Revisiting the Meerwein–Ponndorf–Verley reduction: a sustainable protocol for transfer hydrogenation of aldehydes and ketones

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An economical and sustainable transfer hydrogenation for aldehydes and ketones is described. The general protocol is mild, chemo-selective and, importantly, uses neither precious nor non-precious metals and even no ligands.

Intorduction

The metal-catalyzed transfer hydrogenation of carbonyl compounds known as the Meerwein–Ponndorf–Verley reduction has received much interest because of the immense number of opportunities that exist to prepare high-value products.[1] This reaction is also featured in numerous multi-step organic syntheses and is arguably the most important catalytic reaction for the synthesis of many fine and bulk chemicals.[1–4] Indeed, in the last two decades, there have been several hundred publications in this area. Most of these protocols generally require either a stoichiometric quantity of hydride donors or precious metals and organometallic compounds.[5–7] Adolfsson *et al.* developed an excellent protocol using lithium isopropoxide,[8a] which was recently improved by Ley and coworkers by using a continuous flow method.[8b] Catalyst activity is extensively influenced by the metal as well as ligands and, because of their high activity and wide applicability, a large percentage of known catalysts is based on precious metals such as palladium,[9] rhodium,[10] ruthenium,[11,12] iridium[13] and recently gold.[14] However, due to their expensive nature, inadequate accessibility, and toxicity of these often used metals, there is an urgent need to develop less expensive and easily available catalyst systems for sustainable hydrogenation protocols.[15]

While a single solution to the problem does not exist, one of the best ways to overcome this issue could be the use of non-precious metals such as iron.[16–18] Since iron is less expensive and naturally abundant, the resulting protocol will be economic, benign, and sustainable. Pioneering efforts in this area have resulted in excellent iron-catalyzed processes and led the way to advance this branch of catalysis;[19–22] however, the majority of the reported protocols use exotic iron complexes and expensive ligands, which overshadows the main objective of using iron metal as a catalyst. Thus, the development of a truly sustainable transfer hydrogenation protocol remains a challenge.

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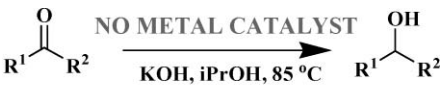
Results and discussion

In view of our ongoing quest for sustainable processes,[23–27] we envisioned a ligand-free catalyst system for transfer hydrogenation of aldehydes and ketones using non-precious iron metal and preferably a method that is devoid of any metal. Serendipitously, we have discovered that, using the appropriate conditions, it is possible to perform transfer hydrogenation reactions without using any transition-metals and ligands, by simply employing potassium hydroxide (KOH) (Scheme 1).



Scheme 1 Catalyst-free transfer hydrogenation of aldehydes and ketones.

As an initial stride in the development of our catalyst-free transfer hydrogenation methodology, we chose to study the reduction of benzaldehyde as a model reaction. The influence of different KOH concentrations on the reaction rate was studied. All the reactions were performed in a 10 mL crimp-sealed thick-walled glass tube using 1 mmol of aldehyde at 85 °C with 3 mL isopropanol as a hydrogen source and solvent. The results from our optimization studies are presented in Table 1.

First, the reaction was conducted with 20 mol% of KOH and 75% conversion was observed within 60 min (entry 1). Further experiments revealed that even with decreases in the KOH amount down to 12 mol% (entry 4), a good conversion (75%) was achieved. However, when the KOH concentration was reduced to 10 mol% (entry 5), only 65% conversion was observed. Thus, using 12 mol% as an optimized KOH concentration, the reaction time was further decreased to 30 min (entry 6). No reaction (NR) took place in absence of KOH (entry 8). Also, with

Table 1 Optimization of reaction conditions

Entry	KOH (mol%)	Reaction time/min	Conversion (%)
1	20	60	75
2	20	120	77
3	15	60	74
4	12	60	75
5	10	60	65
6	12	30	75
7	12	15	60
8	0	120	NR

