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Carbonyl Reduction and Biomass: a Case Study of Sustainable Catalysis

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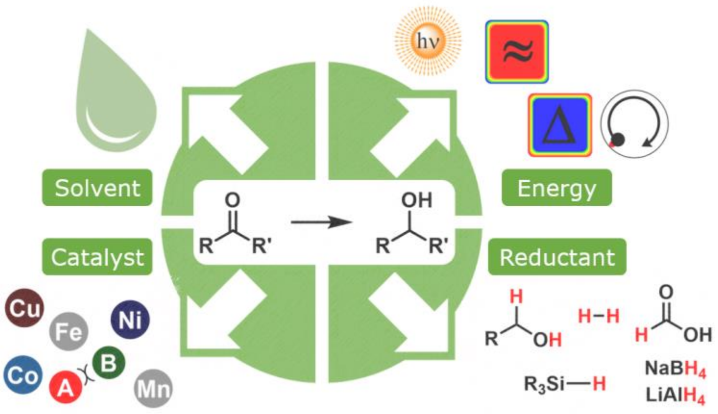
Graphical abstract



Abstract

Catalysis plays a major role at mitigating the environmental impact of the chemical industry, drastically cutting its energy and material consumption. For this perspective, we have chosen C=O reduction in the context of biomass as a benchmark reaction to introduce and illustrate essential aspects of green catalysis. We first covered the most used C=O hydrogenation substrates made from biomass. Then, we looked at alternative energy sources to convective heating, discussed the use of greener solvents and reductants, and listed a few precious metal-free catalytic systems. Finally we looked at various hydrogen sources, including bio-sourced ones. In particular, we emphasized the use of metrics in order to quantify the actual impact of these innovations.

Keywords

Catalysis – Hydrogenation – Biomass – Solvent - Energy

Synopsis (1 sentence 20 words)

C=O reduction of biomass was used as a benchmark to give an overview of recent developments in catalysis

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Introduction

From the inception of green chemistry, catalysis has been considered a key tool to achieve a more sustainable chemical industry, and was coined a “pillar of green chemistry”, in addition to being one of its 12 principles.[1] Indeed catalysis offers the possibility to positively impact a chemical process in many different ways, including lowering energy and materials inputs, increasing conversion and selectivity, thus improving upon separation and purification and favoring less dangerous and toxic reagents. In a quarter century of green chemistry research,[2] catalysis has enabled some of its finest developments. Catalysis has proven a particularly appealing strategy towards tackling the grand challenge of biomass conversion to useful chemicals and fuels.

Catalytic reduction is among the most important chemical transformations in volume in industry and are routinely employed at all scales of chemical production.[3] Reduction is a particularly crucial process in the context of biomass transformation, since the lignocellulosic material is oxygen rich, with a key feature on carbonyl reduction.[4] Indeed, most biomass-derived molecules are naturally C=O/C-O-rich, in contrast to petroleum-based chemicals.[5]

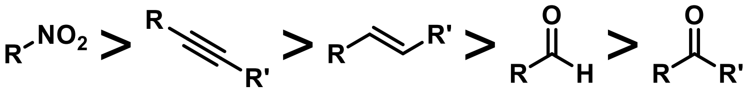
Hydrogen gas is often considered an ideal reducing agent both in terms of cost and atom economy. Indeed, hydrogenation has been largely explored in academia, with the first catalytic example reported in 1874 for olefin hydrogenation.[6] It has become a powerful tool for key processes in the industry, such as the Haber-Bosch process, the Fischer-Tropsch synthesis, or oil refining.[7] Despite its advantages, the use of H_2 gas may be problematic in some settings because of its flammability and the need for pressurization. On the other side of the spectrum, in the pharmaceutical industry, the most common reducing agents used are $LiAlH_4$ and $NaBH_4$. These inorganic salts are particularly reactive toward carbonyls, and have been successfully implemented in large-scale processes (>100 mol scale).[8] Noyori-type catalysts are, on their end, most used for asymmetric prochiral ketone reduction.[9]

In the context of biomass upgrading, H_2 is commonly used as the reducing agent, in conjunction with a catalyst. Platinum group metals (PGMs) such as Pd, Ru as both homogeneous and heterogeneous systems are commonly investigated for their activity and selectivity. These come with their own drawbacks: low abundance,[10] high toxicity,[11] and recycling issues.[12] Thus a lot of research efforts are dedicated to the development of heterogeneous catalysts and/or the use of earth abundant metals in the context of biomass upgrading.[13] Transfer hydrogenation methodologies have also been explored.[4]

For this perspective, we have chosen C=O reduction in the context of biomass as a benchmark reaction to introduce and illustrate essential aspects of green catalysis. We have reviewed some of the most used C=O hydrogenation substrates taken from biomass (1). We looked at alternative energy sources and solvent used in this context (2 and 3). We then explored the development of greener catalysts based on nonprecious metals (4), before exploring the importance of the hydrogen sources, with a special attention to bio-sourced ones (5). Throughout the manuscript, attempts were made to highlight how green chemistry metrics were used to shed light on the relevance of the reported methods. Green metrics are an essential means to bring rational comparison and perspective and their use is encouraged.[14] The field of biomass catalytic reduction is the center of a lot of scientific attention and as such, the reader is encouraged to consult recent reviews of this field.[4]

C=O hydrogenation substrates

Benzylic carbonyls (namely benzaldehyde and acetophenone) are commonly reported as model substrates for the C=O hydrogenation reaction, due to their high reactivity and ease of handling, and are easy first steps in the exploration of a new reduction catalyst. Unsurprisingly reduction of biomass-derived platform molecules, in particular levulinic acid (LA) or 5-hydroxymethylfurfural (5-HMF), is intensely explored as well.[15] They can be made from acidic treatment of glucose or cellulose, and for both, pilot plants dedicated to their production from biomass have been built.[16-17] Their reduction products are useful building blocks available for further functionalization, showing the key role of C=O hydrogenation in chemical industry. Typically, selectivity is an important aspect, with carbonyl hydrogenation being less favored compared to nitroarene, alkyne and alkene hydrogenation (**Error! Reference source not found.**).[18]

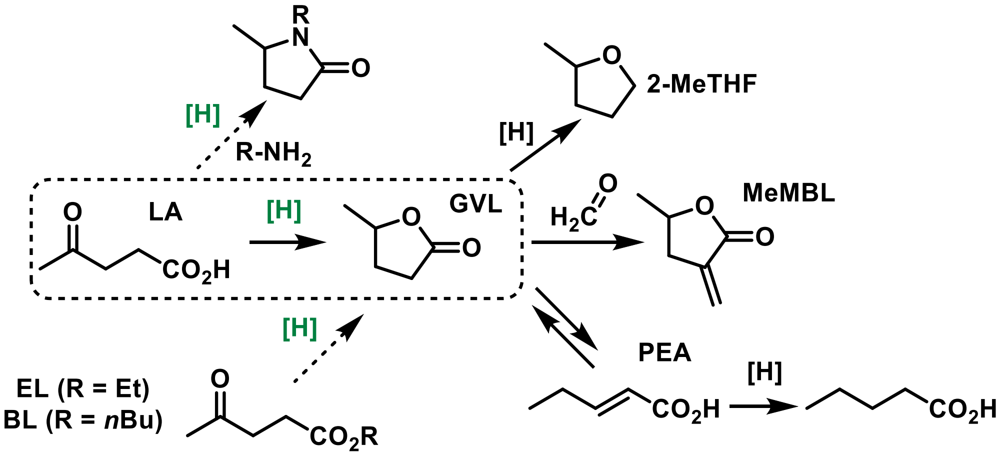


Scheme 1. Usual reactivity trends in hydrogenation.

