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# Facile, green, and functional group-tolerant reductions of carboxylic acids...in water

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ARTICLE

# Facile, green, and functional group-tolerant reductions of carboxylic acids…*in water*

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Facile reductions of carboxylic acids to aldehydes or alcohols can be effected under mild conditions upon initial conversion to their corresponding S-2-pyridyl thioesters. Upon treatment with a commercially available and air-stable nickel pre-catalyst and silane as a stoichiometric reductant, aldehydes are formed in moderate to good yields. Alternatively, the 1-pot conversion of acids to their thioester derivatives can be followed by reduction to the alcohol upon treatment with sodium borohydride. A variety of starting materials ranging from highly functionalized acids to educts from the Merck Informer Library can be transformed using these green reaction media.

## Introduction

Virtually every textbook on introductory organic chemistry discusses reductions of carboxylic acids and their derivatives, such as esters, acid halides, and (mixed) anhydrides, the focus being hydride-containing reducing agents, most notably lithium aluminium hydride (LAH) and di-isobutyl aluminium hydride (DIBAL-H).[1] The former was introduced to organic synthesis back in 1947, while the latter was initially used for olefin polymerization starting in 1960. And while their extensive service to organic synthesis over decades is secure, their intolerance to air and moisture along with reactivity/selectivity issues are also well-known limitations. Moreover, as seen today through green glasses, there is considerable room for approaches that, while equally effective, are not only more functional group tolerant but also in line with the times: where the overall environmental footprint is minimized. In response, many alternative processes have appeared that offer the potential for gaining access to both the derived aldehydes and alcohols, including specialized metal hydride reagents,[5] hydrosilylations,[6] as well as several other noteworthy methods[7-9] that accomplish the intended reductions to either or both types of products. The most relevant prior art to this study involves the time-honored Fukuyama reduction, commonly viewed as a robust method for converting carboxylic acids selectively to aldehydes that proceeds via an alkyl-thioester intermediate employing a Pd catalyst and $Et_3SiH$ as a mild reductant.[10] Advances of late, using "earth-abundant" nickel have emerged as alternative catalytic approaches.[11-13] For example, Iosub, Bergman, and co-workers have recently developed a Ni (10 mol %)-catalyzed process using a mixed anhydride as an intermediate and $Ph_2SiH_2$ as reductant[14] in dilute EtOAc at 40 °C over 24 hours, for converting (mainly) aliphatic carboxylic acids to aldehydes.

The direct reduction of carboxylic acids to alcohols is also a challenging transformation, traditionally falling under the same LAH or DIBAL regime.[15-16] Alternatives such as catalytic hydrogenation of carboxylic acids to alcohols exist,[17-20] although they usually require rather high pressures of hydrogen and may also rely on precious metal catalysts and specialized ligands. While there are numerous examples of hydrosilylations of esters[21] and amides,[22] reductions of free carboxylic acids oftentimes resort to large excesses of the silane reagent and rely on noble metals (e.g., Ru,[23] Rh[24] and Ir[25]). Recently, base metals such as Zn[26] and Mn[27] have been found to reduce acids to alcohols employing a silane reductant. To realize these double reductions, a green technology was envisioned that avoids transition metal-based reagents, takes place efficiently in an aqueous medium under mild conditions, and is very tolerant of functional groups present in the starting acid. The approach developed for both is based on use of dipyridyldithiocarbonate (DPDTC)[28a-c] that converts acids to the corresponding 2-pyridylthioesters that can be easily isolated or used *in situ*. Upon exposure, for example, to amines leads to formation of amide and peptide bonds.[28d,e] As discussed herein, their subsequent treatment in a 1-pot operation using either Ni catalysis together with a silane leads to aldehydes, while exposure to $NaBH_4$ in 95% EtOH at rt directly affords the targeted alcohols.

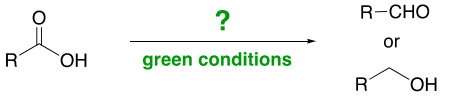


**Figure 1.** Selective reductions of carboxylic acids: no LAH, no DiBAL.

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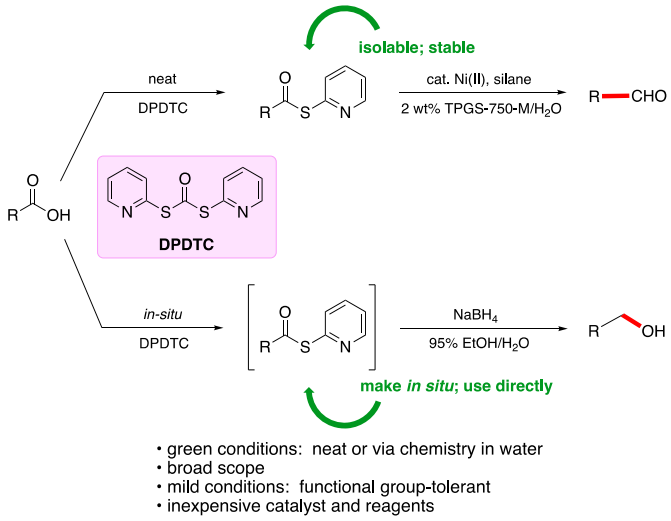
## Results and Discussion

