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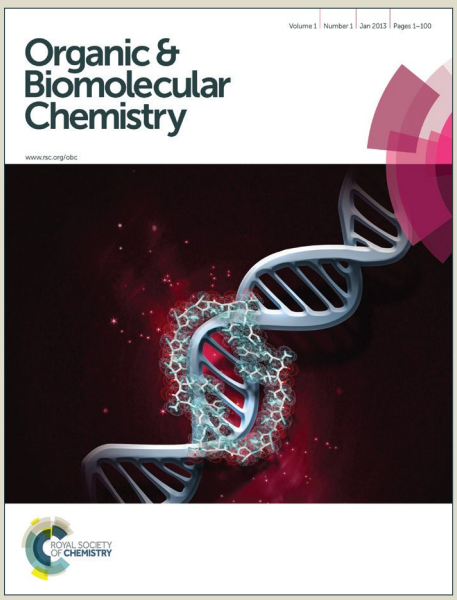

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Synthetic applications of hypophosphite derivatives in reduction

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1. Introduction

Catalytic hydrogenation and reduction using metal hydrides are two of the main reduction tools of modern organic chemistry. Catalytic hydrogenation[1] is often preferred for ecological and economic reasons; the amount of waste in that case produced is much lower (principles 2 and 8 of green chemistry). Nevertheless, the use of aluminum and boron hydrides is still very important mainly because such reagents often allow better regio- and chemo-selectivity. On the contrary, enantioselectivity is generally obtained using hydrogenation with transition metal catalysts.[2]

The development of aluminum and boron hydrides was one of the great successes in the chemistry of the second part of the 20th century.[3] These hydrides are the subject of numerous books, chapters, reviews and are taught in both theoretical and practical courses in University and Chemistry Schools.[4] However, the search for more specific and efficient reagents for large scale industrial applications, with a lower ecological impact remains one of the main objectives of organic chemists.[5] Due to performance issues in reaching high chemo- and stereo-selectivity, the aluminum and boron reagents are still preferred both in academic and industrial strategies for producing complex molecules. Total synthesis of complex molecules was often compared to art, considering the required creativity in a clever association of a large number of different steps and chemical transformations. The versatility and potential of aluminum and boron hydrides are so important that they are among the most-used reagents in multistep syntheses.[6] The production and use of aluminum and boron hydrides altogether represents several thousands of tons which is indicative of the practical interest of such reagents.[7] Nowadays however, requirements in chemistry are changing fast and the drawbacks of such reagents such as their high flammability in contact either with air or water, their use in combination with toxic flammable solvents, dangerous work-up, the production of hazardous salts,[8] and identified safety concerns appear more and more significant. Therefore, with respect to green chemistry principles, they no longer meet ecological, economical or social demands.[9]

More recently, hydrosilanes were proposed as alternatives they have silica as ultimate byproduct. Many results have shown that these reagents may efficiently replace aluminum and boron hydrides, sometimes with better selectivity.[10] Unfortunately, they are also

expensive, toxic and flammable, and in particular conditions, they produce SiH_4 a dangerous pyrophoric gas.[11] These drawbacks might be overcome by using hydrosiloxanes such as TMDS[12] and PMHS[10] but the limitation in case is the relative high cost of the silicon reagent, at least for the moment.

Even before aluminum and boron hydrides were chosen as the main reagents for research and industrial development, other reducing agents were proposed. Formic acid and formate salts were used by Eschweiler in 1905, followed by Clarke in 1933 for reductive methylation of amines.[13] For the same reaction today, sodium borohydride or triacetoxyborohydride is preferred even if the use of these reagents is becoming less attractive due to the ecological impact.[14] Formic acid derivatives were also used for asymmetric reduction of ketones.[15] As well as these successes, formic acid available from CO_2, may be produced with a favorable life-cycle assessment.[16] Nevertheless, like most reducing agents, an excess of reagent has to be used, making heavy the separation and recycling steps.

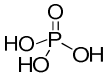
Phosphonic and phosphinic acid derivatives have received less attention but were also proposed as early as the sixties by different pioneer researchers, such as Boyer,[17] Beletskaya,[18] Johnstone[19] and Staskun.[20] During our general study dedicated to finding cleaner reducing agents, we failed reducing aliphatic nitro compounds using hydrosiloxanes such as PMHS and TMDS.[12] Conversely, we discovered that the same substrates may be selectively reduced into amines by hypophosphite (Table 1). These encouraging observations are part of the reasons for our interest in phosphorus-reducing agents. Hypophosphites are produced on a very large scale, at low price and are known to be non-toxic. Moreover, the byproducts of these reagents are phosphorus derivatives which are widely used as fertilizers. The purpose of this review is to collect the current applications in fine synthesis concerning phosphinic derivatives as reducing agents.

2. Hypophosphites and other phosphorus derivatives

Phosphorous and hypophosphorous acid derivatives are part of the oxoacids of phosphorus in which P has an oxidation state less than +5 ($XPO(OH)_2$ and $X_2PO(OH)$ where X = H or P).[21] They are characterized by the P-H bond giving them reducing properties. These compounds are tetravalent and possess at least two P-O bonds (Table 1). Hypophosphorous acid (phosphinic acid) is the least oxygenated derivative and has two P-H bonds while

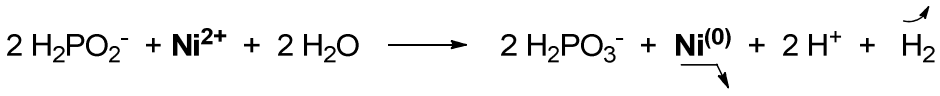
phosphorous acid (phosphonic acid) has only one. Phosphoric acid is fully oxygenated and thus is not a reducing agent.

Table 1. Nomenclature

			
Acids	**Hypo**phosphorous acid **Phosphinic acid** [a]	Phosphorous acid **Phosphonic acid** [a]	**Phosphoric acid** [a]
pKa	1.1[21]	1.3, 6.7[22]	2.2, 7.2, 12.3[22]
Sodium salts	NaH_2PO_2	NaH_2PO_3/Na_2HPO_3	$NaH_2PO_4/Na_2HPO_4/Na_3PO_4$
	Sodium Hypophosphite	Sodium dihydrogen phosphite/ Sodium phosphite/	Sodium dihydrogen phosphate/Disodium hydrogen phosphate/ Trisodium phosphate/
	Sodium Phosphinate[a]	**Sodium Phosphonate**[a]	**Sodium phosphate**[a]

[a] IUPAC name[23]

Sodium hypophosphite and its derivatives are mostly used to reduce metal salts. On an industrial scale, sodium hypophosphite is mainly used for the plating of metals, plastics and ceramics, also called electroless metal plating.[24] Among the different metals that hypophosphites are able to deposit (for example Co, Cu, Ag, Mn, Pt) nickel is by far the most used. The process is identified as electroless nickel plating[25] (ENP) and is the main application of hypophosphites. ENP is the chemical reduction of nickel salts in water to nickel (0) on a surface (Scheme 1). This process is preferred to the conventional electroplating since it provides a coating of uniform thickness, hardness and good resistance to corrosion.