Another industrially relevant and bio-based target is citral. It contains one C=O and two unsaturated C=C bonds with various steric hindrances, making for challenging selectivity issues as well. In the context of using biomass as substrate for hydrogenation, it is important to note that there are still open questions about the sustainability of such resources. One must also take in account the origin of a chemical, as well as its fate after use. Life Cycle Analysis (LCA) comes in as a powerful tool to thoroughly evaluate a chemical's environmental impact through different scopes (e.g. ozone depletion, fossil fuel consumption, ecotoxicity, global warming, etc…).[19] For instance, Montazeri *et al*. compared the LCA of the production of lignin-based *tert*-butyl catechol (TBC) and fossil fuel-based TBC.[20] They showed that the use of dichloromethane as an extraction solvent in the former route heavily penalized its ozone depletion burden by a 1000-fold factor while overall both routes had the same global warming impact (1.25 kg_{CO2}/kg_{TBC}). More work on this field is certainly important to provide context in some of the chemistry described in this review.[21] [22]

Levulinic acid

LA forms γ-valerolactone (GVL) upon hydrogenation and subsequent cyclization (Scheme 2).[23] GVL is useful in itself as a fuel additive or solvent,[24] and can be further reduced to 2-methyltetrahydrofuran (2-MeTHF) for similar purposes. It can be further converted to α-methylene-γ-valerolactone (MeMBL) using formaldehyde, and serves as a methyl methacrylate upgrade in its polymerisation.[25] Indeed, it increases the glass transition temperature of the resulting copolymer by 100°C compared to pure poly-methyl methacrylate. GVL can also reversibly convert to pentenoic acid (PEA),[26] which can be further hydrogenated to pentanoic acid (PA). All these intermediates can be decarboxylated or used as chemical building blocks or fuel additives.[27] Another closely related pathway to carbonyl hydrogenation is reductive amination, from which LA can form 2-pyrrolidinone derivatives.[28] In practice, since the carboxylate function in LA can poison catalyst surfaces, ethyl levulinate (EL) and butyl levulinate (BL) can be used instead. Both of them can be easily converted to GVL by C=O reduction.[29]

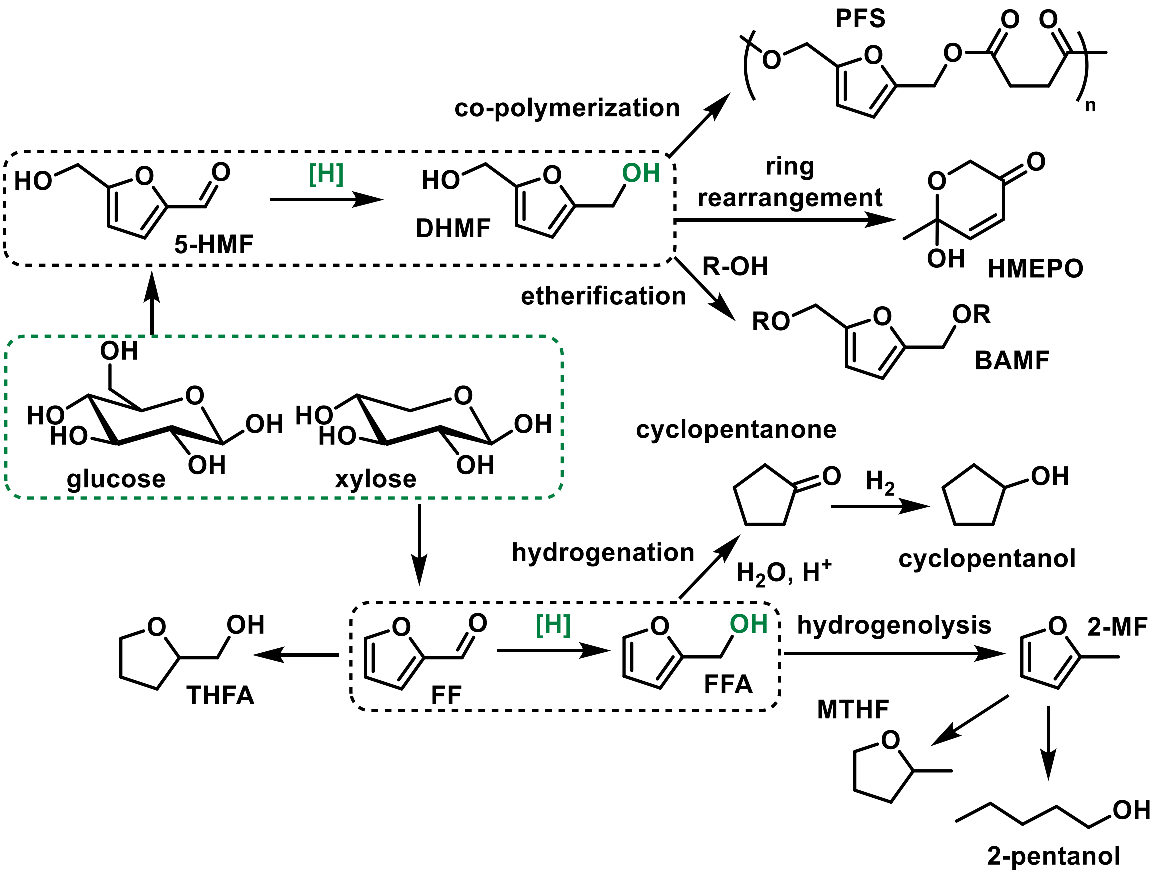


Scheme 2. LA hydrogenation and further upgrade pathways.

Furfural and 5-Hydroxymethylfurfural

Furfural (FF) and 5-HMF are both furan derivatives that can be generated from the acid-catalyzed dehydration of biomass-derived xylose and glucose respectively.[30] Both of them constitute promising substitutes building blocks derived from petrochemicals in the production of plastics and fine chemicals.[31]

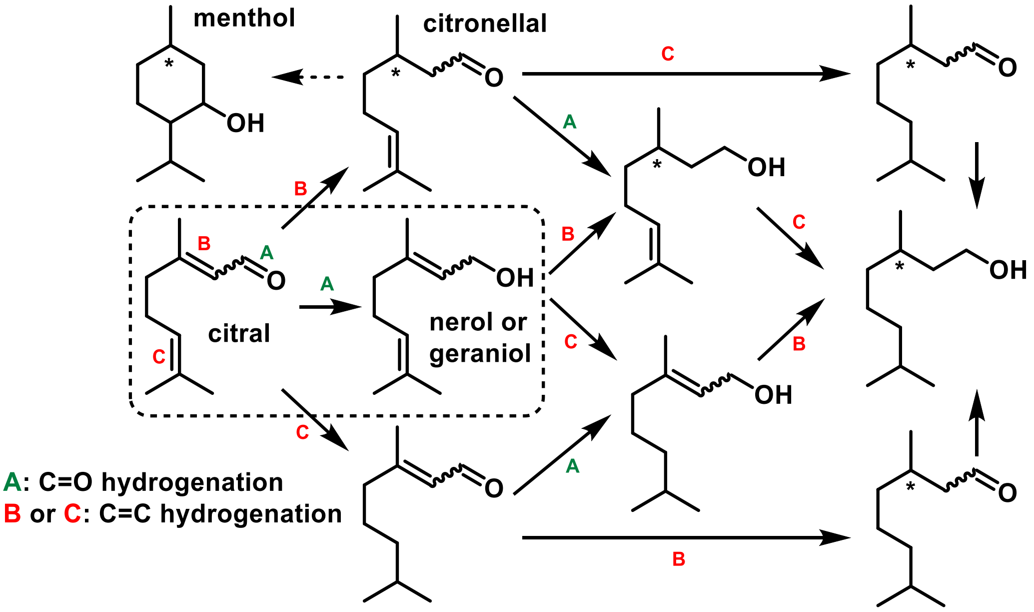
The reduction of 5-HMF into 2,5-dihydroxymethylfuran (DHMF) has been covered by Hu *et al.* (Scheme 3).[32] This symmetrical diol can be directly used as a co-monomer, for example with succinic acid to form poly(2,5-furandimethylene succinates) (PFS).[33] It can also be etherified using various short chain alcohols to form 2,5-bis(alkoxymethyl)furan (BAMF) that can be used as fuel additives.[34] Lastly, it can be re-arranged into 6-hydroxy-6-methyl-4-enyl-2H-pyran-3-one (HMEPO), an intermediate for the synthesis of sugar analogues and compounds with excellent biological activities.[35] Furfural can be reduced to furfuryl alcohol (FFA), that can be mostly converted to fuel additives (2-methylfuran and 2-methyltetrahydrofuran) and solvents (tetrahydrofurfuryl alcohol).[36] FFA can also be hydrogenated then isomerized into cyclopentanone, an important chemical intermediate to produce insecticides and rubber chemicals.[37]



Scheme 3. FF and 5-HMF hydrogenation and further upgrade pathways.

Citral

Citral, a monoterpenoid containing three unsaturations (1 C=O bond and 2 C=C bonds), is distilled from essential oils such as lemongrass oil. It is responsible for the 'citrus effect' in perfumes and other flavored consumer goods, and widely used as such. It can be cyclized into other flavors such as menthol.[38] Stolle *et al.* have identified citral hydrogenation as a challenging process, considering the selectivity issue stemming from the presence of three double bonds (making up to 8 potential products, Scheme 4).[39] Carefully designed catalytic systems, composed of transition metals Ag, Ru or Os, combined with acidic promoters such as In_2O_3, CeO_2 or MgO, have enabled breakthrough toward improved reactivity and selectivity in favor of C=O reduction.[40]



Scheme 4. Citral hydrogenation selectivity issues (each hydrogenation pathway is indicated above the arrows).