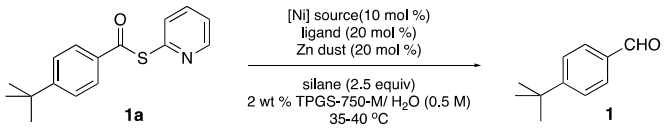
*Reductions of carboxylic acids to aldehydes (Scheme 1)*. Initial studies looking to reduce model thioester **1a** to aldehyde **1** focused on optimizing the source of commercially available Ni, the ligand, and the silane (Table 1). Use of $NiCl_2$(dme) as pre-catalyst and 4-4'-di-*t*-butyl-2,2'-dipyridyl (dtbbpy) as ligand led to the desired reduction forming the corresponding benzaldehyde **1**, the reaction being run in 2 wt % aqueous TPGS-750-M solution. To activate the nickel pre-catalyst, zinc metal was added to convert Ni(II) to Ni(0).[29a,30] Several silane sources were also screened, including triethylsilane, poly(methylhydrosiloxane) (PMHS), and tetramethyldisiloxane (TMDS; Table 1, entries 1, 2, and 4). Each gave only traces of the desired aldehyde, while diphenylsilane afforded ca. 48% yield of product **1** (by NMR; entry 3). Using diphenylsilane ($Ph_2SiH_2$) several sources of nickel were then screened (Table 1). Of these, $NiBr_2$(dme) gave the best results (entry 6). Surprisingly, the nickel(0) source $Ni(COD)_2$ (entry 7) led to only 15% of the aldehyde (by NMR).

The nature of the counterion associated with the initial nickel salt also seemed crucial, as switching from bromide to chloride (i.e., $NiCl_2$(dme)) gave inferior results. Insofar as other ligands are concerned,[29] dtbbpy proved to be the most effective in catalyzing these reductions. This observation may be reflective of the ease in the reductive elimination step of the catalytic cycle due to increased electron density as well as the bulkiness imparted by the *t*-butyl groups. Nickel-based catalysts are known to potentially lose activity[31] (i.e., are poisoned) resulting from metal chelation by the presence of heteroatoms in the starting materials, or products/by-products formed. Under these aqueous conditions, a similar observation was made due to chelation of nickel by the 2-mercaptopyridine released from DPDTC. Addition of zinc chloride was very effective as a thiol scavenger, leading to the complete reduction of acids to the corresponding aldehydes in good yields (by NMR) (see ESI, Table S4).



