Conversion (%) determined by ^1H NMR, [c] isolated crude yield.

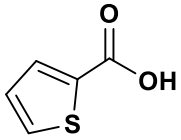
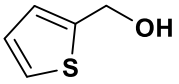
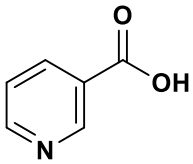
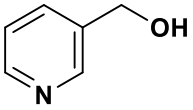
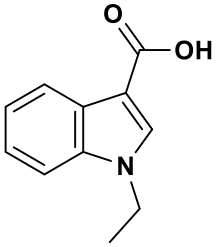
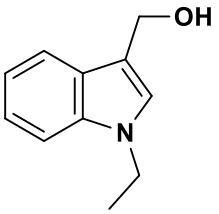
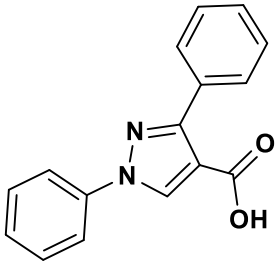
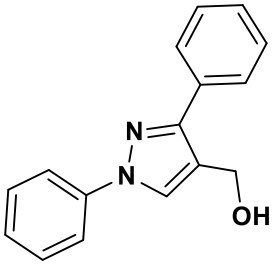
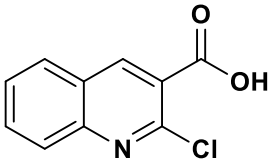
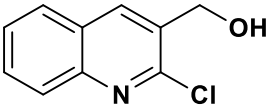
Therefore, the above study concluded that hydrogenation reaction is circumscribed to 2.5 equivalent $NaBH_4$, 3 mol% of $CuSO_4$ under methanol solvent condition, prior activation of the CTCR bound acid-based substrates. 3 equivalents of DIPEA base had a significant stimulus on the loading of varied substrate to CTCR under DCM solvent. The scope of our catalytic system on varied substrate with appended acid functionality were studied *via* adaptation of activated CTCR to corresponding alcohols in prompted time and excellent yield 92-97 % (Table-4).

Table -4 Reduction scope of CTCR bound carboxylic acids derivatives by $CuSO_4$:$NaBH_4$



Entry	Substrate	Product	Conversion (%)/ Selectivity (%) [b]	Yield (%) [c]
1	Cl-CH_2-COOH	Cl-CH_2-CH_2-OH	>99/>99	93(95)[d]
2	CH_3-$(CH2)_{15}$-CH_2-COOH	CH_3-$(CH2)_{15}$-CH_2- CH_2-OH	>99/--	96
3			>99/--	97(97)[d]
4			>99/--	94(96)[d]
5			>99/--	95(95)[d]

6			>99/--	96
7			>99/>99	93(94)[d]
8			>99/>99	95(95)[d]
9			>99/>99	96(95)[d]
10			>99/>99	95
11			>99/>99	94
12			>99/>99	96(96)[d]
13			>99/>99	96
14			>99/>99	92
15			>99/--	95

16			>99/--	95
17			>99/--	94
18			>99/--	96
19			>99/--	94
20			>99/>99	91

[a] Reaction condition: 65 °C, 20 min., 1 mmol of substrate, 2.5 equivalent of $NaBH_4$ to the substrate, 3 mol % of $CuSO_4$ catalyst to the substrate, 5 mL of methanol, [b] Conversion (%) and selectivity (%) determined by ^1H NMR, [c] Isolated crude yield, [d] Upscaling by factor 4 and isolated crude yields are given in brackets.

We observed effectual reduction of long chain and chloro substituted short chain aliphatic carboxylic acid achieved in good yields (Table 4, entry 1-2), similar was the case with aromatic carboxylic acid substrates (Table - 4, Entry 3-6). Further since halogen groups are extremely susceptible to dehalogenation under exposure of basic polar protic environment, nevertheless under charisma of our protocol, such mono or di halogen substituted substrates (Table 4, Entry 7-11 and 20) underwent acid-to-alcohol transformation without incident of dehalogenation. Likewise, appreciable yield of the corresponding alcohol was obtained from the substrates with unaffected ether and nitrile functionalities after the hydrogenation (Table 4, Entry 12-14). In addition to this, irrespective of steric hinderance, bulky heteroaromatic acid substrates were reduced to alcohols with impressive conversion and yield were achieved (Table 4, Entry 15-20).