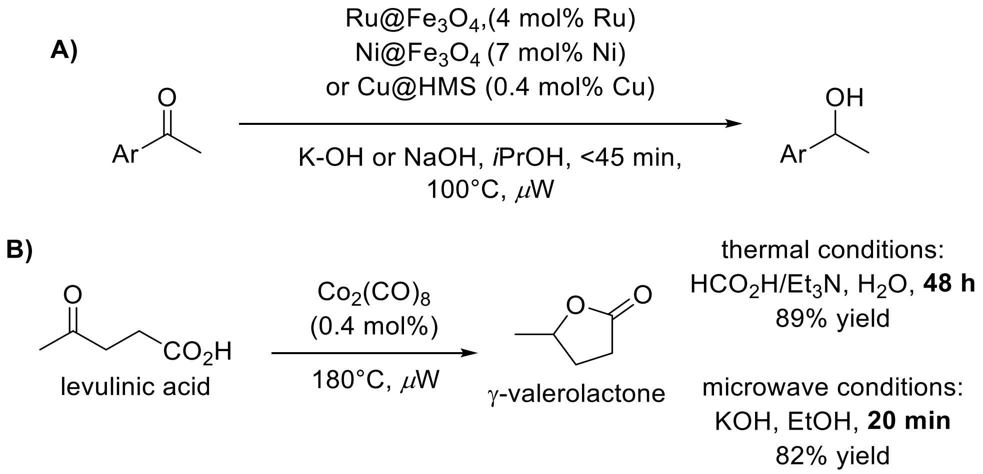
Alternative energy sources

As outlined by Varma *et al.*, a number of alternative energy inputs have been successfully applied to both organic chemistry and material synthesis.[41] These all constitute an effort towards improving the efficiency of a reaction from an energetic perspective. Indeed, most organic reactions are conducted using convective heating, a slow method relying on convection currents and thermal conductivity to transfer energy to the reaction mixture.[42]

Microwave heating

Microwave irradiations occur in the 0.3-300 GHz range and are typically used in chemistry at 2.45 GHz. This frequency corresponds to a wavelength of 12.24 cm, and photon energy of 0.0016 eV, thus lower than Brownian motion.[43] Instead, microwave dielectric heating relies on the capacity of the reaction medium to absorb microwave energy and dissipate it into heat through a dipole oscillating field alignment then friction phenomenon, along with an ionic conduction mechanism.[44] In the case of conducting or semi-conducting materials such as metals, ohmic heating phenomenon can be involved as well.[45] Overall, this results in a faster and more homogeneous heating of the reaction medium, and has been successfully applied to both organic chemistry and nano-material synthesis.[41] By drastically reducing reaction time,[46] energy efficiency is increased compared to conventional heating (>30%).[47]

Early examples (1997-2002) of the use of microwave heating were straightforward transposition of known transfer hydrogenation reactions, namely $NaBH_4$ reduction[48-49] and the Meerwein-Ponndorf-Verley reaction.[50-51] Later, the advent of microwave reactors adapted to organic reactions led to better controlled chemical processes. In 2008, Varma and co-workers reported Ni supported on a magnetite support, using dopamine as a linker ($Ni@Fe_3O_4$).[52] Later on, they published a similar report using Ru supported on a magnetite core with a silica shell ($Ru@Fe_3O_4$).[53] Yoshida *et al.* also reported the preparation of Cu supported on hexagonal mesoporous silica (Cu@HMS) under microwave.[54] These three catalysts share similar performances for the transfer hydrogenation of ketones using *i*PrOH in microwave, requiring a base (NaOH or KOH), and showing high recyclability with no metal leaching (Scheme 5A). Gowda *et al.* reported the use of non-noble metal carbonyls (Fe, Mo, Co, W) as *in situ* precursors to nanocatalysts for LA hydrogenation to GVL (Scheme 5B).[55] While under conventional heating HCO_2H/NEt_3 reductant was required, EtOH under microwave served as both solvent and reductant in the reaction with a drastic reaction time decrease (from 48 h to 20 min).

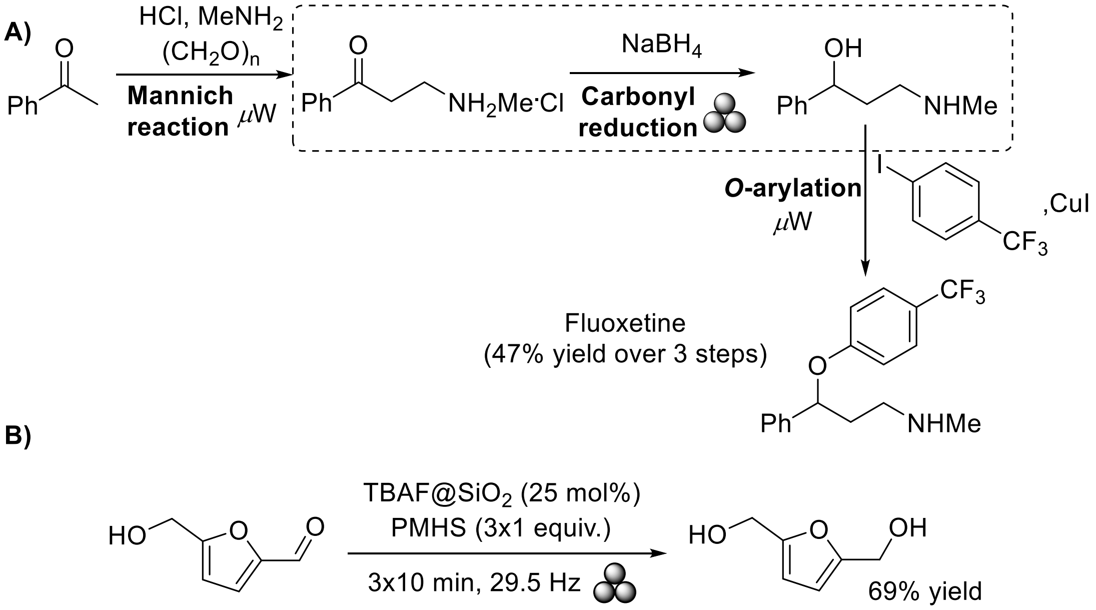


Scheme 5. Microwave heating for catalytic carbonyl transfer hydrogenation.

Mechanochemistry

20 million tons of organic solvents are produced every year, and make up to 85% in mass of waste emission for the synthesis of active pharmaceutical ingredients.[56] These large quantities are required not only to ensure the homogenization of a chemical mixture, but also to perform extraction, purification and cleaning purposes.[57] A mechanochemical reaction is defined by the IUPAC as 'a chemical reaction that is induced by the direct absorption of mechanical energy", through impact and/or shearing with a milling apparatus.[58] Furthermore, the absence of solvent can favor an acceleration of reaction rate through high concentration, and offers an opportunity to solve substrate solubility issues.

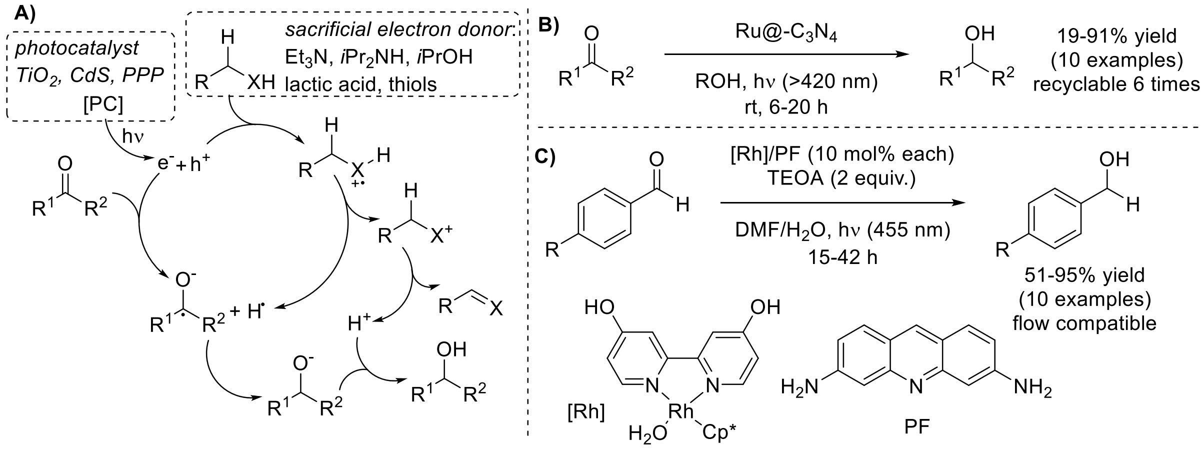
In fact, mechanochemical reactions are the oldest and simplest techniques used in history, as mortars and pestles have been well documented throughout the history of food and medicine preparation. $NaBH_4$-induced carbonyl reduction has been readily transposed to mechanochemistry, starting with an early report by Toda *et al.* using manual grinding and improved by Cho *et al.* with the addition of acids (benzoic acid, *p*-toluene sulfonic acid or H_3BO_3).[59-60] Mack *et al.* reported the first mechanochemical reduction of carbonyls using a ball-mill mixer, with a further mechanistical study by Naimi-Jamal *et al.*[61-62] Notably, the addition of LiCl salt could induce the *in situ* formation of $LiBH_4$ that is reactive enough to reduce esters. Lastly, Solà *et al.* reported a sustainable route for the synthesis of Fluoxetine (Prozac), using microwave heating and ball-milling.[63] In their second step, ball-milling with $NaBH_4$ was successfully applied for the reduction of an aminoketone (Scheme 6A). Our group contributed to mechanochemical reduction of carbonyls. In this case the source of hydrogen was not conventional $NaBH_4$, but a solid waste from the silicone industry, polymethylhydrosiloxane (PMHS), activated by *tert*-butyl ammonium fluoride on silica (TBAF@SiO_2) as a catalyst.[64] Notably, 5-HMF was reduced through the fractioned addition of PMHS in three portions, reaching a 69% yield (Scheme 6B). Interestingly separation of product and reagent was simplified compared to the solution-based method.