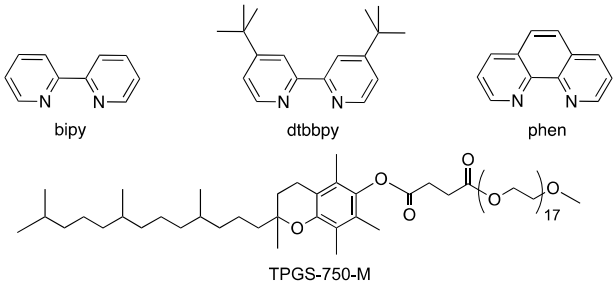

**Scheme 1.** Reductions of carboxylic acids to either aldehydes or alcohols.

**Table 1.** Initial optimization of thioester reduction to the aldehyde.



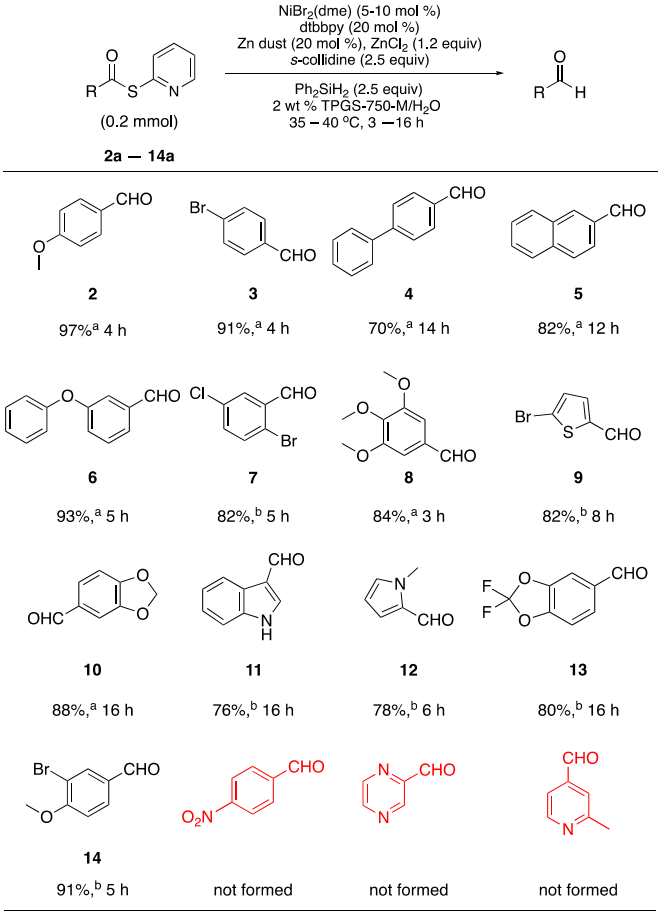

| entry[a] | [Ni] source | ligand | silane | yield (%)[b] |
|---|---|---|---|---|
| 1. | $NiCl_2$(dme) | dtbbpy | $Et_3SiH$ | trace |
| 2. | $NiCl_2$(dme) | dtbbpy | PMHS | trace |
| 3. | $NiCl_2$(dme) | dtbbpy | $Ph_2SiH_2$ | 48 |
| 4. | $NiCl_2$(dme) | dtbbpy | TMDS | trace |
| 5. | $Ni(acac)_2$ | dtbbpy | $Ph_2SiH_2$ | trace |
| **6.** | **$NiBr_2$(dme)** | **dtbbpy** | **$Ph_2SiH_2$** | **52** |
| 7. | $Ni(COD)_2$ | dtbbpy | $Ph_2SiH_2$ | 15 |
| 8. | $NiBr_2$(dme) | bipy | $Ph_2SiH_2$ | 30 |
| 9. | $NiBr_2$(dme) | phen | $Ph_2SiH_2$ | 13 |

[a] Run on a 0.2 mmol scale. [b] Yields determined by NMR using 1, 3, 5 - trimethoxybenzene as an internal standard (see ESI).




While zinc bromide gave similar results, other thiol scavengers like copper thiocarboxylate (CuTC),[32] CuMeSal,[33] and *N*- ethylmaleimide (see ESI, Table S4) resulted in little-to-no product being observed. To neutralize the HCl released by $ZnCl_2$, several bases were examined. 2,6-Lutidine and 2,4,6-collidine gave similar results, whereas triethylamine and Hunig's base gave inferior results (see ESI, Table S6). 2,4,6-Collidine, therefore, was chosen over lutidine because it afforded better emulsification properties of the aqueous reaction mixture. Inorganic bases were not considered because of possible precipitation with 2-mercaptopyridine, resulting in inadequate stirring of the reaction mixture. Lowering the catalyst loading to 5% Ni(II) still provided sufficient reactivity (see ESI, Table S7), although this was substrate-dependent. Control experiments confirmed that both the nickel catalyst as well as zinc dust were essential for the reaction to occur (see ESI, Table S8). When the reaction was carried out in the absence of base, the yield dropped. In terms of temperature, at 60 °C a slightly lower yield was observed due to hydrolysis of the thioester. Based on these studies the optimized conditions were determined to be: 40 °C at 0.5 M in 2 wt % TPGS-750-M/$H_2O$, using 5-10 mol % $NiBr_2$(dme) as pre-catalyst, 1.2 equiv of zinc chloride as thiol scavenger, and 2.5 equiv of the base and reducing agent. Under these newly established conditions, the scope of the reduction of S-2-pyridyl thioesters to the corresponding aldehydes was explored. As summarized in Scheme 2, electron-neutral and electron-rich carboxylic acids gave the corresponding

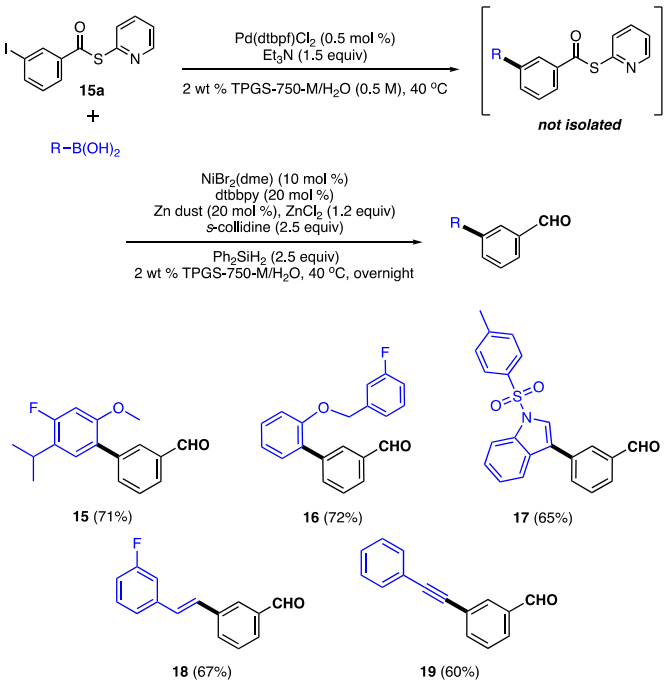
aldehydes in good-to-excellent yields. Substrates with reducible functionality such as an aryl or heteroaryl bromide or chloride were unaffected, as shown by formation of products **3**, **6**, **7**, and **14**. Carboxylic acids containing thiophene, benzodioxole, indole, pyrrole (products **9** – **13**) were reduced in moderate-to-good yields. Unfortunately, acids present within electron-*deficient* heterocycles including pyridine, pyrazine, pyrimidine, etc. are seemingly not amenable to aldehyde formation. Moreover, the presence of electron-withdrawing groups such as $CF_3$, nitro, nitrile, ester, etc. on an aromatic ring, likewise, resulted in almost no conversion to the




corresponding aldehydes, perhaps due to the slow reductive

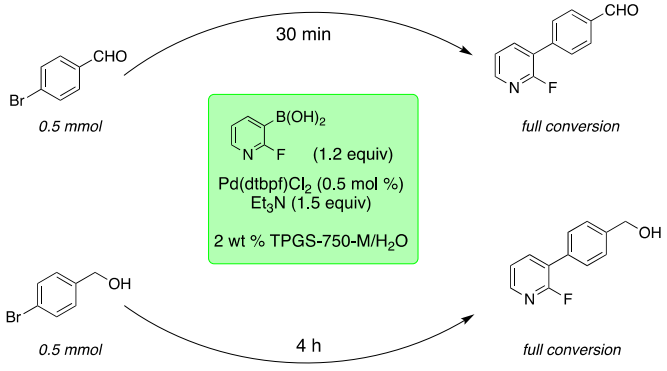
**Scheme 2.** Reduction of S-2-pyridyl thioesters to aldehydes. [a]5 mol % [Ni]; [b]10 mol % [Ni].