RECYCLING OF CTCR:

The reuse of recovered CTCR is very significant for green aspects as well as commercial applicability. Finally, we examined the reusability of recovered CTCR by conducting the reduction of benzoic acid as a model reaction under our likewise protocol conditions. Before each cycle of reduction, the former procedure of washing, drying and reactivation had to be performed prior to reusing the CTCR.

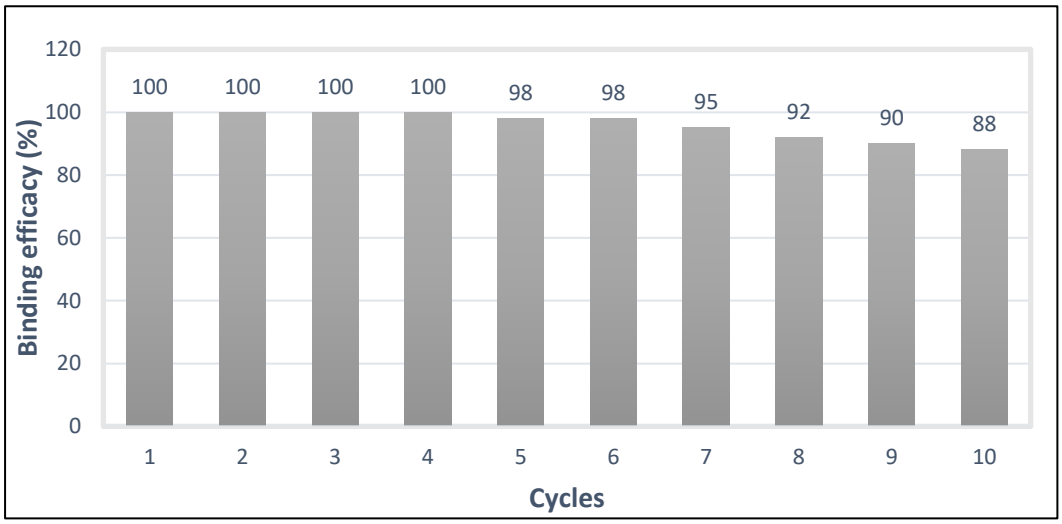


Figure-1 Recycling of CTCR

The loading efficacy (%) was elucidated in terms of each reduction cycles. As demonstrated in Figure-1, we can reuse the CTCR until four cycles without any loss in catalytic efficacy, however after fourth cycle, a bit gradual decrease up to 88 % conversion were observed eventually till ten cycles. Therefore, the CTCR could be reused up to 10 cycles whilst still retaining good binding efficacy resulting in promising reduction of acid derivatives upon addition of $CuSO_4$ and $NaBH_4$.

CONCLUSION:

In summary, we have established an *in situ* robust transfer hydrogenation protocol of industrially important acid substrates in presence of other functionalities with brilliant conversion. Under perseverance of our $CuSO_4$ based catalytic system variety un/substituted carboxylic acid loaded on to the CTCR were furnished to corresponding alcohols in excellent yield in prompted time utilizing the hydrogen resource of $NaBH_4$. This method involves a very simple activation by loading step which offers an advantage over those traditional methods which require long loading times associated with commercial resin application. Inexpensive reagents, green solvent, reusability of recovered resin, easy work procedure and product isolation represents the imperative consequences of this methodology. Most of the products are known compounds and their spectra were easily characterized and compared with those reported compounds spectra.

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SUPPLEMENTARY INFORMATION:

The supporting information contains copies of ^{1}H NMR and ^{13}C NMR spectra of the products.

CONFLICTS OF INTEREST:

The authors declare no conflict of interest.