Scheme 6. A) Sustainable synthesis of Fluoxetine B) Mechanochemical reduction of 5-HMF.

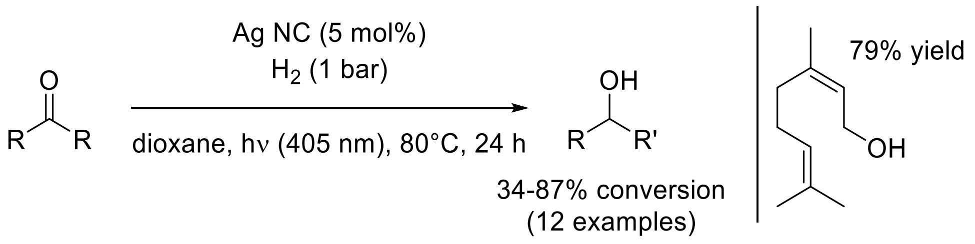
Photochemistry

Photocatalysis is a mode of catalysis where a dye is used to absorb light and cause chemical activation of substrate molecules, usually through the separation of e^-/h^+ pairs. Early carbonyl hydrogenation photocatalysts consisted in light absorption semi-conductors such as CdS NPs,[65] TiO_2 NPs,[66-67] or poly(*p*-phenylene) (PPP),[68] using sacrificial electron donors such as Et_3N, *i*Pr_2NH, β-mercaptoethanol and lactic acid (Scheme 7A). Sharma *et al.* reported Ru supported on graphitic carbon nitride (Ru@g-C_3N_4), using and short chain alcohols as reductants (EtOH, *n*PrOH, *i*PrOH).[69] C_3N_4 is a visible light absorbing heterogeneous semi-conducting material, that could be recycled up to 6 times (Scheme 7B). König *et al*. reported the synergistic activity of proflavine (PF) as a dye and a Rh complex for aldehyde reduction, functioning under blue light (455 nm) and being compatible with flow conditions (Scheme 7C).[70] Call *et al.* eventually showed that an earth abundant, oxygen- and water-stable photocatalytic tandem based on Cu and Co was suitable as well.[71] Although outside the scope of this perspective, the field of CO_2 reduction by photoactivation has been particularly dynamic in the past few years, and the reader is directed towards recent reviews for more details.[72] [73] Interestingly there, water is used as a H_2 source, via a water splitting scheme.



Scheme 7. A) General scheme for photo-induced reduction of carbonyls. B) Ru@g-C_3N_4 as a photocatalyst C) [Rh]/PF as a photocatalytic duet.

Plasmonic catalysis. Plasmonic photocatalysis is based on visible-light absorption of metal NPs resulting from their localized surface plasmon resonances (LSPR).[74] Indeed, visible light can enable the collective oscillation of the valence electrons of coinage metal NPs (Au, Ag, Cu) and Al NPs, allowing them to act as catalyst through the generation of high-energy electrons. Hao *et al.* used Au NPs supported on SiC (Au@SiC) as plasmonic catalysts for the C=O-selective transfer hydrogenation of α,β-unsaturated carbonyls under visible light (Scheme 8).[75] Similarly, our group exploited the same phenomenon with Ag nanocubes (Ag NC, Scheme 8).[76] Under mild H_2 pressure (1 bar), especially for Ag NPs, Landry *et al.* successfully reduced a range of 12 carbonyls including aliphatic ketones and cinnamaldehyde at the C=O position. Citral was selectively reduced into geraniol in high yields (79%).



Scheme 8. Plasmon-driven selective reduction of carbonyls using Ag NC.

Solvents

A number of organic solvents are harmful, toxic and environmentally damaging. However, they are crucial in most organic reactions to dissolve chemical compounds, enable heat dispersion and ensure proper mass transfer. Substituting them or alleviating their use is no simple task, as many factors (such as safety, separation cost, viscosity, solvation properties, chemical stability) must be taken in account to evaluate their impact.[77] As stated earlier, switching to solvent-free processes is a viable option, whether it is in liquid or solid phase. Not using solvents allows higher reaction rates due to higher concentration (for bimolecular reactions and beyond), as well as lower costs. However, low diffusion rates and heat dispersion issues due to higher mixture viscosity can be encountered in solvent-free conditions. Ultimately, the impact of a solvent on the performance of a reaction or on the economics of a process are the governing parameters, respectively in academia and industry.

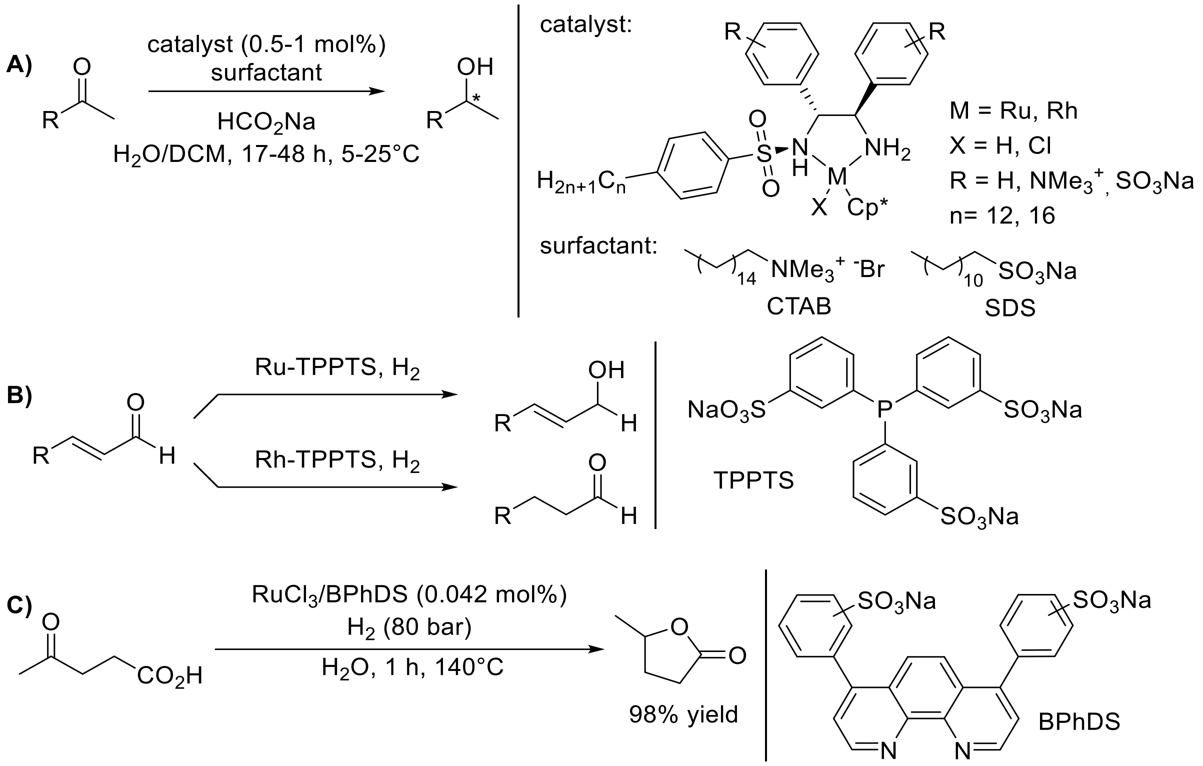
In 2010, Prof. Jessop conducted a survey aiming at identifying solvents causing the least environmental damage. Most parameters pointed at supercritical CO_2, water and carefully chosen traditional organic solvents (these 3 categories added up to 75% of the total poll responses).[78] This puts in perspective the importance given to Ionic Liquids (ILs), in particular in the *Green Chemistry* journal where 50% of the papers describe results with this class of solvents. These high-end and very polar solvents come with a heavy synthetic cost, although they can be used to treat usually insoluble biomass polymers such as lignin and cellulose.[79] In the context of C=O reduction in particular, ILs featured poorly as they favor C=C reduction instead.[80-81] Finally, Prof. Jessop listed a few scientific challenges in green solvent development, such as developing more diverse solvents in terms of polarity and hydrogen bond donor capacity (cf. Kamlet-Taft diagram), while taking in account the synthetic route and safety parameters. For instance, developing a sustainable low boiling-point polar aprotic solvent is still highly desirable. Besides, solvent choice is now made easier *via* the published guides produced by pharmaceutical companies (Pfizer,[82] GSK,[83-84] Solvay[85]) and the ACS Green Chemistry Institute (ACS-GCI) Pharmaceutical Roundtable.[86] In a holistic approach, these aggregated several key parameters such as safety and waste treatment, conveniently helping the process chemist in choosing the most appropriate solvent.