elimination of the presumed intermediate nickel complex.[34] Related attempts at reductions of aliphatic carboxylic acids under the same aqueous micellar conditions afforded only traces of the desired aldehyde, the major product being the corresponding hydrocarbon, potentially formed via decarbonylation of a Ni-acyl intermediate. Although there are clearly limitations in terms of scope, those acids that do participate and form aldehydes can be further functionalized in a 2-step, 1-pot fashion, as illustrated by products shown in Scheme 3. Thus, the thioester of 3-iodobenzoic acid was first subjected to a Suzuki-Miyaura coupling followed by reduction in the same pot



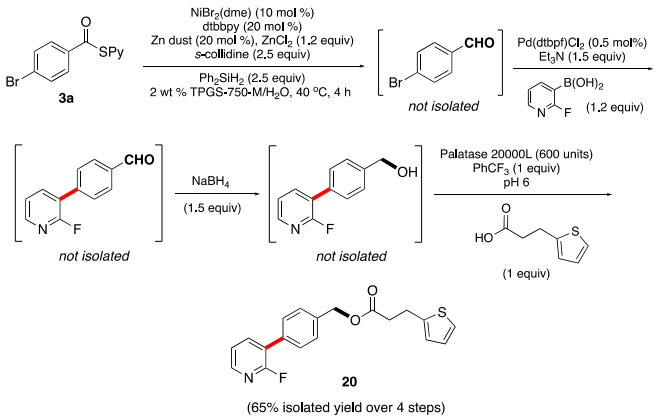

**Scheme 3.** 2-Step, 1-pot sequence to synthesize functionalized aldehydes.

using our catalytic system to the corresponding aldehyde. Within the toolbox associated with micellar catalysis lies its enabling properties in the area of biocatalysis. Thus, just having this amphiphile present in a buffered aqueous medium can dramatically enhance the extent of substrate conversion, where the nanomicelles present serve to accommodate the water-insoluble products that otherwise can accrue, leading to enzymatic inhibition.[35a] By minimizing this undesired phenomenon, greater levels of product formation allow for 1-pot chemoenzymatic sequences which include ketoreductases (KRED),[35a] ene-reductases (ERED),[35b] lipases,[35c] and aminotrans-ferases (ATA)[35d] in the aqueous reaction media. The advantages from such sequences leading to both "pot"[36] and "time"[37] economy, among others (e.g., minimizing waste creation) are the subject of recent reports[38] and reviews.[39] A 4-step, 1-pot sequence, therefore,




**Scheme 4.** Demonstration of fast reactivity of 4-bromobenzaldehyde *vs.* 4-bromobenzyl alcohol.

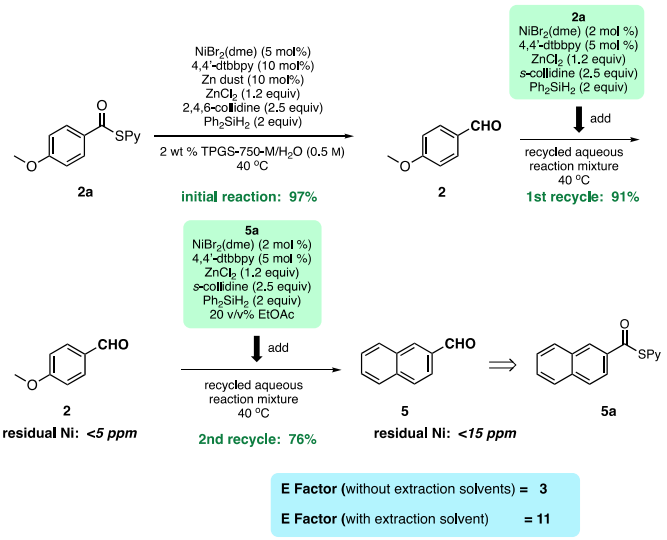
was developed involving reduction of a carboxylic acid. In this case, formation of the derived aldehyde provides an activating group, enhancing the facility associated with the oxidative addition step required for a Pd-catalyzed cross coupling, notwithstanding its eventual further reduction. The extent of this activation can be seen from the relative rates of the Suzuki-Miyaura couplings involving both the benzaldehyde and the benzyl alcohol (Scheme 4). Hence, initial reduction of *S*-(pyridin-2-yl)-4-bromobenzothioate (**3a**) led to 4-bromobenzaldehyde which, without isolation, readily participated in a Suzuki-Miyaura coupling using only 5000 ppm (0.5 mol %) of $Pd(dtbpf)Cl_2$ to afford the biaryl intermediate. Introduction of sodium borohydride resulted in the corresponding primary alcohol. Subsequent adjustment of the reaction mixture to pH 6 followed by addition of Palatase 20000L[35c] provided the corresponding ester (**20**) in 65% yield over 4 steps (Scheme 5).