Scheme 1. Nickel reduction by hypophosphite

Hypophosphite derivatives can reduce other inorganic compounds such as germanium oxide in the presence of HCl into trichlorogermane ($HGeCl_3$) which is a synthetic intermediate[26,27] of organo-germanium compounds studied for medical (as they have biological activities[26] as antitumor agents) or for potential technological applications.[27]

Sodium hypophosphite has also been reported in the reduction of calcium carbonate into calcium formate under CO_2 pressure (2 bar) catalyzed by rhodium and ruthenium complexes of *meta*-monosulfonated triphenylphosphine.[28]

Hypophosphites and its derivatives are also used as chemical intermediates for the synthesis of phosphorous precursors, which are interesting either for their biological activities[29] (for example as analogues of Fosmidomycin[29a] or modified oligonucleotides[29b]) or their ligand properties[30] among other applications.

Hypophosphites lead to phosphinate derivatives[31] by nucleophilic addition on carbonyl derivatives or by addition on double bonds *via* a radical mechanism.[32] Phosphites react similarly leading to phosphonic derivatives but the use of the organic phosphites is generally preferred to the inorganic phosphorous acid and its salts.[33] Phosphonic derivatives can also be obtained by oxidation of the corresponding phosphinates. More recently, metal catalyzed phosphorus coupling allowing P-C and P-O bond formation from different kind of partners[34] received much interest. Although organic hypophosphites and phosphites are still preferred for these transformations, methodologies using the cheaper and easier to handle inorganic salts and acids are being developed. The end issue addressed is the substitution of $POCl_3$ in phosphorous chemistry. Green development is emerging as well on the asymmetric synthesis of H-phosphinate esters from these salts that would allow a much more straightforward synthesis of chiral ligands.[35]

Hypophosphites are also employed as additives to reduce the excess of peroxides in epoxidized vegetable oils[36a] and as stabilizers of fatty alcohols.[36b] Concerning polymer applications, hypophosphites are used as catalysts,[37] heat stabilizers for polymers,[38] whitening agents,[39] and as flame retardant in polymers[40] and cotton fabrics.[41]

Applications in life science and technology have been also reported. Hypophosphites displayed anti-microbial activities by inhibiting the formation of enterotoxin from *Clostridium botulinum* in smoked meat products.[42] In addition, hypophosphites have been used as a source of phosphorous in veterinary and human medicine.[43] Calcium and magnesium hypophosphites are used on cows suffering from *parturient paresis*[44] and have been suggested as good candidates for obesity treatment in humans.[45]

Sodium hypophosphite, hypophosphorous and phosphorous acids are all available in bulk quantity in Europe (up to 10,000 tons/year) and registered in REACH.[46] Sodium

hypophosphite is considered as "non-hazardous substance" for both humans and the environment.[47] Oral LC_{50} in rats is higher than 1440 mg/kg, showing low acute toxicity.

Hypophosphites are manufactured from pure yellow phosphorus sludge which is a waste product of the wet process of the synthesis of phosphoric acid,[48] or from an electrothermal phosphorus plant producing white phosphorus.[49] Reaction of elemental phosphorus with alkaline and alkaline earth hydroxides produces hypophosphite with phosphine, hydrogen and phosphite. To obtain pure hypophosphite, the phosphite contaminant has to be removed by precipitation of calcium phosphite followed by a separation. The remaining solution is purified by acid/base treatment and ion exchange. The hypophosphorous acid is mostly produced by cation exchange of a hypophosphite salt by sulfuric acid[50] or ion exchange resin.[51] Historically, barium salt was used. However, due to its poor solubility in water, a large amount of water is required for the process, which explained the replacement of barium salt by sodium salt nowadays.[52]

On heating, hypophosphites and phosphites disproportionate notably into phosphine and phosphoric acid.[21,53] Hyphosphorous / phosphonic acids and their salts display high solubility in water (Table **2**). Some of them can be dissolved in acetic acid and in alcohols (mainly ethanol, glycerol and ethylene glycol). Hypophosphorous and phosphorous acids are more soluble than their salts in water and organic solvents. In terms of acidity, hypophosphorous acid (pKa = 1.1) and phosphorous acid (pKa = 1.3, 6.7) are strongly acidic (Table 1).[21,22]

Table 2. Solubility expressed in percentage by weight of the salt (or acid) in the indicated solvent

Reagent	Water	Ethanol	Other
$Ca(H_2PO_2)_2$	13[54]	Insoluble[22]	Glycerol (2-3%)[55]
$NH_4H_2PO_2$	51[56]	Soluble[57]	
NaH_2PO_2	58[58]	Soluble[55]	Acetic acid (42%),[58] Ethylene glycol (25%),[59] Propylene glycol (9%)[60]
H_3PO_2	Very soluble[22]	Soluble[22]	Ether (soluble)[22]
H_3PO_3	75[22]	Very soluble[22]	
Na_2HPO_3	Very soluble[60]		

Hypophosphite and phosphite derivatives are powerful reductants.[22] The general trend is as follows: acids are weaker reducing agents than their corresponding salts and hypophosphite derivatives are more powerful reductants than the phosphite derivatives (see Table 3).[61]

Table 3. Standard reduction potentials[22]

Entry	Half equation	E° (V)
1	$HPO_3^{2-} + 2\ H_2O + 2\ e^- \rightleftharpoons H_2PO_2^- + 3\ OH^-$	-1.65
2	$PO_4^{3-} + 2\ H_2O + 2\ e^- \rightleftharpoons HPO_3^{2-} + 3\ OH^-$	-1.05
3	$H_3PO_3 + 2\ H^+ + 2\ e^- \rightleftharpoons H_3PO_2 + H_2O$	-0.5
4	$H_3PO_4 + 2\ H^+ + 2\ e^- \rightleftharpoons H_3PO_3 + H_2O$	-0.28

In reduction, hypophosphites are oxidized to phosphites and phosphates. Phosphates are non-toxic[47] side-products mainly used as fertilizers in millions of tons per year.[21,34,62]

3. Cleavage of carbon-heteroatom single bonds

3.1. Dehalogenation reaction

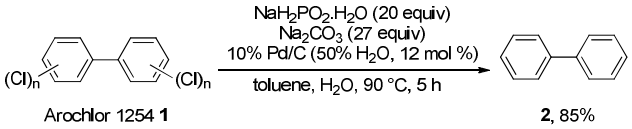
Dehalogenation reactions are often used in order to eliminate chlorine, bromine or iodine introduced as a directing group on an aromatic substrate or even more often to eliminate halogenated (mainly chloro-derivative) products which are known not only to be toxic but also persistent in the environment.