H_2O

For a long time, H_2O as a solvent has been deemed as unsuitable for organic chemistry, despite reactions in nature taking place as aqueous enzymatic processes. Breslow *et al.* made a first breakthrough in 1980 by showing that Diels-Alder cyclization of cyclopentadiene with butanone proceeded 700 times faster *faster* in H_2O than in *iso*-octane.[87] In the context of carbonyl reduction, the authors exploited H_2O as well to tune selectivity to the most hydrophobic substrate. Shen *et al.* analyzed by surface vibrational spectroscopy H_2O-hexane and H_2O-air interfaces, showing that in all cases, about 25% of surface water molecules at the hydrophobic interface have one dangling -OH group, protruding into the hydrophobic layer without making hydrogen bonds.[88] Thus, these dangling bonds have been hypothesized to decrease activation barriers, effectively accelerating chemical reactions where the transition state benefits from hydrogen bonding with H_2O.[89]

Surfactants can be employed to maximize water/organic layer interface, while using minimal amounts of organic solvents and metal catalysts (up to ppm levels).[90] Overall, switching to micellar catalysis drastically reduces the E-factor of a reaction initially conducted in organic media, up to a tenth of its original value.[91] Surfactants have been applied for great effect on metal-catalyzed asymmetric ketone transfer hydrogenation using HCO_2Na, based on [Cp^*Ru(TsDPEN)]-like complexes grafted on a sodium dodecyl sulfate (SDS) surfactant (Scheme 9A).[92-95]

Alternatively, metal complexes can be made recyclable by making them water-soluble.[96] Typically, this is done by the grafting of hydrophilic groups on the ligand, such as sulfonate groups on triphenylphosphine (TPPTS).[97] Grosselin *et al.* explored this ligand with Ru and Rh for the hydrogenation of α,β-unsaturated aldehydes in H_2O.[98] Interestingly, the metals were respectively selective towards C=O and C=C reduction (Scheme 9B). More recent developments were applied to LA hydrogenation, using water-soluble phenanthroline ligands (BPhDS, Scheme 9C) .[99-100]

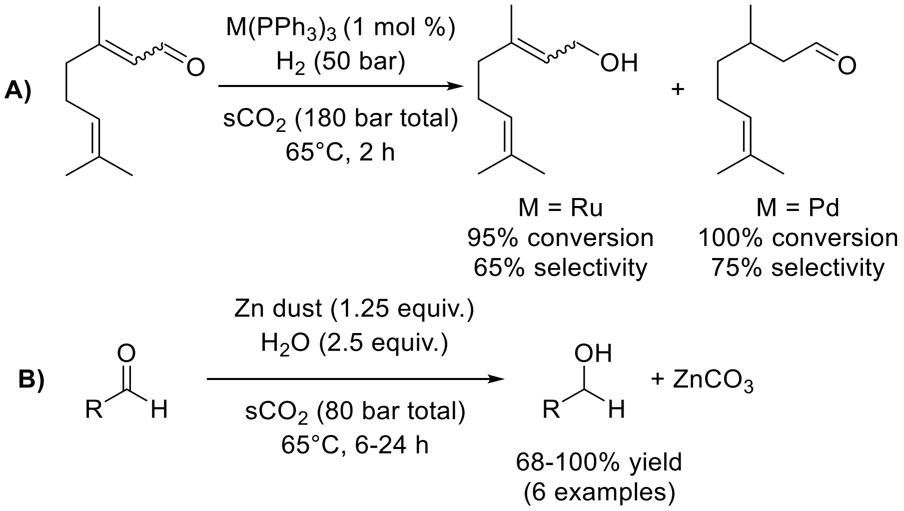


Scheme 9. Approaches for carbonyl reduction in H_2O: A) Using surfactants B) Using water-soluble catalysts C) Application to LA hydrogenation.

Supercritical carbon dioxide

Supercritical CO_2 (sCO_2) has seen great applications in hydrogenations due its mild critical point (304 K, 73.8 atm), the innocuous nature and non-flammability of CO_2, the ease of post-synthesis removal, and notably the full miscibility of H_2 in sCO_2.[101-103] In comparison, at ambient temperature and atmospheric pressure the molar solubility of H_2 in various solvents is as following: $0.8.10^{-3}$ M in H_2O, $1.95x10^{-4}$ M in EtOH and 2.64 $x10^{-4}$ M in acetone.[104]

Furthermore, sCO_2 promotes selective C=O reduction due to the dielectric constant of CO_2 increasing with pressure, making it a polar solvent.[105-103, 106] Arai *et al.* exploited this property for citral hydrogenation, attaining C=O and C=C reduction selectivity with Ru and Pd respectively (65% and 75% selectivity, Scheme 10A).[107] Interestingly, Li *et al.* exploited sCO_2 as a medium for Zn/H_2O-mediated reduction of aldehydes, through *in situ* H_2O splitting (Scheme 10B).[108] Harada *et al.* also reported a catalyst-free carbonyl reduction process in supercritical *i*PrOH (508 K, 48 bar).[109-110]



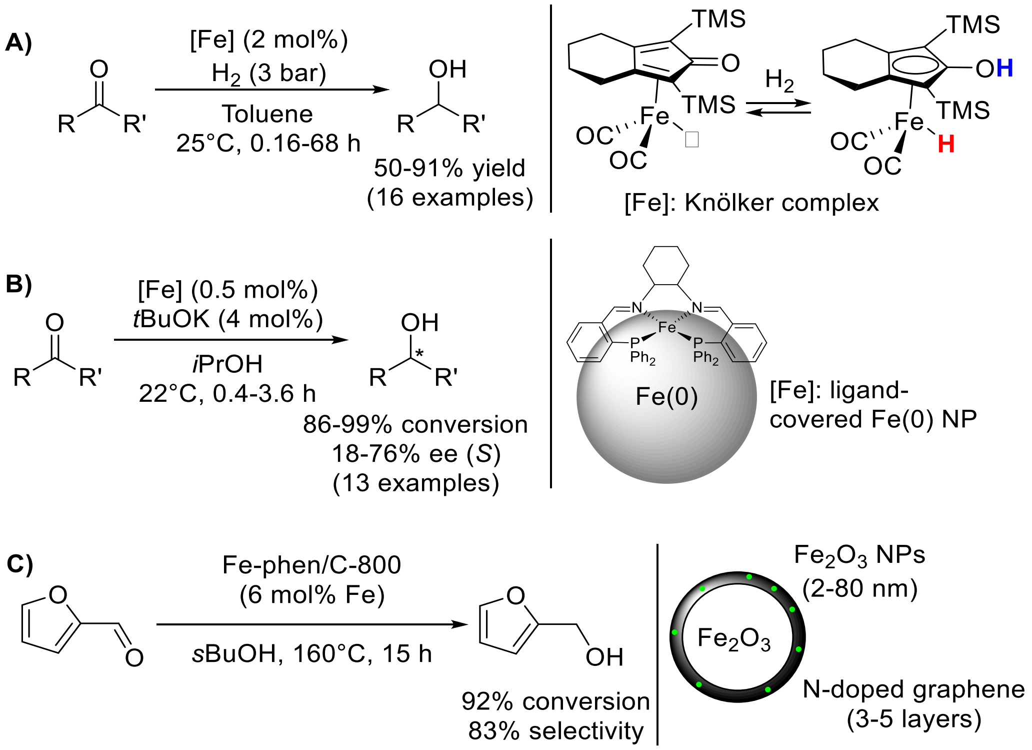
Scheme 10. sCO_2 for: A) citral C=O reduction B) Zn/H_2O-induced carbonyl reduction.