**Scheme 5.** 1-Pot, 4-step chemoenzymatic sequence, in water.

Often used metrics that indicate the level of "greenness" associated with an organic reaction include recyclability, in this case of the aqueous reaction mixture, as well as calculation of an E Factor, as first described by Sheldon.[40] Following an initial reaction from **2a** to **2** (Scheme 6), product recovery is readily accomplished by in-flask extraction using minimal amounts of recyclable EtOAc. Reuse of the water remaining in the same vessel for two additional cycles led to good results in terms of product formation, even when using a different substrate (**5a** to **5**). However, due to salt build-up and precipitation, further recycling could not be carried out. The E Factors associated with this sequence of steps was 3 (when recyclable extraction solvent EtOAc is not considered as waste; see ESI, section S4, for calculations) and 11 (considering EtOAc as waste; see ESI, section S4). Importantly, ICP-MS analysis of products **2** and **5** from the recycled aqueous medium showed low levels of residual metal: 13 ppm Ni (see ESI, section S6), after silica gel chromatography, which is below the FDA-allowed 22 ppm per day per dose.[41]

*Reductions of carboxylic acids to alcohols (Scheme 1)*. Initial activation of the carboxylic acid via a S-2-pyridyl thioester was carried using DPDTC in an identical fashion as seen previously (vide

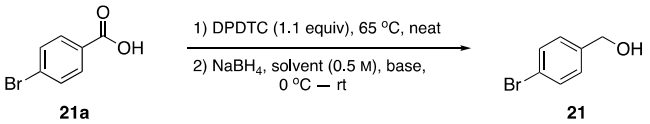



**Scheme 6.** Recycling of the aqueous reaction medium and calculation of E Factors.

supra). Subsequent reduction was accomplished using sodium borohydride. Optimization began for the conversion of **21a** to **21** (Table 2) under aqueous micellar conditions using a 2 wt % TPGS-750-M solution. Although the reduction went smoothly with full conversion of the thioester, considerable foaming was observed when $NaBH_4$ was added to the micellar medium due to the evolution of $H_2$ gas, which was difficult to control even on a small scale. As a result, the switch was made to an aqueous solution of 2 wt % Coolade,[42] a low foaming surfactant developed for precisely this purpose. Using 1.1 equivalents of DPDTC to make the thioester and then four equivalents of sodium borohydride to facilitate reduction, several bases were screened as the stability of sodium borohydride increases under basic conditions in water.[43] $Et_3N$, Hunig's base, and 2,6-lutidine gave similar yields of alcohol by NMR (Table 2, entries 2 and 3). Even though the reaction could be carried out under aqueous micellar conditions, the formation of unwanted side products, i.e., the hydrolysis of the thioester back to the carboxylic acid under basic conditions, could not be avoided. This led to screening of several green solvents. Both 95% $EtOH/H_2O$ and absolute ethanol gave similar yields of product, whereas methanol and 2-propanol afforded inferior results (Table 2, entries 4–7). The reaction with methanol gave the corresponding methyl ester as the major side product, as determined by crude NMR. 95% $EtOH/H_2O$ was selected as the medium of choice given its commercially availability and low cost (i.e., it is a biomass derived product).[44] Decreasing the number of equivalents of $NaBH_4$ from 4 to 1.5 reduced the yield to 50% (by NMR; see ESI, Table S10). As a result, three equivalents of $NaBH_4$ were used in all cases. Under these optimized conditions, the scope of reductions of carboxylic acids to alcohols was then explored. As summarized in Scheme 7, a wide range of functionality can be tolerated under these conditions. Aliphatic substrates bearing a reducible moiety, such as an alkene, alkyne, thioether, etc. gave good results without impacting these functionality groups (entries **23**, **34,** **42**). For aryl-acetic acid and aryl-propionic acid derivatives, the

electronic nature and position of the substituents on the ring could be varied widely, with products **27**, **28**, and **29** all being obtained in high yields. Aromatic carboxylic acids containing heterocycles like thiophene, benzofuran, indazole, pyridine, benzodioxole, etc.,