Table 2 Metal catalyst-free transfer hydrogenation of aldehydes[a]

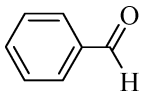
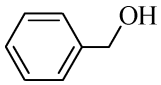
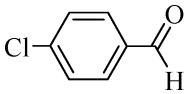
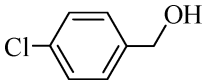
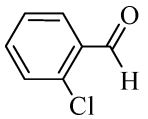
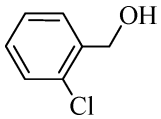
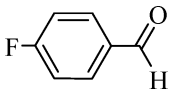
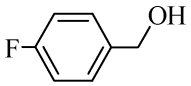
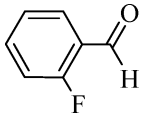
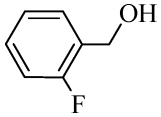
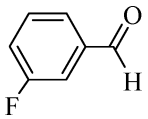
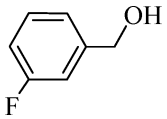
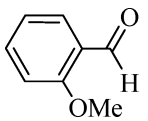
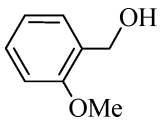
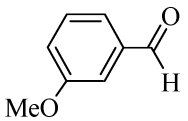
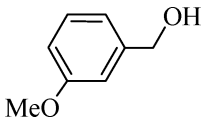
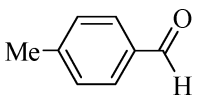
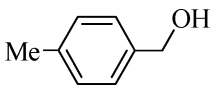
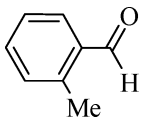
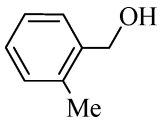
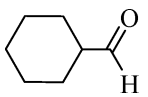
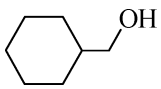
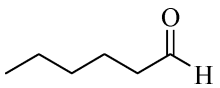
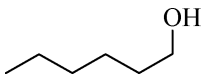
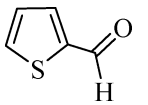
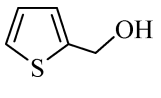
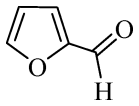
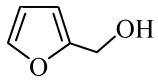
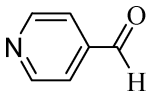
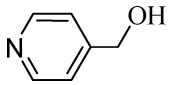
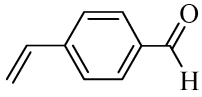
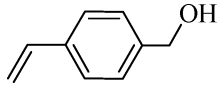
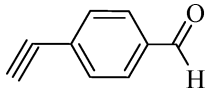
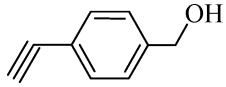
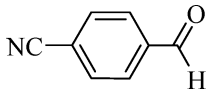
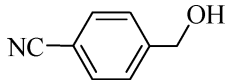
Entry	Aldehydes	Product	Yield[b] (%)
1			75
2			76
3			74
4			76
5			75
6			72
7			74
8			72
9			65
10			68
11			67
12			10
13			72

Table 2 *(Contd.)*

Entry	Aldehydes	Product	Yield[b] (%)
14			70
15			68
16			64
17			62
18			66

[a] Reactions were carried out with 1 mmol of aldehydes, 12 mol% of KOH in 3 ml of *i*PrOH at 85 °C for 30–45 min, [b] Yield was determined by GC.

an increase in the temperature above 85 °C, no effect on the reaction rate and substrate conversion was noticed; however below this temperature, conversion was lowered even with longer reaction times.

After the optimized conditions were established, we investigated the scope and the limitations of this transfer hydrogenation protocol for a variety of aldehydes (Table 2).