3.1.1. Dechlorination

Remediation by reductive dechlorination may be a solution for groundwaters contaminated by chlorinated molecules. In the present policy related to environmental and ethical issues, these problems have been studied since the early 1980s, with the report of reductive dechlorination of perchloroethene (PCE) and trichloroethene (TCE) under microbiological conditions.[63] This investigation domain has received considerable attention in order to discover greener methods for dehalogenation reactions.

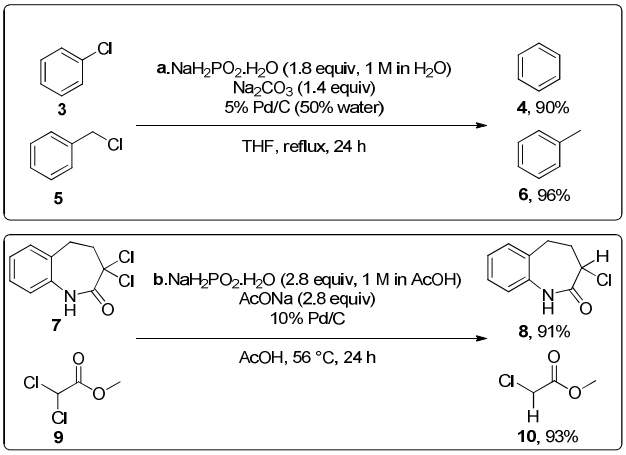
In 1985, Boyer from the Ciba-Geigy company described a mild and efficient process for dehalogenation processes of polyhalogenated aromatics including PCBs. Arochlor 1254 **1** (PCB mixture containing 13.8% of tetrachlorobiphenyls, 61.9% of pentachlorobiphenyls, 23.3% of hexachlorobiphenyls and 1% of heptachlorobiphenyls), was submitted for

dechlorination in toluene in the presence of a large excess of sodium hypophosphite, sodium carbonate and Pd/C 10% at 90 °C during 5 hours, leading to biphenyl **2** in 85% isolated yield (Scheme 2).[64]



Scheme 2. Dechlorination of Arochlor 1254 (**1**)

Under the above conditions, chlorobenzene, 1,4-dibromobiphenyl, 4-chloro-anisole and 1,2,4-trichlorobenzene were completely converted into the de-halogenated products.[64b] The reaction was efficiently extended to chloroaromatics (such as benzene, naphthalene, quinolone and pyridine) or activated chloroalkanes (benzyl chlorides).[64a] For example, chlorobenzene **3** or benzyl chloride **5** were de-halogenated with yields higher than 90% (Scheme 3, conditions a). The reduction of chlorocyclohexane ran to failure indicating the limitation of the method to activated chlorinated derivatives.[17] Therefore, unfortunately, compounds such as Lindane (hexachlorocyclohexane) used as pesticides until 2007 in large quantities, but also known as being toxic[65] cannot be destroyed by this process.



Scheme 3. Dechlorination reaction

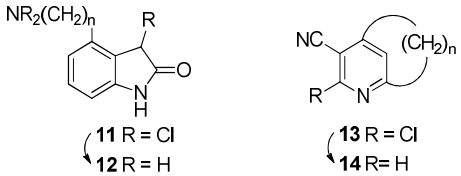
The challenging selective monohydrogenolysis of polyhalogenated compounds activated in α position of a carbonyl group proceeded efficiently by using sodium hypophosphite in combination with a buffer solution of sodium acetate/acetic acid to neutralize the HCl released. The geminal dichlorolactam **7** and methyl dichloroacetate **9** were successfully converted into the corresponding monochlorinated derivatives **8** and **10** with excellent yields

(Scheme 3, conditions b). Carbon tetrachloride was also cleanly reduced into chloroform (90% yield).

The above pioneering work of Boyer was later adapted for the reduction of polyhalofluoroalkanes such as 1,1,1-trifluorotrichloroethane into 2,2-dichloro-1,1,1-trifluoroethane with 92% isolated yield with platinum on charcoal instead of palladium which required a longer reaction time.[66] Catalytic hydrogenolysis of water-soluble chlorinated substrates (substituted benzoic acids, phenols and anilines) was described by Beletskaya et al. using catalytic $PdCl_2$ in alkaline aqueous medium.[18] The following optimized conditions were used for exemplification: chloroarene (1 equiv), NaOH (3 equiv), $PdCl_2$ (5 mol %), $NaH_2PO_2.H_2O$ (5 equiv) in water, during 6 to 8 hours at 50-70 °C. *Para*-chloro benzoic acid and phenol were dehalogenated with excellent yields of 94% and 83%, respectively. A drastic decrease in yield was observed for the chloro-substituent in *ortho* position (<20%). The hydrogenolysis of chloropyridines and 3,5-chloropicolinic acid remained inefficient under all the conditions tested with isolated yields lower than 15%.

Physical activation techniques were used with hypophosphite and Pd/C to reduce chlorinated molecules. In alkaline solution under microwave activation, the chlorobenzene afforded a mixture of phenol and benzene.[67] Dechlorination has been also carried out in a planetary ball-mill in the absence of solvent, for example on hexachlorobenzene, to afford benzene in a mixture of partially chlorinated benzenes.[68]

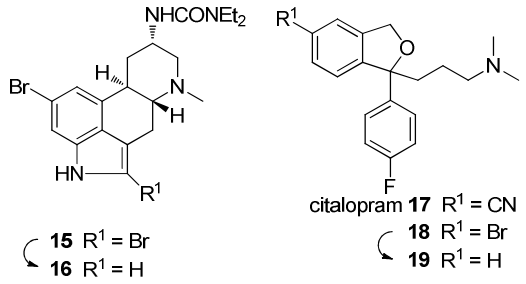
Multiphase solvent systems composed of isooctane and water in the presence of a phase transfer catalyst (PTC) such as Aliquat 336 or Tween 20 increased the kinetic constants of the dechlorination reaction with quantitative yields.[69] PTC conditions improved the transfer of hypophosphite species from the aqueous phase to the palladium surface, as well as the neutralization of hydrochloric acid. The catalytic hydrogen-transfer reduction mediated by sodium hypophosphite has been used to synthesize reactive intermediates[70a] and molecules of therapeutic interest[70b,c] such as substituted indolones[71] **12** or with supramolecular assembly application such as 5-cyano[*n*](2,4)pyridinophanes[72] **14** (Scheme 4). Under these conditions, nitriles and amides were not reduced as well as pyridine ring. Chlorine in alpha position of an amide and an aromatic as can be found in **11** was selectively reduced in the presence of unactivated aliphatic bromine into **12** with an excellent yield of 89%. Interestingly as well, in the reduction of chloropyridine **13** into **14**, sodium hypophosphite and Pd/C were preferred to hydrazine with Pd/C giving only moderate yield of 51%.[72]