REFERENCES:

i Wade L. G.; Comprehensive organic transformations: a guide to functional group transformations; *J. Chem. Educ.*; 1991, **68**, A86.

ii Utley J. H. .; Reductions in organic chemistry; *Endeavour*; 1985, **9**, 108.

iii Karrer P.; Portmann P.; Suter M.; L-Valinol und L-Tyrosinol; *Helv. Chim. Acta*; 1949, **32**, 1156.

iv Barrett A. G. M.; Reduction of Carboxylic Acid Derivatives to Alcohols, Ethers and Amines; , in *Comprehensive Organic Synthesis*, B. M. Trost, I. Fleming, (Ed.), Pergamon Press, Oxford, U. K.; 1991, **8**, 235.

v Ito A.; Takahashi R.; Baba Y.; A New Method to synthesize α-Aminoaldehydes; *Chem. Pharm. Bull.*; 1975, **23**, 3081.

vi Gugelchuk M.; Silva III L. F.; Vasconcelos R. S.; Quintiliano S. A. P.; Sodium Bis (2-methoxyethoxy) aluminum Hydride; *Encycl. Reagents Org. Synth.* L.A. Paquette (Ed.), John Wiley & Sons; 2007.

vii Yoon N. M.; Pak C. S.; Brown H. C.; Krishnamurthy S.; Stocky T. P.; Selective Reductions. XIX. The Rapid Reaction of Carboxylic Acids with Borane-Tetrahydrofuran. A Remarkably Convenient Procedure for the Selective Conversion of Carboxylic Acids to the Corresponding Alcohols in the Presence of Other Functional Groups; *J. Org. Chem.*; 1973, **38**, 2786.

viii Cho S. D.; Park Y. D.; Kim J. J.; Falck J. R.; Yoon Y. J.; Facile reduction of carboxylic acids, esters, acid chlorides, amides and nitriles to alcohols or amines using NaBH4/BF3· Et2O; *Bull. Korean Chem. Soc.*; 2004, **25**, 407.

ix Tudge M.; Mashima H.; Savarin C.; Humphrey G.; Davies I.; Facile reduction of malonate derivatives using NaBH4/Br2: an efficient route to 1,3-diols; *Tetrahedron Lett.*; 2008, **49**, 1041.

x Kanth J. V. B.; Periasamy M.; Selective Reduction of Carboxylic Acids into Alcohols Using NaBH4 and I2; *J. Org. Chem.*; 1991, **56**, 5964.

xi McKennon M. J.; Meyers A. I.; Drauz K.; Schwarm M.; A Convenient Reduction of Amino Acids and Their Derivatives; *J. Org. Chem.*; 1993, **58**, 3568.

xii Simek J. W.; Tuck T.; Bush K. C.; Reduction of carboxylic acids with sodium borohydride and an electrophile; *J. Chem. Educ.*; 1997, **74**, 107.

xiii Abiko A.; Masamune S.; An improved, convenient procedure for reduction of amino acids to aminoalcohols: Use of NaBH4-H2SO4; *Tetrahedron Lett.*; 1992, **33**, 5517.

xiv Zhu H. J.; Pittman C. U.; Reductions of carboxylic acids and esters with NaBH4 in diglyme at 162°C; *Synth. Commun.*; 2003, **33**, 1733.

xv Suseela Y.; Periasamy M.; Reduction of carboxylic acids into alcohols using NaBH4 in the presence of catechol and/or CF3COOH; *Tetrahedron*; 1992, **48**, 371.

xvi Narasimhan S.; Madhavan S.; Prasad K. G.; Facile Reduction of Carboxylic Acids by Zinc Borohydride; *J. Org. Chem.*; 1995, **60**, 5314.

xvii Itsuno S.; Sakurai Y.; Ito K.; Reduction of some functional groups with zirconium tetrachloride/sodium borohydride; *Synth.*; 1988, **12**, 995.