Catalysts

Catalysis relies on the principle that a catalyst does not get consumed during a reaction, but rather remains active to engage into further reactive cycles. Practically though, their life time can be limited by inactivation, or simply by the difficulty of their separation from the product and reuse. Not only it is problematic from an economical perspective, it causes toxicity issues in the final product, both for PGMs and more abundant metals (Ni, Cu).[111] One option, which is favored in industry, is the use of heterogeneous catalysts due to their easy recyclability, although they tend to feature lower activity and selectivity compared to homogeneous complexes. In high-added value synthesis such as pharmaceutical compounds, the use of PGM-containing homogeneous catalysts remains essential. Nonetheless, efforts towards diminishing metal loading or shifting to base metals are on the rise.[112]

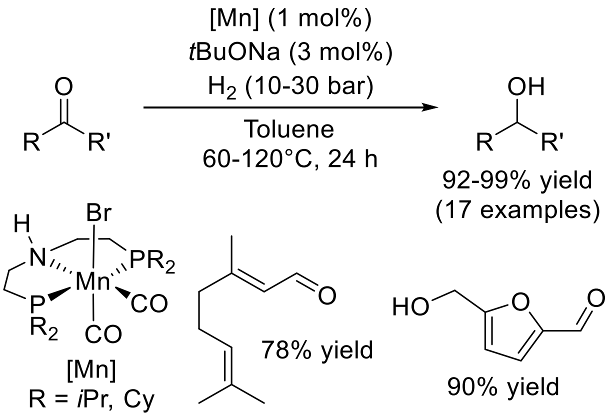
Base-metal catalysts

Iron. Fe has seen tremendous development in the field of carbonyl hydrogenation, through its cooperation with specifically tailored ligands or supports for H_2 activation.[113] A prime example is the Knölker complex, where Fe is assisted by a cyclopentadienone ligand for the splitting of H_2.[114-117] Casey and Guan were the first to show its potency for carbonyl hydrogenation (Scheme 11A),[118] followed by Fleischer *et al.*[119] In parallel, Morris *et al.* reported a family of Fe-PNNP pincer complexes.[120-122] In some cases, it was shown that the active species was actually PNNP-covered Fe(0) NPs (Scheme 11B).[123-124] Finally, Fu *et al.* explored furfural hydrogenation using Fe_2O_3 NPs supported on N-doped graphene, with the catalytic activity stemming from the interaction between Fe and the N atoms of the support.[125]



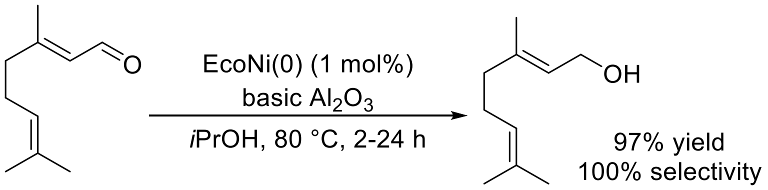
Scheme 11. Ligand and support-assisted Fe-catalyzed hydrogenation: A) Knölker complex B) Morris' PNNP pincer ligand C) Fe_2O_3 NPs supported on N-doped graphene

Manganese. Homogeneous Mn has seen tremendous developments in the last two years, since the original breakthrough by Beller and co-workers in 2016.[126-129] The Mn contamination limit in pharmaceutical compounds is 250 ppm compared to 10 ppm for Ru, added to the fact Mn is the third most abundant transition metal in the Earth's crust after Fe and Ti. Using an air-stable PNP pincer ligand complex (Scheme 12), they reduced a range of nitriles and carbonyls in high yields (92-99% yield for carbonyls).[130] Citral and 5-HMF was successfully reduced at their carbonyl position (78% and 90% yield respectively). Yet, the introduction of phosphine moieties within a ligand design greatly increases its cost, superseding the price tag of the metal itself. Since then, phosphine-free ligands have been explored such as NNN pincers, aminopyridine or aminotriazole ligands.[131-133] These few examples published in only 2 years reveal the scientific excitement around Mn-based complexes, with special relevance to biomass conversion.



Scheme 12. Mn catalysis for carbonyl hydrogenation.

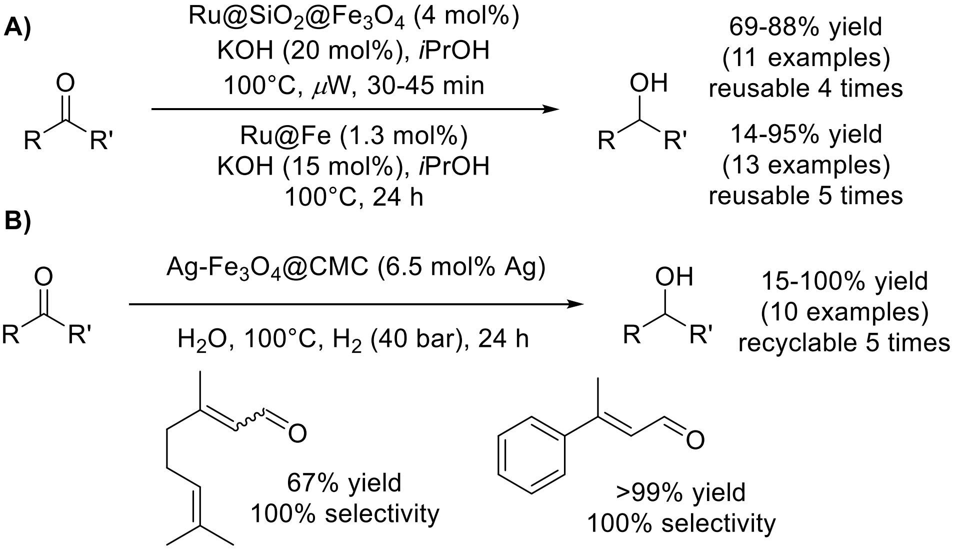
Nickel. Early mentions of homogeneous Ni for carbonyl transfer hydrogenation using *i*PrOH were performed with halide salts ($NiCl_2$, $NiBr_2$), coupled with NaOH or KOH.[134-136] But contrary to Fe and Mn, heterogeneous Ni for carbonyl transfer hydrogenation has then been massively investigated.[137] For instance $Zr_{0.8}Ni_{0.2}O_2$,[138] Raney Ni,[139] Ni@CeO_2,[140] or Ni(0) NPs generated by the reduction of $NiCl_2$ using metallic Li all proved competent for carbonyl reduction using *i*PrOH.[137, 141] Interestingly, Escande *et al.* prepared EcoNi(0) from the thermal decomposition of a Ni-hyperaccumulating plant, *Psychotria gabriellae,* found in New Caledonia (Scheme 13).[142] The authors used Al_2O_3 as a base and the catalyst was tolerant to -NO_2, -CN and C=C groups. Typically, citral was fully selectively reduced to citronellol (97% yield, 6 h).



Scheme 13. EcoNi(0)-catalyzed carbonyl transfer hydrogenation.

Magnetic catalysts

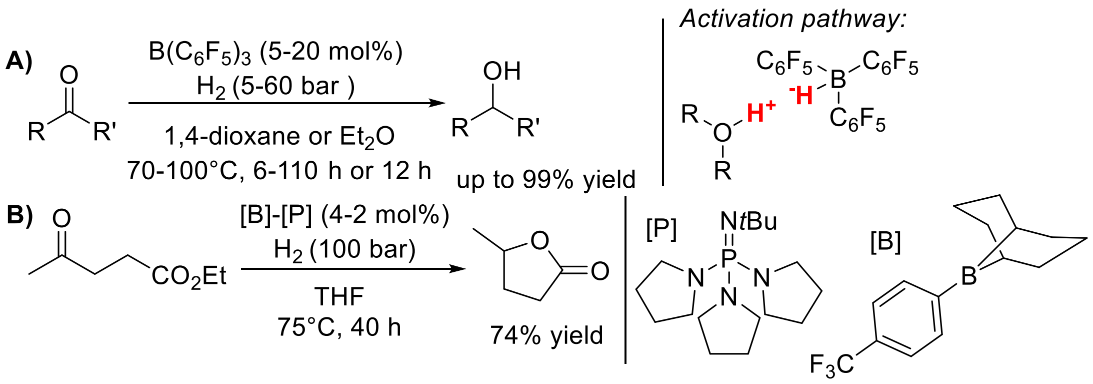
A convenient method to simplify catalyst separation is to use magnetically recoverable NPs (MNPs), either directly as catalysts or as supports for homogeneous or heterogeneous catalysts.[143] A few different strategies exist around this concept: the MNPs can be used directly as catalysts for carbonyl reduction such as magnetic $CuFe_2O_4$ NPs in conjunction with PMHS as reductant.[144] Alternatively, magnetic supports such as Ni on Fe_3O_4 NPs can be used to support the catalyst.[145] Our group, along with Baig *et al.*, has explored this concept with Ru for transfer hydrogenation in *i*PrOH (Scheme 14A).[53, 146] In both cases the catalyst was easily recyclable up to 4 times. We also immobilized Ag on Fe_3O_4 NPs, made by microwave using carboxymethyl cellulose as a reductant and linker (Ag-Fe_3O_4@CMC).[147] The catalyst was used for the hydrogenation of carbonyls in water, exhibiting full selectivity to C=O bonds for citral and α-methyl-*trans*-cinnamaldehyde (Scheme 14B).



Scheme 14. A) Ru@SiO_2@Fe_3O_4 and Ru@Fe for carbonyl transfer hydrogenation B) Ag-Fe_3O_4@CMC-catalyzed hydrogenation of aldehydes in water

Frustrated Lewis Pairs

Frustrated Lewis Pairs (FLPs) are a combination of Lewis acids and bases, in which sterics are designed to hinder dative bond formation.[148-149] Stephan and co-workers were first to show that FLP were to be able to split H_2, constituting attractive metal-free hydrogenation catalysts.[150] A major breakthrough in this field was made simultaneously by both the Stephan[151-152] and the Ashley[153-154] group, showing that a strong Lewis acid such as $B(C_6F_5)_3$ could catalytically reduce carbonyls, in conjunction with Et_2O or THF as a weak Lewis base (Scheme 15A).[155] Mummadi *et al.* adopted the opposite approach from the previous authors, using an aryl-substituted 9-BBN borane as a *weak* Lewis acid, in conjunction with a *strong* Lewis base (Scheme 15B).[156] Their system worked on the gram-scale for EL conversion to GVL (74% yield).