Scheme 4. Application of the dehalogenation methodology

3.1.2. Debromination

As the bond dissociation energy of C-Br, evaluated at 285 kJ.mol^{-1}, is weaker than that of the C-Cl bond (around 331 kJ.mol^{-1}), the previously described methods for hydrodechlorination are even easier on bromo-substituted benzene, pyridine, quinolone, phenetol, phenanthrene, pyrimidine, indole, furan, benzonitrile[64b] and polybromofluoroalkanes with chemoselectivity.[66] Debromination was performed on bromide **15** affording ergoline derivative **16**, which has potential antidopaminergic properties, with 44% yield (Scheme 5).[73] As part of a purification process of citalopram (**17**), an antidepressant, contaminated with 5-bromoisobenzofuran (**18)**, a debromination process based on hypophosphite reducing agent (NaH_2PO_2, EtOAc, Pd/C, reflux, 2 h) was successfully developed by Sun Parmaceuticals (Scheme 5).[74]

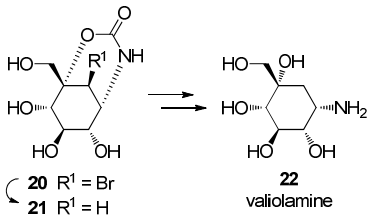


Scheme 5. Application of the debromination reaction

Hypophosphorous acid alone allowed the debromination of 2-bromo-3,4,5-trinitrothiophene in 76% yield.[75] This procedure allowed the mono-debromination of 2,5-dibromo-3,4-dinitrothiophene in 85% yield.[76]

Radical conditions were first developed by Barton and coworkers in 1992 using H_3PO_2/triethylamine/AIBN.[77] The radical initiator could be AIBN, Et_3B/air or hydrophilic azoamidine radical initiator (known as azo polymerization initiators)[78] and reductions were performed with H_3PO_2/triethylamine,[77] sodium hypophosphite[32] and $(Bu_4N)^+H_2PO_2^-$.[79] The use of a base such as triethylamine with H_3PO_2 or NaOH with sodium hypophosphite has been studied to prevent decomposition of acid-labile substrates such as nucleoside derivatives, with this specific case, an acetonitrile/water solvent mixture. Processes for preparing 6,7,8-

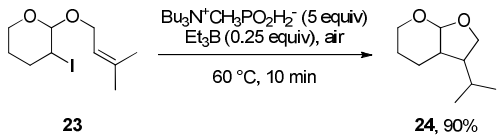
trihydroxy-1-(hydroxymethyl)-3-oxo-2-oxa-4-azabicyclo-[3.3.1]nonane were patented by the Yuhan Corporation with a key step of reduction by hypophosphite to obtain valiolamine (**22**), displaying α-glucosidase inhibitory activity and used for preventing/treating hyperglycemic disorders (Scheme 6). Intermediate **20** could be applied to an industrial scale mass production.[80]



Scheme 6. Access to valiolamine

3.1.3. Deiodination

Similarly to the debromination of bromothiophene derivatives,[75] the deiodination of iodo-2,4,6-trinitrobenzene was done with hypophosphorous acid alone in quantitative yield.[81] These conditions modified by the addition of a radical initiator were later applied for the dehalogenation of aromatic and aliphatic derivatives in the presence of carboxylic acids, ketones, ketals, ethers and esters.[77,82] The radical formed during the dehalogenation step can react with a double bond to afford cyclic compounds exo trig cyclization (Scheme 7).[83] Intermolecular versions of this transformation were also reported.[84]



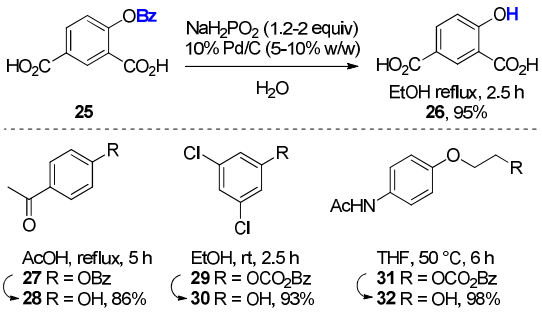
Scheme 7. Application of the dehalogenation methodology to C-C bond formation

An example of a deiodination reaction was reported by Hu and co-workers in 1991[66] as part of a study devoted to the selective reduction of polyhalofluoroalkanes. In the presence of an almost stoichiometric quantity of sodium hypophosphite (1.1 equiv) and sodium acetate (1.1 equiv) with platinum catalyst in acetic acid at 40 °C for 6 hours, $CF_3(CH_2)_5I$ was reduced to $CF_3(CH_2)_5H$ with 81% yield. Use of Pd/C required a longer reaction time.

Deiodination was also observed with sodium hypophosphite and Raney nickel during a reductive desulfurization.[85]

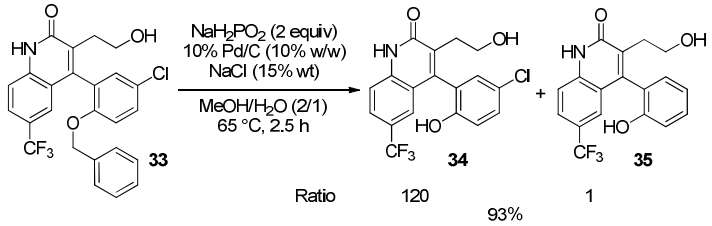
3.2. C-O bond cleavage – Reductive cleavage of benzyl ether and benzyl carbonate

Sala and co-workers described the cleavage of benzyl ethers and benzyl carbonates with sodium hypophosphite (1.2-2 equiv) and Pd/C (5-10% w/w) in high yields (86-98%) (see scheme 8).[86] With these conditions, benzyl ethers can be hydrogenolyzed with a good chemoselectivity towards carboxylic acid (**26**) and aromatic ketone (**28**). Benzylcarbonates **29** and **31** were selectively cleaved in the presence of halogens or acetamides (Scheme 8).