xviii Kano S.; Tanaka Y.; E. Sugino und S. Hibino; Reduction of some functional group with titanium (iv) chloride/sodium borohydride; *Synthesis (Stuttg).*; 1980, **9**, 695.

xix Jaita S.; Kaewkum P.; Duangkamol C.; Phakhodee W.; Pattarawarapan M.; Solvent-free reduction of carboxylic acids to alcohols with NaBH4 promoted by 2,4,6-trichloro-1,3,5-triazine and PPh3 in the presence of K2CO3; *RSC Adv.*; 2014, **4**, 46947.

xx Sinica D. C. *et al.*; Reduction of carboxylic acids to alcohols using phosphonitrilic chloride and sodium borohydride; *Der Chem. Sin.*; 2015, **6**, 104.

xxi Nagendra G.; Madhu C.; Vishwanatha T. M.; Sureshbabu V. V.; An expedient route for the reduction of carboxylic acids to alcohols employing 1-propanephosphonic acid cyclic anhydride as acid activator; *Tetrahedron Lett.*; 2012, **53**, 5059.

xxii McGeary R. P.; Facile and chemoselective reduction of carboxylic acids to alcohols using BOP reagent and sodium borohydride; *Tetrahedron Lett.*; 1998, **39**, 3319.

xxiii Falorni M.; Porcheddu A.; Taddei M.; Mild reduction of carboxylic acids to alcohols using cyanuric chloride and sodium borohydride; *Tetrahedron Lett.*; 1999, **40**, 4395.

xxiv Nikawa J.; Shiba T.; Reduction of carboxylic acids to alcohols through 1-succinimidyl esters with NABH4 ; *Chem. Lett.*; 1979, **8**, 981.

xxv Saeed A.; Ashraf Z.; Sodium borohydride reduction of aromatic carboxylic acids via methyl esters; *J. Chem. Sci.*; 2010, **122**, 451.

xxvi Barlos K.; Gatos D.; Kapolos S.; Poulos C.; Schäfer W.; Wenqing y. A. O.; Application of 2-chlorotrityl resin in solid phase synthesis of (Leu15)-gastrin I and unsulfated cholecystokinin octapeptide: Selective O-deprotection of tyrosine; *Int. J. Pept. Protein Res.*; 1991, **38**, 555.

xxvii Barlos K.; Gatos D.; Kutsogianni S.; Papaphotiou G.; Poulos C.; Tsegenidis T.; Solid phase synthesis of partially protected and free peptides containing disulphide bonds by simultaneous cysteine oxidation-release from 2-chlorotrityl resin; *Int. J. Pept. Protein Res.*; 1991, **38**, 562.

xxviii Chatzi K. B. O.; Gatos D.; Stavropoulos G.; 2-Chlorotrityl chloride resin; *Int. J. Pept. Protein Res.*; 2009, **37**, 513.

xxix Barlos K.; Gatos D.; Schäfer W.; Synthesis of Prothymosin α (ProTα)—a Protein Consisting of 109 Amino Acid Residues; *Angew. Chemie Int. Ed. English*; 1991, **30**, 590.

xxx Barlos K.; Chatzi O.; Gatos D.; Stavropoulos G.; 2-Chlorotrityl chloride resin; *Int. J. Pept. Protein Res*; 1991, **37**, 513.

xxxi Wenschuh H. *et al.*; Stepwise Automated Solid Phase Synthesis of Naturally Occurring Peptaibols Using FMOC Amino Acid Fluorides; *J. Org. Chem.*; 1995, **60**, 405.

xxxii Shankar B. B.; Yang D. Y.; Girton S.; Ganguly A. K.; One pot solid phase synthesis of isoxazolines; *Tetrahedron Lett.*; 1998, **39**, 2447.

xxxiii McNally J. J.; Youngman M. A.; Dax S. L.; Mannich reactions of resin-bound substrates: 2. A versatile three-component solid-phase organic synthesis methodology; *Tetrahedron Lett.*; 1998, **39**, 967.