A wide range of aldehydes were successfully reduced to the respective alcohols in high yields. Substituted aromatic aldehydes reacted readily and the rates were slightly influenced by the electronic effects of the substituents on the aryl ring of the aldehyde. Aldehydes with electron-donating groups showed less reactivity (entries 9, 10) as compared to substrates with electron-withdrawing groups (entries 2–7). However, the location of a particular substitution at the *para*, *ortho*, or *meta* position (entries 4–6) of the aromatic ring did not hamper the reactivity. Several functionalized benzaldehydes with reduction-susceptible functional groups, such as halides (entries 2–6), alkene (entry 16), alkyne (entry 17) and nitrile (entry 18), remained unchanged during the reaction, showing high chemoselectivity of this protocol. This aspect bodes well for its application in the total synthesis of drug molecules, wherein it is possible to reduce carbonyl groups while preserving other functional groups, which can be used for further elaboration in synthetic chemistry. Aliphatic cyclohexane aldehyde gave good yield of the corresponding alcohol (entry 11); however, in the case of hexanal, a low yield of corresponding alcohol was observed due to the competitive aldol reaction (entry 12). The heterocycle-based aldehydes such as thiophene, furan and pyridine (entries 13–15), extensively used as building-blocks in drug discovery, also underwent transfer hydrogenation reaction with high yield, proving the suitability of this protocol for assembly of bio-molecules.

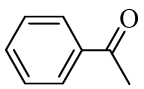
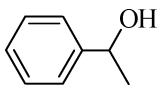
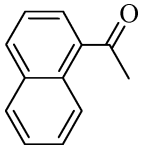
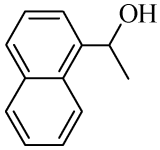
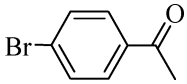
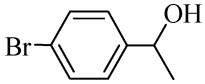
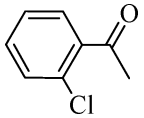
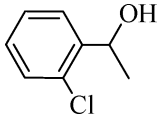
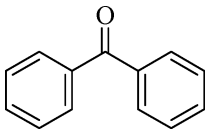
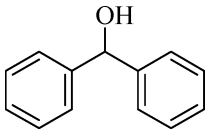
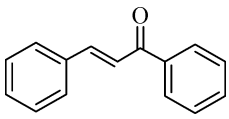
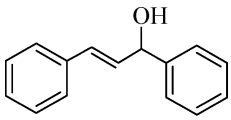
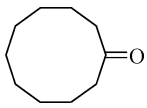
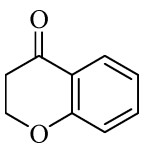
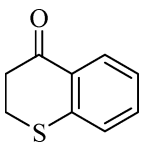
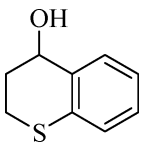
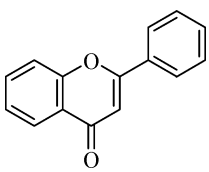
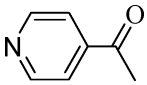
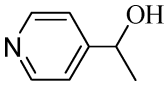
Despite the wide applications of secondary alcohols in the production of high value products and fine chemicals, sustainable and economical hydrogenation of ketones remains a challenge. To broaden the scope of this catalyst-free process, we set out to attempt the transfer hydrogenation of ketones. Although this catalyst-free system was found to be capable of reducing ketone carbonyl, reaction conditions optimized for aldehydes were not suitable for ketones. After several experiments for hydrogenation of acetophenone as a test reaction, with different KOH concentrations, reaction temperatures and times, we observed that heating 1 mmol of acetophenone with 25 mol% of KOH in isopropanol at 85 °C resulted in the slow consumption of starting materials; the reaction needed 18 h to achieve good conversion (73%). Using these optimized reaction conditions, the results for the transfer hydrogenation of assortment of ketones are summarized in Table 3.