Scheme 8. Hydrogenolysis of benzyl ethers and carbonates

Selective cleavage of benzyl ethers in the presence of chloro substituents was studied in the synthesis of 4-arylquinolin-2(1*H*)-ones **34** (Scheme 9).[87] Sodium chloride was used as an additive to deactivate the cationic Pd sites and thus lead to excellent chemoselectivity (Scheme 9). Extension of this methodology was described for the synthesis of indole intermediates of Peroxisome Proliferator Activated Receptors (PPARs)[88] developed by Eli Lilly or farnesoid X receptor modulators.[89]



Scheme 9. Application of the benzyl ether cleavage

Use of K_2CO_3 in the presence of THF has been also reported for the deprotection of benzyl ether with sodium hypophosphite and Pd/C[17] but with a concomitant dechlorination under these conditions.

3.3. Se-Se bond cleavage

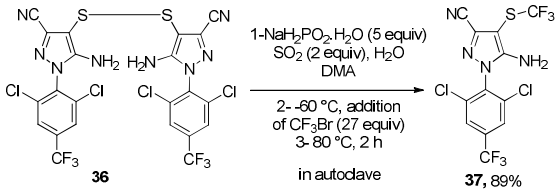
Reduction of diselenide to selenol was reported by action of 1 molar equivalent of 50% aqueous hypophosphorous solution at 80 °C under nitrogen atmosphere.[90] For example, dimethyl diselenide was reduced in methylselenol in 88% yield. Only phosphorous acid was formed as side product and was unable to reduce diselenide. Azobenzene, sulfoxide and thio

ether were not reduced by hypophosphorous acid alone. However, the presence of a catalytic quantity of diselenide allowed their reduction. This methodology of reduction of diselenide to selenol was preferred to the reduction by $NaBH_4$ which was exothermic and led to gas evolution.[91] It was applied to the synthesis of organic selenide derivatives.[91,92] A recent example concerned the synthesis of 2-organylselanyl pyridines in glycerol.[93]

3.4. C-S and S-S bond cleavage

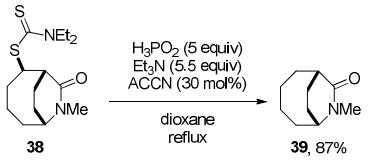
Disulfide can be cleaved by hypophosphorous acid in the presence of a catalytic quantity of diselenide.[90] For example, bis(2-trimethylammonium ethyl)disulfide iodine $((CH_3)_3N^+-CH_2CH_2S)_2I$ was cleaved in 90% yield.

One synthesis of trifluoromethylsulfide **37**, an intermediate in the synthesis of Fipronil, an insecticide, was reported.[94] Disulfide **36** was reduced to thiol by sodium hypophosphite in the presence of an over stoichiometric amount of SO_2 in DMA/water. The thiol was alkylated *in situ* by trifluoromethylbromide at 80 °C for 2 h in **37** with 89% yield (Scheme 10).



Scheme 10. Reduction of disulfide to thiol and *in situ* alkylation to thio ether

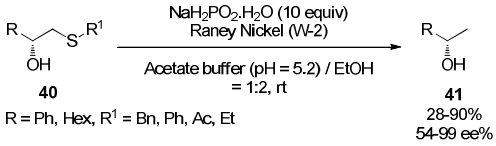
The reduction of the C-S bond in xanthates[95] or dithiocarbamates[96] was performed with hypophosphorous acid in the presence of triethylamine and a radical initiator (AIBN or ACHN: 1,1'-azobis(cyclohexanecarbonitritrile)). These reductions were compatible with the presence of amide function (example of **38** converted in 87% yield into **39**) but also with ketones and alcohols (Scheme 11).



Scheme 11. Reduction of dithiocarbamates

Node found that a combination of Raney nickel (W-2)-sodium hypophosphite in ethanol and acetate buffer (pH 5.2) was an excellent combination for the desulphurization of thio ethers or sulfoxides bearing an optically-active secondary alcohol without any loss of the optical activity (Scheme 12).[97] Under these conditions, benzylthio- or phenylthio-ethers can

be cleaved selectively in the presence of benzyl ether. It was observed that the order of addition of reagents (Raney Ni and $NaH_2PO_2.H_2O$) to the starting material solution was critical to the desulphurization. This system was later employed in various applications.[98,85]



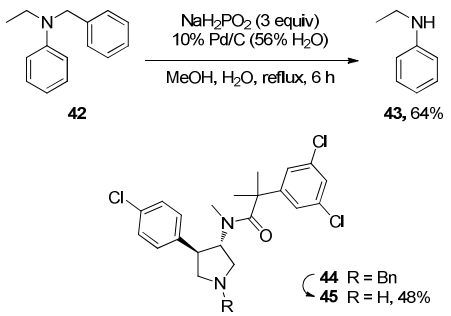
Scheme 12. Desulphurization of chiral alcohols

3.5. Reductive C-N bond cleavage

Only a few publications reported the debenzylation of secondary and tertiary benzylamine or the deprotection of carbamate. The reductive cleavage of C-N bond mainly focused on the dediazotation reaction.

3.5.1. Reductive cleavage of benzyl amine and benzyl carbamate

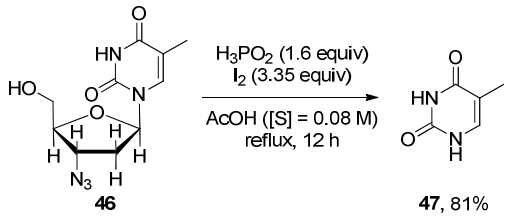
The metal-catalyzed debenzylation of tertiary benzylamines was achieved with sodium hypophosphite and Pd/C but with lower efficiency in comparison to other hydrogen donors investigated (ammonium formate, hydrazine hydrate).[99] *N*-Benzyl-*N*-ethylaniline **42** was quantitatively hydrogenolyzed in **43** with sodium hypophosphite (Scheme 13) with 64% isolated yield. This moderate yield may come from the partially water solubility of the aniline salt.



Scheme 13. Conditions of *N*-debenzylation

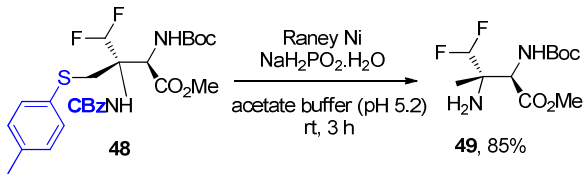
The application of *N*-debenzylation in molecules of therapeutic interest has been described in recent patents. In a patent filed by Hoffmann la Roche, the selective debenzylation of pyrrolidine **44** bearing chlorosubstituents was done in the presence of NaH_2PO_2 (2 equiv), Pd/C, an aqueous solution of NaCl, in MeOH at 65 °C for 4 hours in 48% yield in **45** (Scheme 13).[100]

The metal-free cleavage of benzylamines and aliphatic amines by phosphinic acid / I_2 in acetic acid has also been reported in good yields (66-93%). Under these conditions nitro-derivatives, ureas and carboxylic acids were neither reduced nor degraded. In addition, amides were tolerated as can be seen in the reductive cleavage of hemiaminal **46** to **47** in 81% yield (Scheme 14).[101] The presence of thioether did not impair the reduction.