**Table 2.** Initial optimization of carboxylic acid reduction to alcohols.



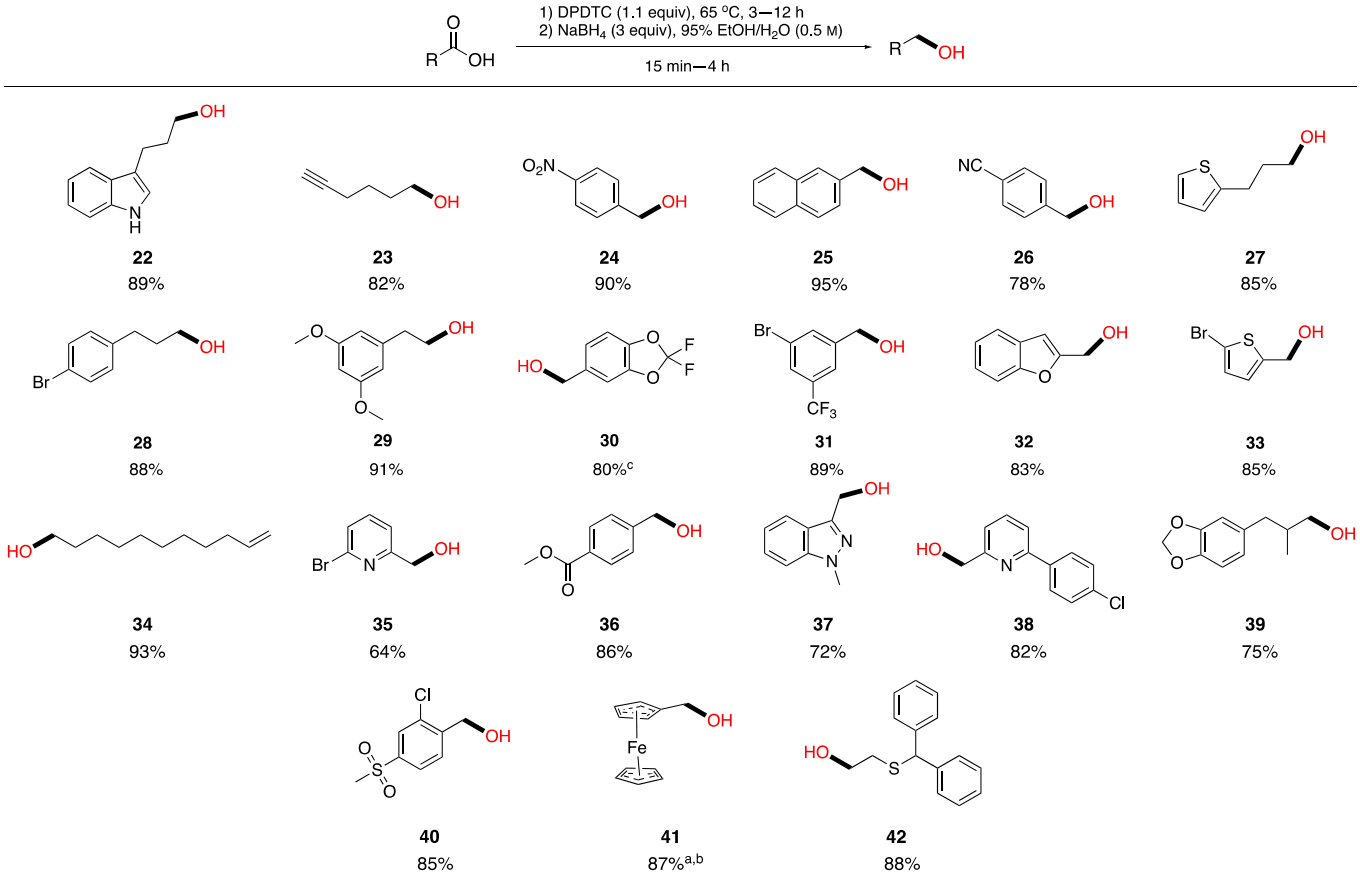

**21a** **21**

| entry[a] | solvent | $NaBH_4$ (equiv) | yield (%)[b] |
|---|---|---|---|
| 1. | 2 wt % TPGS-750-M/$H_2O$[d] | 4 | N/D[f] |
| 2. | 2 wt % Coolade/$H_2O$[d] | 4 | 83 |
| 3. | 2 wt % Coolade/$H_2O$[e] | 4 | 85 |
| 4. | MeOH | 4 | 45[c] |
| 5. | *i*-PrOH | 4 | 86 (82)[c] |
| 6. | 95% EtOH/$H_2O$ | 4 | 98 (94)[c] |
| 7. | absolute EtOH | 4 | 95 (91)[c] |
| 8. | 95% EtOH/$H_2O$ | 2 | 80 |
| **9.** | **95% EtOH/$H_2O$** | **3** | **98 (94)[c]** |