This methodology is applicable to a wide range of ketones (Table 3). Aromatic ketones yielded excellent yields of corresponding alcohols and a variety of functional groups, such as bromo- (entry 3), chloro- (entry 4), and alkene (entry 6), were tolerated under these conditions. In the case of aliphatic cyclodecanone (entry 7), 4-chromanone (entry 8) and flavanone (entry 10) no reaction (NR) was observed; thiochroma-4-one (entry 9) produced a modest 20% of the corresponding alcohol. Notably, heterocyclic 1-(pyridin-4-yl)ethanone (entry 11) reacted efficiently with 75% yield.

To eliminate the possibility of any catalytic contamination and to demonstrate unequivocally that the reaction is indeed metal-free, we used virgin glassware and stirring bar, semiconductor grade (99.99% on trace metals basis) potassium hydroxide and absolute (99.9%) isopropanol in an operation that was devoid of a metal spatula, and reactions (entries 1 and 2) proceeded well.

The developed metal catalyst-free protocol is superior to known processes in terms of reactivity and economics of the entire process. The yield and activity of a recently reported gold catalyzed protocol[14] are comparable to the results we obtained without any metals, thus raising the question, why use expensive gold metal, when we really don't need any metal? Although Beller's iron-catalyzed procedure[28] is one of the most sustainable methods to date, it requires toxic phosphine ligands, in contrast to our ligand-free protocol. Also, most of the other previous catalytic hydrogenations require metals and the removal of metal-impurities from the reaction product is extremely difficult but is a required condition in the production of fine chemicals because of toxicity concerns. It is always preferable to develop transition metal-free protocols so that these catalytic systems leave no remnants of metal within the end product, as metal contamination is highly regulated by pharmaceutical industry. Importantly, since no catalyst was used in our system, there is absolutely no possibility (as confirmed by AES-ICP analysis) of any transition-metal contamination in the final product, which will make this a process of first choice for pharmaceutical and chemical industries.

Table 3 Metal catalyst-free transfer hydrogenation of ketones[a]

Entry	Ketones	Product	Yield[b] (%)
1			73
2			76
3			75
4			74
5			82
6			50
7		—	NR
8		—	NR
9			20
10		—	NR
11			75

[a] Reactions were carried out with 1 mmol of ketones, 25 mol% of KOH in 3 ml of *i*PrOH at 85 °C, [b] Yield was determined by GC.

Conclusions

In conclusion, we have developed a transfer hydrogenation protocol which uses neither precious metals nor non-precious metals and even no ligands. This unprecedented, mild, and chemo-selective process is highly economical and truly sustainable. In the present scenario of world economy and environment, performing chemistry in a sustainable manner is a key aspect

and this work may shed light on newer possibilities in transfer-hydrogenation methods for aldehydes and ketones.

Experimental

Transfer hydrogenation of aldehydes

The aldehydes (1 mmol) were placed in a 10 mL crimp-sealed thick-walled glass tube containing 3 mL of isopropanol. 12 mol% of KOH (from the stock solution prepared by sonicating 0.5 g of KOH in 10 mL isopropanol for 15–20 min) was then added to the reaction mixture and the sealed tube was heated in a preheated oil bath at 85 °C for 30–45 min, under continuous stirring. The reaction was monitored by GC-MS and yield was determined by GC. After completion of the reaction, isopropanol was evaporated under vacuum and the residue was dissolved in 2 mL ethyl acetate. It was then washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated in a vacuum to yield crude product, which was further purified by column chromatography.

Transfer hydrogenation of ketones

The ketones (1 mmol) were placed in a 10 mL crimp-sealed thick-walled glass tube containing 3 mL of isopropanol. 25 mol% of KOH (from the stock solution prepared by sonicating 0.5 g of KOH in 10 mL isopropanol for 15–20 min) was then added to the reaction mixture and the sealed tube was heated in a preheated oil bath at 85 °C for 18–24 h, under continuous stirring. After completion of the reaction, product workup similar to aldehydes was followed.

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