Scheme 14. Cleavage of amine by H_3PO_2 / I_2 / AcOH

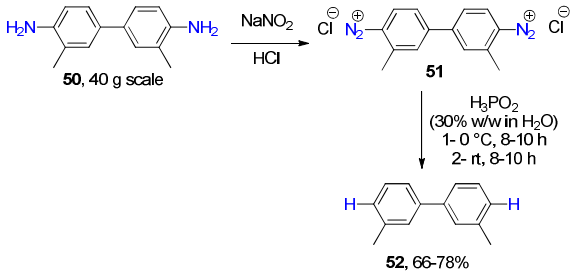
One example of carbamate deprotection has been reported with sodium hypophosphite in the presence of Pd/C, K_2CO_3 in THF / H_2O.[17] Carbamate can also be removed by sodium hypophosphite in the presence of Raney nickel in acetate buffer at room temperature as illustrated by the reduction of **48** with simultaneous desulfurization to **49** in 85% yield over two steps (Scheme 15).[102]



Scheme 15. Example of chemoselective carbamate deprotection

3.5.2. Hydro-dediazoniation

Mai was one of the first to report the reduction of an arene diazonium salt to the corresponding arene by phosphinic acid.[103] Phosphinic acid reduction of diazonium salts can be catalyzed by $KMnO_4$, $K_2Cr_2O_7$, $CuSO_4$, $FeSO_4$ and Cu. A mechanistic study has been carried out by the team of Kornblum[104] who showed a free radical chain reaction. Although other reducing systems are available for the hydro-dediazoniation, the use of phosphinic acid is recommended for its efficiency and ease of operation[105] on the multigram scale (Scheme 16).[106]



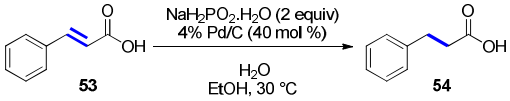
Scheme 16. Reduction of diazonium salt on multigram scale

More recently, calcium hypophosphite in association with iron sulfate was used instead of phosphinic acid. Exploring the potential of $Ca(H_2PO_2)_2$ directly represents an economy of steps.[107]

4. Reduction of C-C multiple bonds

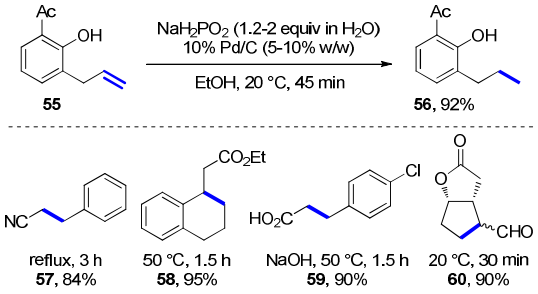
4.1. Alkene reduction

In 1972, Bakulina studied the decomposition of sodium hypophosphite for the reduction of alkene as a substitute for molecular hydrogen on small-scale reactions.[108] The comparison of reduction with molecular hydrogen and sodium hypophosphite was carried out on cinnamic acid **53** over Pd/C at 30 °C (Scheme 17). In both cases, the reduction rate was independent of the cinnamic acid concentration. The hydrogen transfer with sodium hypophosphite was slower than classical hydrogenation, and was attributed to the adsorption of hypophosphite on the catalyst surface. However, the authors highlighted the ease of operation at laboratory scale of the reduction mediated by sodium hypophosphite.



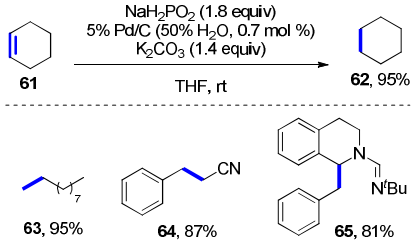
Scheme 17. Reduction of cinnamic acid

Sala reported the hydrogenolysis of benzyl ethers and in the same paper described the reduction of alkenes into alkanes.[86] The reaction conditions are similar to those used for the debenzylation procedure, with slight changes in temperature and time. A good chemoselectivity was observed with a tolerance towards aliphatic nitrile, ester, carboxylic acid, aromatic halide and even aliphatic aldehyde functions (Scheme 18). Some substrates were efficiently reduced in DMF and alkaline water which are rarely used with hypophosphites.



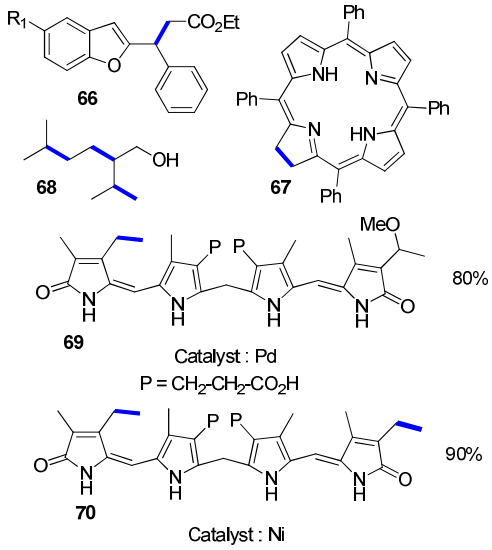
Scheme 18. Sala's conditions for the reduction of C=C (Reduced bonds in blue)

Slight modifications of the reaction conditions do not affect the issue: base such as K_2CO_3 in THF as solvent instead of EtOH can be used (Scheme 19).[17] Simple alkenes could be reduced efficiently in alkanes **62** and **63**, as well as conjugated alkenes into **64** and **65**. Selectivity toward aliphatic nitrile was also observed with the reduction of cinnamonitrile into dihydrocinnamonitrile **64** with 87% yield. Selectivity towards imine was also observed with the synthesis of **65** with 81% yield from the corresponding alkene.