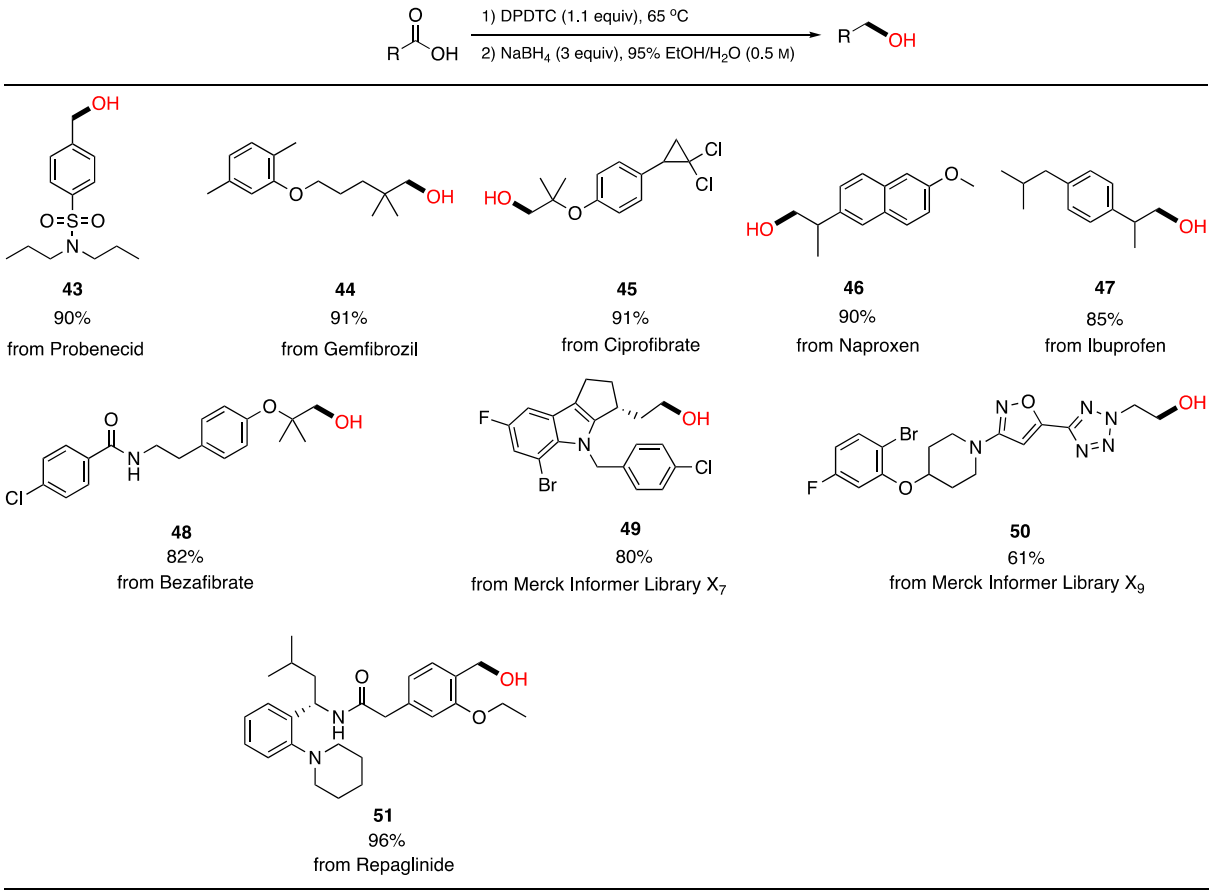
[a] Run on a 0.25 mmol scale; [b] Yields determined by NMR using 1, 3, 5 - trimethoxybenzene as an internal standard (see ESI); [c] isolated yield; [d] 2, 6 - Lutidine (2 equiv) used as base; [e] $Et_3N$ (2 equiv) used as base; [f] Yield could not be determined due to excessive foaming of the reaction mixture (see ESI).

(products **30**, **32, 33, 35, 37, 38**) were well tolerated. Electron-withdrawing groups such as nitrile, nitro, ester, and a *p*-tolylsulfonyl group on the aromatic ring seemed to perform better (entries **26, 24, 36, 40**) as compared to the previous cases wherein there was no reaction with moieties containing electron-withdrawing groups. It is interesting to note that the reduction of the intermediate thioester to the corresponding alcohol achieves full conversion (TLC and crude NMR). However, the slightly lower yields of some substrates can be attributed to the first step, i.e., formation of thioesters from acids.

To further test the generality of this method, some late-stage functionalized substrates and bioactive molecules were also screened (Scheme 8). Reduction of biologically active aryl-propionic acids used as non-steroidal anti-inflammatory drugs naproxen and ibuprofen (entries **46, 47**) proceeded smoothly. Probenecid, a drug used to treat gouty arthritis, and Repaglinide, a drug used to treat diabetes, were both reduced in excellent yields (products **43** and **51**, respectively). Lastly, the fibrates, which are a class of lipid lowering drugs including gemfibrozil (**44**), ciprofibrate (**45**), and bezafibrate (**46**) were all reduced to the corresponding alcohols in excellent yields. It is interesting to note that the *gem*-dichlorocyclopropane moiety in ciprofibrate derivative **45** remains intact under these mild and green reducing conditions. To test the limits of this reaction, we also examined highly functionalized cases from the Merck informer




**Scheme 7.** Representative reductions of carboxylic acids to alcohols. [a] Reaction time: 4 h; [b] 4 equiv $NaBH_4$; [c] 10 mol % DMAP used in step 1.

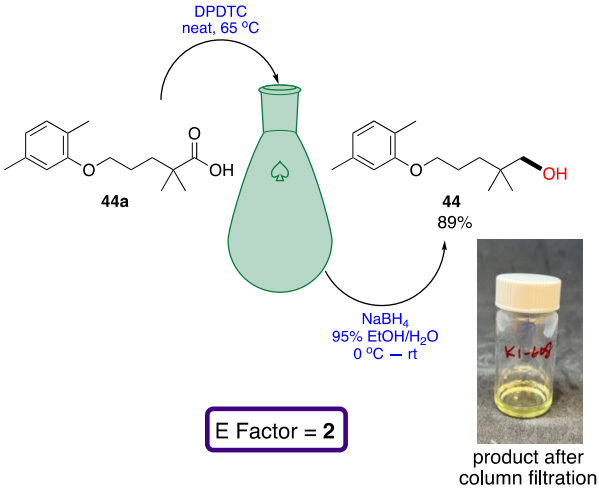



**Scheme 8.** Reduction of late-stage functionalized carboxylic acids to alcohols.

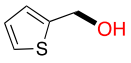
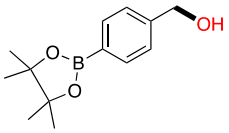
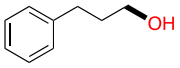
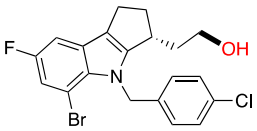
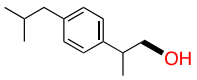
library,[45] which gave the corresponding alcohols in good, isolated yields (entries **49, 50**).