xxxiv Hoekstra W. J.; Greco M. N.; Yabut S. C.; Hulshizer B. L.; Maryanoff B. E.; Solid-phase synthesis via N-terminal attachment to the 2-chlorotrityl resin; *Tetrahedron Lett.*; 1997, **38**, 2629.

xxxv Nash I. A.; Bycroft B. W.; Chan W. C.; Dde—A selective primary amine protecting group: A facile solid phase synthetic approach to polyamine conjugates; *Tetrahedron Lett.*; 1996, **37**, 2625.

xxxvi Bernhardt A.; Drewello M.; Schutkowski M.; The solid-phase synthesis of side-chain-phosphorylated peptide-4-nitroanilides; *J. Pept. Res.*; 1997, **50**, 143.

xxxvii Mellor S. L.; McGuire C.; Chan W. C.; N-Fmoc-aminooxy-2-chlorotrityl polystyrene resin: A facile solid-phase methodology for the synthesis of hydroxamic acids; *Tetrahedron Lett.*; 1997, **38**, 3311.

xxxviii Meloni M. M.; Taddei M.; Solid-phase synthesis of β-lactams via the Miller hydroxamate approach; *Org. Lett.*; 2001, **3**, 337.

xxxix Redwan I. N.; Grøtli M.; Method for activation and recycling of trityl resins; *J. Org. Chem.*; 2012, **77**, 7071.

xl García-Martín F.; Bayó-Puxan N.; Cruz L. J.; Bohling J. C.; Albericio F.; Chlorotrityl

chloride (CTC) resin as a reusable carboxyl protecting group; *QSAR Comb. Sci.*; 2007, **26**, 1027.

xli Yoo S. E.; Lee S. H.; Reduction of organic compounds with sodium borohydride-copper(II) sulfate system; *Synlett*; 1990, **1990**, 419.

xlii Kalola A. G.; Prasad P.; Mokariya J. A.; Patel M. P.; A mild and selective Cu(II) salts-catalyzed reduction of nitro, azo, azoxy, N -aryl hydroxylamine, nitroso, acid halide, ester, and azide compounds using hydrogen surrogacy of sodium borohydride; *Synth. Commun.*; 2021,1.

xliii FNMR002360.pdf (sigmaaldrich.com), (October-2021)

xliv Fatty Alcohols (aocs.org), (October-2021)

xlv Neyt N. C.; Riley D. L.; Mild and selective reduction of aldehydes utilising sodium dithionite under flow conditions; *Beilstein J. Org. Chem.*; 2018, **14**, 1529.

xlvi FNMR002312.pdf (sigmaaldrich.com), (October-2021)

xlvii FNMR000756.pdf (sigmaaldrich.com), (October-2021)

xlviii FNMR000611.pdf (sigmaaldrich.com), (October-2021)

xlix FNMR001316.pdf (sigmaaldrich.com), (October-2021)

l FNMR009684.pdf (sigmaaldrich.com), (October-2021)

li FNMR001362.pdf (sigmaaldrich.com), (October-2021)

lii FNMR010535.pdf (sigmaaldrich.com), (October-2021)

liii FNMR001812.pdf (sigmaaldrich.com), (October-2021)

liv https://spectrabase.com/spectrum/4MLx3tnrrV1, (October-2021)

lv FNMR002373.pdf (sigmaaldrich.com), (October-2021)

lvi FNMR011439.pdf (sigmaaldrich.com), (October-2021)

lvii FNMR011322.pdf (sigmaaldrich.com), (October-2021)

lviii Zhang C.; Xu D.; Wang J.; Kang C.; Efficient Synthesis and Biological Activity of Novel Indole Derivatives as VEGFR-2 Tyrosine Kinase Inhibitors; *Russ. J. Gen. Chem.*; 2017, **87**, 3006.

lix Aravinda T.; Bhojya Naik H. S.; Prakash Naik H. R.; 1,2,3-triazole fused quinoline-peptidomimetics: Studies on synthesis, DNA binding and photonuclease activity; *Int. J. Pept. Res. Ther.*; 2009, **15**, 273.

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