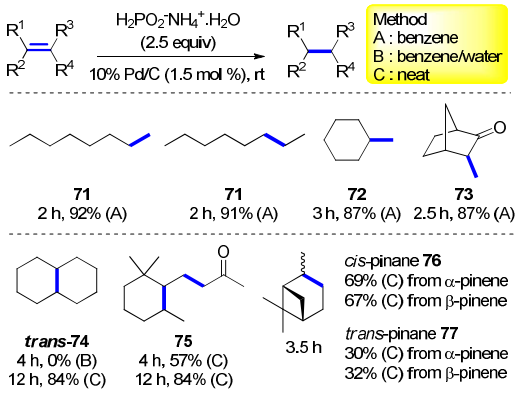
Scheme 19. Boyer's work on C=C reduction

Similar conditions were recently applied to the total reduction of (*R*)-4,8-dimethylnona-1,7-diene, [109] of conjugated alkenes with aromatic and heteroaromatic rings **66**, [110] of tetraphenylporphyrins **67**,[111] of dehydrolavandulol to tetrahydrolavandulol **68**[112] (used in the fragrance industry as a substitute for the scent of roses) or 18-devinyl-18-(1-methoxyethyl)bilirubin into **70** (Scheme 20).[113]



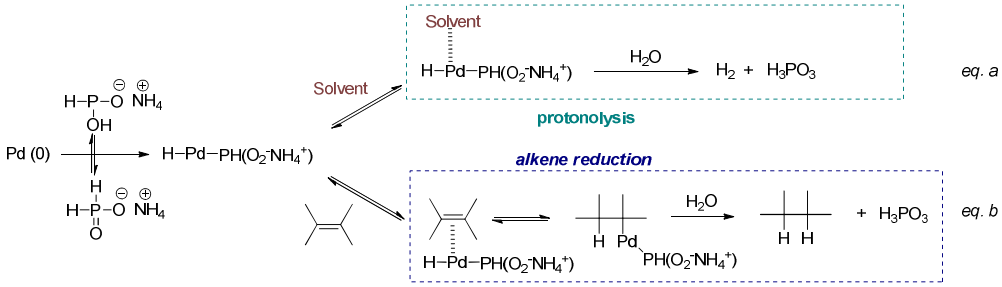
Scheme 20. An example of the use of hypophosphite for the reduction of complex substrates

Later, the reduction of sterically-hindered alkenes was studied with ammonium hypophosphite in the presence of palladium on charcoal (1.5 mol % at room temperature) (Scheme 21).[114] A strong solvent effect was observed. For example, in the presence of benzene (Method A) or biphasic benzene/H_2O (Method B), mono- and di-substituted alkenes were completely reduced while tetra-substituted alkenes led to zero conversion. Method A proved its efficiency in reduction of oct-1-ene, oct-2-ene, methylene cyclohexane and 3-methylene-2-norbornanone into **71-73,** respectively, with yields higher than 87% in less than 3 h. The conditions in Method B (benzene/H_2O solvent) could not reduce $\Delta^{9,10}$-octalin into **74** after 4 h and in a more general extent tetrasubstituted alkenes. The hypothesis was made that benzene competes with the substrate on the palladium surface. Thus, neat conditions (Method C) were applied allowing the reduction of sterically-hindered $\Delta^{9,10}$-octalin, β-ionone and pinene in high yields. $\Delta^{9,10}$-Octalin was reduced under thermodynamic control into *trans*-decalin; ***trans*-74** was predominantly obtained (ratio *trans* / *cis* : 92 / 8). On the contrary, the reduction of pinene mainly led to *cis*-pinane **76**.



Scheme 21. Reduction of alkenes with ammonium hypophosphite

In order to explain the strong solvent effect observed, the authors proposed a mechanism (Scheme 22) with a competition between two reactions: the desorption of hydrogen to produce molecular hydrogen (Scheme 22, eq. a) and the transfer hydrogenation of the alkene (Scheme 22, eq. b). The production of hydrogen by decomposition of hypophosphite in the presence of water on palladium on charcoal in the absence of reducible substrate is known.[17] In the presence of a reducible functional group, the competition between the solvent, the hypophosphite and substrate for the catalyst surface will determine the extent of the reduction.



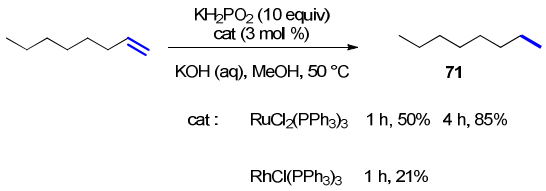
Scheme 22. Competition between hydrogen production and alkene reduction

From the results obtained, mono- and di-substituted alkenes follow the mechanism proposed in *eq. b*. Palladium has more affinity for these alkenes than for benzene. On the contrary, the absence of reduction of tetra-substituted alkenes under Methods A and B would follow *eq. a*. This means that benzene has a better affinity with the palladium than the tetra-substituted alkenes. This hypothesis is partially confirmed by the quantitative reduction of tetra-substituted alkenes under neat conditions.

More recently, the transfer hydrogenation of 3-buten-1-ol by sodium hypophosphite on Pd-black film pointed out[115] the concentration of hypophosphite was the main factor controlling

the rate of reaction and selectivity. Ni-P electroless alloys have also been studied on the reduction of 3-buten-1-ol.[116]

A homogeneous reduction of oct-1-ene was reported using KH_2PO_2 in an alkaline solution of aqueous methanol.[117] The reduction into octane **71** catalyzed by $RuCl_2(PPh_3)_3$ reached 50% yield after 1 h and 85% yield after 4 h (Scheme 23). In comparison, the reaction in the presence of the Wilkinson catalyst ($RhCl(PPh_3)_3$) reached only 21% yield after 1 h and 45% of isomerization in 2-octene was observed. The chemoselectivity was not studied under these conditions.



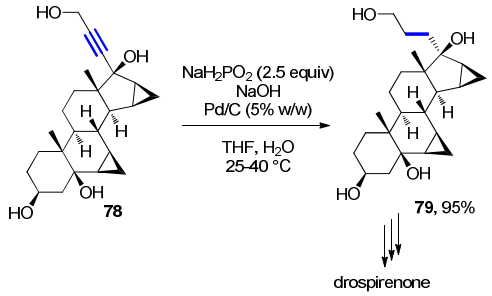
Scheme 23. Reduction of oct-1-ene catalyzed by homogeneous catalyst

Alkenes have been also reduced by H_3PO_2 / I_2.[118] Interestingly, the thiophene nucleus did not impair the reaction contrary to basic nitrogen and electron-withdrawing substituents.