Scheme 15. FLP-catalyzed hydrogenation of carbonyls.

Due to the novelty of FLPs in hydrogenations, no formally heterogenized version has been reported so far. A few closely related systems are worth mentioning though, as they could give some hint on the future of heterogeneous FLPs. Primo *et al.* reported in 2014 exfoliated graphene as a C=C hydrogenation catalyst.[157-158] While the nature of the active sites remains unclear, the authors did mention the co-existence of basic and acidic sites on their material, effectively exerting a FLP-induced H_2 activation.

From the examples covered throughout in this section, the following themes have been tackled:

-Investigation of base metal catalysis. Indeed, base metals such as Co, Cu, Fe, Ni and Mn are more abundant than most PGMs but have remained comparatively underdeveloped.[48-49, 159-160]

-Improvement of post-reaction catalyst separation and recyclability. This is also possible on homogeneous catalysts, for example by using hydrosoluble complexes,[96] IL-soluble complexes[161] or by using magnetically tractable supports. PGM would benefit in particular from a better catalyst re-usability due to their higher cost and toxicity.

-High level of reduction activity and selectivity. In the context of carbonyl reduction, this means that investigation on C=O/C=C selectivity, low H_2 pressure and/or mild reductants should be further pursued.[162]

Hydrogen sources

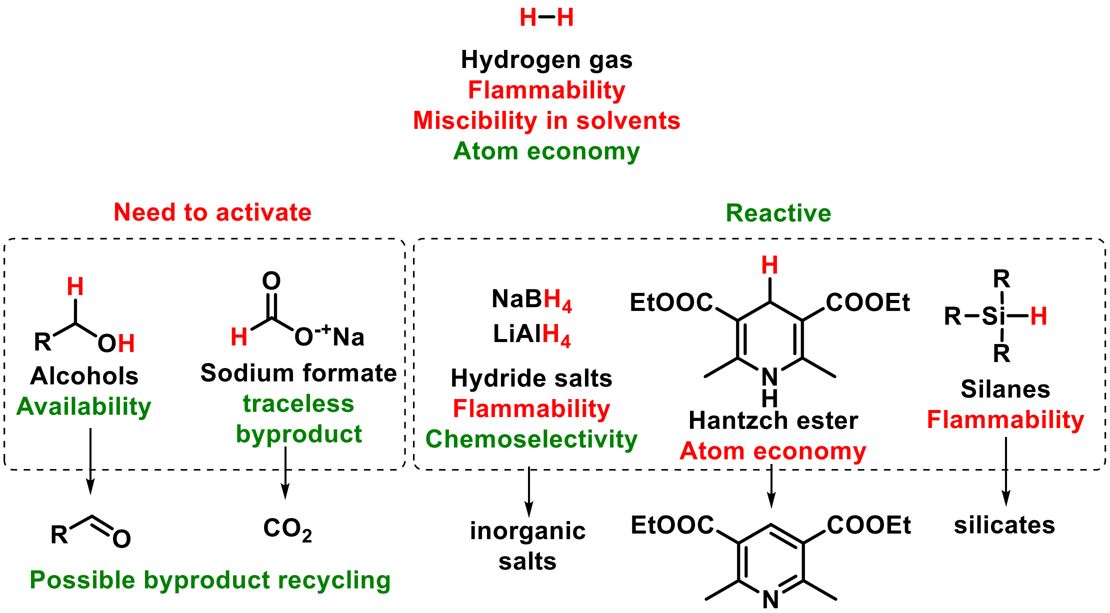
Carbonyl hydrogenation illustrate well the importance of metric choice. One of the first green chemistry metrics, concept of atom economy (AE), was developed by Prof. Trost in 1991[163] and it translates the conversion efficiency of a process to integrate every atom of the reactants into the desired product. Unsurprisingly, H_2 gas exhibits a full efficiency in terms of atoms employed to reduce a carbonyl, while the atom efficiency of any other reductant falls below 11% (Table 1). However, safety (regarding the use of pressure, or flammability), reactivity, recycling, as well as the sourcing of the reducing agent is not taken into account in AE. [164-165] Thus transfer hydrogenation is a viable alternative to direct hydrogenation.[166]

Reductant	% Active H
H_2	100%
$NaBH_4$	11%
PMHS	7%
HCO_2H	4%
*i*PrOH	3%
glycerol	2%
NaH_2PO_2	2%
glucose	1%
Hantzsch ester	0.7%

Table 1. Common reductants in carbonyl reduction-atom economy.

Similarly to what the ACS-GCI did with solvents, they recently published an online reagent guide, comparing for a given process several reagents with considerations on their environmental impact and scalability.[86] Furthermore, the field of transfer hydrogenation will greatly benefit from future progresses in hydrogen storage, as reviewed by Sordakis *et al*.[167]

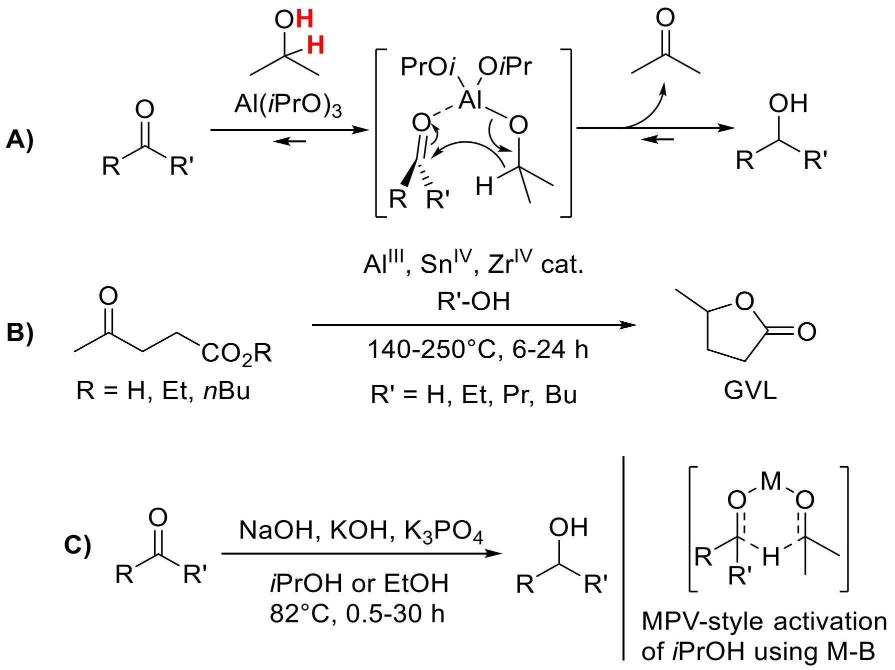
The most popular hydrogen sources in the pharmaceutical industry, shown by their prevalence in large scale processes, are hydride salts ($NaBH_4$, $LiAlH_4$). These are obtained from respectively the treatment of $B(OMe)_3$ with NaH (discovered in 1953[168]) and $AlCl_3$ with LiH (discovered in 1947[169]). Hydride salts must be used in stoichiometric amounts, despite efforts made to use them in catalytic amounts,[170] and they mostly suffer from flammability and cumbersome waste generation. Alcoholic hydrogen sources are available from biomass (EtOH, MeOH) and their byproduct can be potentially recycled (Scheme 16).[164] Moreover, some waste chemicals from the biodiesel and silicon industry can be re-used as reductants (respectively glycerol and PMHS), opening up new avenues in sustainable transfer hydrogenation. Other unusual reductants such as glucose[171] or NaH_2PO_2[172] have been explored as well for carbonyl reduction.



Scheme 16. An overview of hydrogenation sources.