To demonstrate the practical utility of the method, this process was performed on a gram scale, as illustrated in Scheme 9. As expected, this one-pot thioesterification/reduction proceeded quite efficiently. Moreover, it was demonstrated that the ethanol used for the reduction step can be recycled in subsequent reactions (see ESI, section S5). The isolated product exhibited high purity, as evaluated by $^{1}$H and $^{13}$C NMR, while an E Factor of only 2 was calculated as a measure of greenness. This collection of data, obtained on a 1.5 g scale, showcases the potential synthetic utility of this reduction in an industrial setting.

Lastly, direct comparison cases of this new technology with existing literature techniques [25-27] are illustrated in Scheme 10. Formation of 2-thiophenemethanol (**52**) and (4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanol (**53**) highlight the avoidance of endangered metals to facilitate this reduction ($Zn(OAc)_2$[26] *vs.* $NaBH_4$). Reduction of 3-phenyl propionic acid to 3-phenyl propanol (**54**) demonstrates time economy and avoids use of otherwise extreme reaction conditions (6 MPa $H_2$ gas, 180 °C)[25b] and expensive catalysts. In the case of more challenging substrates, recent literature conditions[27] that utilize $Mn(CO)_5$ as catalyst were investigated. Reduction of Ibuprofen (**47**) and the Merck Informer Library-derived alcohol **49**, are both illustrative of the higher efficiency of this methodology as compared to current literature methods.[46]




**Scheme 9**. Gram-scale synthesis of gemfibrozil alcohol.

| *this work* | | *literature conditions* |
|---|---|---|
| 1) DPDTC (1.1 equiv), 65 °C<br>2) $NaBH_4$ (3 equiv), 95% EtOH/$H_2O$ (0.5 M), 0 °C — rt, 30 min — 1 h<br>**84%** |  <br>**52** | $Zn(OAc)_2$ (10 mol %), $PhSiH_3$ (2 equiv)<br>NMM (10 mol %)<br>2-MeTHF, 80 °C, 16 h<br>**72%**[26] |
| 1) DPDTC (1.1 equiv), 65 °C<br>2) $NaBH_4$ (3 equiv), 95% EtOH/$H_2O$ (0.5 M), 0 °C — rt, 30 min —1 h<br>**68%** |  <br>**53** | $Zn(OAc)_2$ (10 mol %), $PhSiH_3$ (2 equiv)<br>NMM (10 mol %)<br>2-MeTHF, 80 °C, 16 h<br>**64%**[26] |
| 1) DPDTC (1.1 equiv), 65 °C<br>2) $NaBH_4$ (3 equiv), 95% EtOH/$H_2O$ (0.5 M), 0 °C — rt, 30 min — 1 h<br>**90%** |  <br>**54** | $H_2$ (6 MPa)<br>$IrPCy_2$ (2 mol %)<br>NaH (6 - 12 mol %)<br>$ZrCl_4(THF)_2$ (1-2 mol %)<br>*n*-BuOH (2 equiv)<br>toluene<br>180-190 °C, 28 h<br>**87%**[25b] |
| 1) DPDTC (1.1 equiv), 65 °C<br>2) $NaBH_4$ (3 equiv), 95% EtOH/$H_2O$ (0.5 M), 0 °C — rt, 30 min — 1 h<br>**80%** |  <br>**49** | 1) $[Mn(CO)_5]$ (2 mol %), $PhSiH_3$ (2.0 - 2.5 mol %)<br>2-MeTHF (2 M), 80 °C, 2-16 h<br>2) hydrolysis<br>**48%**[27] |
| 1) DPDTC (1.1 equiv), 65 °C<br>2) $NaBH_4$ (3 equiv), 95% EtOH/$H_2O$ (0.5 M), 0 °C — rt, 30 min — 1 h<br>**85%** |  <br>**47** | 1) $[Mn(CO)_5]$ (2 mol %), $PhSiH_3$ (2.0-2.5 mol %)<br>2-MeTHF (2 M), 80 °C, 2 - 16 h<br>2) hydrolysis<br>**73%**[27] |

**Scheme 10.** Direct comparisons with literature processes.

## Conclusions

In summary, environmentally responsible methods for reductions of carboxylic acids to aldehydes and alcohols has been developed utilizing green and recyclable reaction media. These transformations rely on inexpensive and commercially available catalysts and reagents. Moreover, and unlike prior reports, this technology offers a broad selection of substrate types, including functionalized educts suggesting its potential applications to late-stage functionalization of value in medicinal chemistry. The overall environmental impact appears to be relatively modest based on an E Factor analysis. Lastly, a 1-pot, 4-step sequence is illustrative of surfactant-enabled chemo-enzymatic catalysis involving this type of catalysis. Further applications, including esterification and thioesterification using this technology, will soon be disclosed in a forthcoming publication.

## Author Contributions

All authors have given approval to the final version of the manuscript. K.I. optimized the reaction conditions, carried out the substrate scope, collected analytical data, and drafted the manuscript. C.N. helped in optimization, substrate scope, and collected analytical data. B.H.L. oversaw the work and aided in drafting the manuscript.

## Conflicts of interest

There are no conflicts to declare.

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