Short chain alcohols

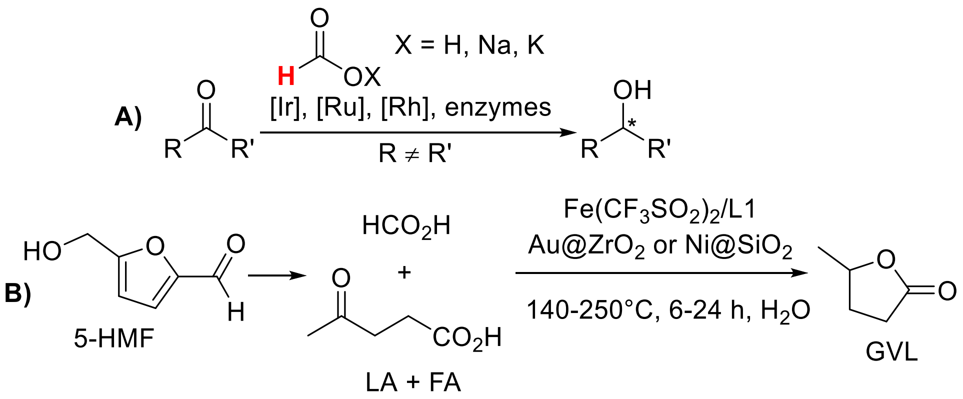
The discovery of hydride salts as reductants allowed in their time supplanting the 'classical' reduction methods such as the Meerwein-Ponndorf-Verley (MPV) reduction, discovered in the 1920s.[173-176] In this process, the carbonyl is introduced to an excess of reducing alcohol (*i*PrOH), with an Al or B-based transfer agent such as Al(O*i*Pr)$_3$. Upon coordination of an alkoxide to Al^{3+} or B^{3+}, its α-hydride can be readily transferred to the carbonyl through a 6-member transition state (Scheme 17A). Since the process is reversible, an excess of *i*PrOH and Al(O*i*Pr)$_3$ is required to drive the reaction to completion, as well as typically long reflux times (3-8 h).[177] However, the prospect of using alcohols as safe reducing agents sparked interest into improving over the original MPV reaction, that remained an inspiring system. For instance, it has been discovered that adding trifluoroacetic acid or using sterically hindered Al/B complexes helped drastically cutting reaction down time (up to 15 min).[177-181] The MPV reaction has seen in the last 5 years much development on GVL production, based on Al[182-183] and Zr[184-188] oxides as catalysts for LA and derivatives reduction (Scheme 17B).[189] Lately, a more recent variant of MPV reactions was discovered by using cheap and widely available metal alkali such as NaOH or KOH.[190-191] Similarly to Al^{3+} and B^{3+}, K^+ and Na^+ cations are also able to mediate the direct hydride transfer through a similar 6-member intermediate (Scheme 17C).



Scheme 17. MPV reduction: A) Mechanism B) LA reduction C) Base-catalyzed version.

Formate

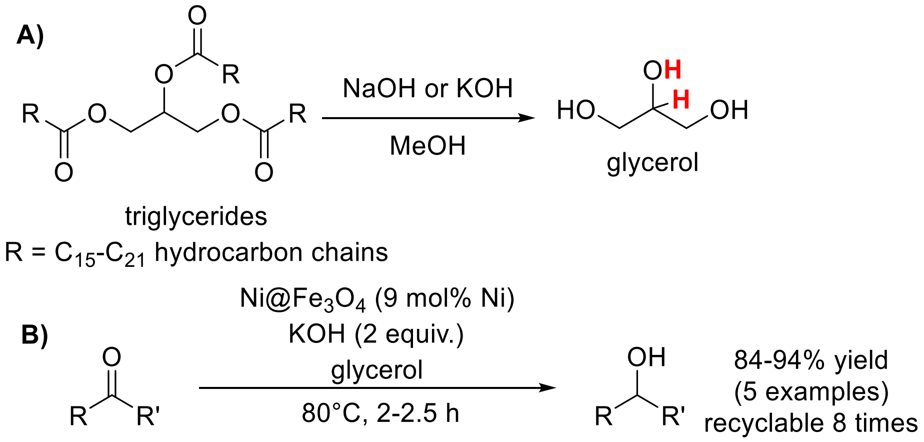
Formic acid (HCO_2H, FA) is the simplest of carboxylic acids, made from the carbonylation of MeOH into HCO_2Me, and subsequent hydrolysis.[192] The direct synthesis of formic acid from CO_2 reduction with H_2 or water by photoelectrocatalysis is a very active research topic.[193] In conjunction with a base (such as Et_3N) or as sodium formate, formic acid has been widely used as a reducing agent, decomposing into CO_2 and H_2 under catalytic conditions.[194] It has been particularly useful in prochiral ketone reduction into secondary alcohol, using Ir,[195] Ru,[196-198] Rh complexes,[199] or enzymes[200] (Scheme 18A). Furthermore, LA is co-generated with LA 5-HMF acidolysis,[17] giving a strong incentive to use FA to reduce LA.[4] A seminal example was reported by Du *et al.*, using small Au NPs supported on ZrO_2 (Au@ZrO_2).[201] The catalyst was tested on freshly prepared solutions of LA/FA mixture made from the treatment of carbohydrates with H_2SO_4, establishing the robustness of their method. The Fu group also showed the viability of homogeneous Fe/Tris[(2-diphenylphosphino)ethyl]phosphine complexes for LA reduction.[202] Finally, Varkolu *et al.* used Ni supported on SiO_2 (Ni@ SiO_2) and applied in continuous flow for GVL synthesis (Scheme 18B).[203]



Scheme 18. Formic acid/akali metal formate in A) prochiral reduction and B) Co-generation of LA and FA from 5-HMF and subsequent reduction to GVL.

Glycerol

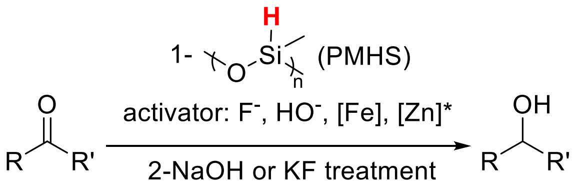
Glycerol is a non-toxic, non-hazardous, and non-volatile liquid, the 1,3-dihydroxylated analogue of *i*PrOH.[204] Contrary to *i*PrOH though, glycerol is a biomass waste from manufacture of biodiesel fuel from vegetable oils (100 kg generated per ton of biodiesel fuel produced, Scheme 19A).[205] Thanks to its low price, there has been a strong economic incentive to use it as a solvent and a reducing agent. In catalytic carbonyl reduction, homogeneous Ru and Ir complexes in conjunction with KOH have been mostly used[206-208] except for Ni@Fe_3O_4 reported by Gawande et *al*. (Scheme 19B).[209]



Scheme 19. A) Glycerol production from biomass B) Ni@Fe_3O_4 for carbonyl reduction in glycerol.

PMHS

In contrast to most silanes, PMHS is an inexpensive and non-toxic reducing agent. In the absence of an activator, it is an inert and easy to handle liquid. It was first prepared by Sauer and co-workers,[210] and has been since reported in a substantial number of reduction processes.[211] Upon treatment with $BF_3 \cdot OEt_2$, the resulting PDMS byproduct can be recycled into $MeSiH_{3-x}F_x$ synthons that are useful building blocks in the silicon industry.[212] Early reports consisted in using Sn salts as activators,[213-215] and since then a wider variety of activators, especially in metal–free schemes, has been reported. Nucleophilic activators such as fluorides,[216] phosphines[217] or bases[218] have been successfully applied to PMHS-mediated ketone hydrosilylation (Scheme 20). Eventually, non-noble metals such as Fe[219-221] and Zn were shown to activate PMHS as well, with Zn being able to enantioselective prochiral ketones into chiral secondary alcohols.[222-225]



Scheme 20. PMHS for carbonyl reduction.

Conclusion

As seen throughout the plethora of examples of carbonyl reduction exposed here, a broad and diverse toolbox of chemical methods is available to organic chemists in order to design a performant reduction process in the context of biomass upgrading. We have attempted here to illustrate efforts to introduce various green chemistry concepts including the choice of substrate, energy, solvent, catalyst and reducing agent. Our hope is to show, educate, and ease the application of sustainability methods to the chemists to come. These examples showcase an interesting trend in the field. While the use of water, or mechanochemistry are very hot topics and are certainly innovative, they both rely in much older concepts. Water has always been the solvent of choice in biochemical pathways, and on Earth's lifetime scale the use of organic solvents in modern organic chemistry can be seen as an historical anomaly. Likewise, mechanochemistry has been used in human history long before the first oil bath was ever used,[226] and photochemistry or iron catalysis has been fully exploited by nature for even longer, as plants and blood cells can testify. These re-discovered techniques are key to tackle long-standing challenges. In fact, some fundamental chemical considerations such as solvent effect, substrate solubility or reaction chemoselectivity are worth considering through these new scopes.[40]

Authors biography

Alain Li received his MSc. in organic chemistry from l'Ecole Nationale Supérieure de Chimie of Montpellier, France in 2013. He then obtained his PhD in 2019 from McGill university in Montréal, Canada, working under the co-supervision of Prof. Audrey Moores and Prof. Chao-Jun Li on sustainable catalysis applied to carbonyl reduction.

Audrey Moores received her BSc (2001), MSc (2002) and PhD (2005) from Ecole Polytechnique, Palaiseau in France. She did a post-doctoral fellowship at Yale University, before starting her independent carrier at McGill University, Montréal, Canada as a Canada Research Chair in Green Chemistry in 2007. She became an Associate Professor in 2014. Between 2012 and 2016 she was the co-associate director of the Center for Green Chemistry and Catalysis. Since 2017, she co-leads the McGill Sustainability Systems Initiative-Materials. Her research focuses on catalysis and photocatalysis using metal, metal oxide and biomass-based nanomaterials, with a special emphasis on sustainable processes and use of earth abundant starting materials. She also develops solid phase methods to access nanomaterials and functional polymers. She was selected as an emerging leader in 2017 by the RSC journal Green Chemistry

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