4.2. Alkyne reduction

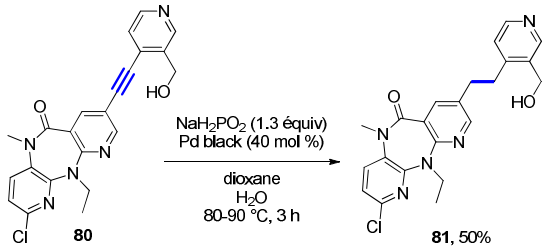
4.2.1. To alkanes

A reduction of alkyne **78** into alkane **79** was reported with sodium hypophosphite in the presence of palladium on carbon with 95% yield in a recent patent describing the access to drospirenone (Scheme 24),[119] a progestin and active pharmaceutical ingredient of Yasmin®, a birth control pill.



Scheme 24. Reduction of alkyne to alkane in the synthesis of dropirenone

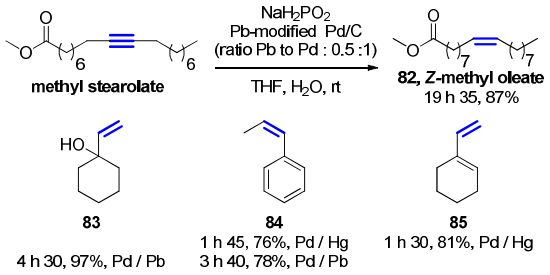
The alkyne **80** was also reduced to the alkane **81** in the presence of aryl chloride and pyridines in 50% yield as illustrated in Scheme 25 with potential application as inhibitors of HIV-1 reverse transcriptase.[120]



Scheme 25. Chemoselective reduction of alkyne to alkane

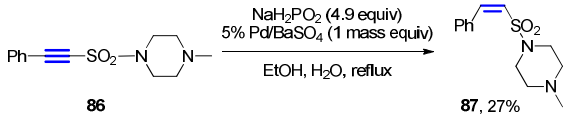
4.2.2. To alkenes

Johnstone reported a stereoselective and specific reduction of alkyne to *cis*-alkene with sodium hypophosphite in a water / THF solvent mixture in the presence of palladium on carbon modified with Pb or Hg.[121] Hydrogen donors such as phosphinic acid, phosphinates, phosphorous acid and phosphites were also tested. Sodium hypophosphite was the most efficient for the rapid conversion of alkynes into olefins. Amongst the catalysts investigated under these conditions, Pt, Rh and Ru were found to be inactive. However, palladium was the most active alone leading to no selectivity and with an over reduction in favor of the alkane. The rate of reduction was too fast to allow the isolation of alkenes in reasonable yields. The combination of Pb or Hg with palladium allowed the reduction into olefins. The reaction conditions proved to be chemoselective towards the ester (**82**), alcohol (**83**) and olefin (**84**) (Scheme 26). In a conjugated ene-yne system, only the alkyne was reduced leading for example to **85** without trace of double bond migration.



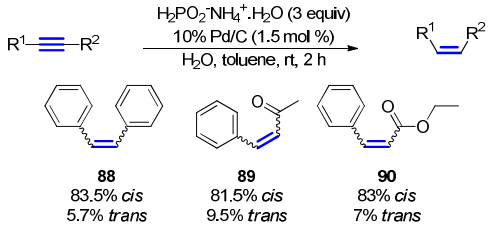
Scheme 26. Selective reduction of alkyne to (*Z*)-alkene with modified Pd/C catalysts

Epoxysulfonamides,[122] displaying interesting biological activity for example as antifilarial agents, were prepared from ethynesulfonamides **86** by hydrogenation under similar conditions previously developed by Johnstone[121] (barium sulfate poisoned palladium catalyst) (Scheme 27).



Scheme 27. Ethylenesulfonamide synthesis

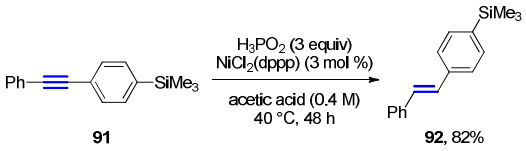
Inspired by the work of Johnstone using a modified palladium catalyst, Khai reported the reduction of alkyne to alkene with a commercially-available Pd/C and ammonium hypophosphite in a water/benzene solvent mixture.[114] After 2 hours at room temperature, diphenylacetylene was converted into stilbene **88** with high stereoselectivity (83.5% *cis* and 5.7% *trans*). Alkane, the over-reduction product, was isolated with 8% yield. The reaction also needed careful monitoring in order to avoid over reduction which increased significantly with the reaction time. 4-Phenyl-3-butyn-2-one and ethyl phenyl propiolate were reduced with comparable yields and stereoselectivities in **89** and **90,** respectively (Scheme 28).



Scheme 28. Selective alkyne reduction to (*Z*)-alkene

Recently, a selective reduction of alkynes to (*E*)-alkenes was reported in the presence of hypophosphorous acid and catalyzed by 1,3-bis(diphenylphosphino)propane nickel(II) chloride ($NiCl_2$(dppp)) in acetic acid (Scheme 29).[123] These conditions were efficient on diphenylalkynes providing (*E*)-stilbenes in 55-86% with *E*:*Z* selectivity higher than 98:2 and a good chemoselectivity. Halogen (Cl, F), ester, ether, boronic acid functions and thiophene nucleus were not reduced. Easily hydrolysable trimethylsilyl group was tolerated and the reduction of **91** afforded the corresponding stilbene **92** with 82% yield (Scheme 29). Dialkylalkyne such as dodec-6-yne was reduced in moderate yield (44%) due to a competitive reaction of hydration leading to 6-dodecanone. Terminal alkyne, such as phenylacetylene, was even more sensitive to hydrolysis affording acetophenone and no alkene was detected. The optimization showed that with homogeneous palladium catalysts ($Pd_2(dba)_3$, $PdCl_2(PPh_3)_2$ and $Pd(PPh_3)_4$), the selectivity was in favor of the (*Z*)-alkene contrary to nickel catalysts ($NiCl_2(PPh_3)_2$ and $NiCl_2$(dppp)). The reduction in acetic acid was more efficient than in DMSO, DMF, dioxane, THF, toluene or hexane. The authors showed that an isomerization of

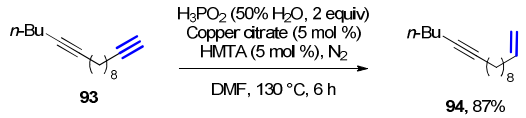
(*Z*)-alkene to (*E*)-alkene occurred under these conditions only in the presence of hypophosphorous acid.



91 **92**, 82%

Scheme 29. Reduction of internal alkynes to alkenes by hypophosphorous acid catalyzed by $NiCl_2$(dppp)

Aromatic and aliphatic terminal alkynes were selectively reduced to alkenes by hypophosphorous acid catalyzed by copper citrate (5 mol %), HMTA (5 mol %) in DMF at 130 °C in high yields.[124] No reduction of ether, halogens, ketone, ester, carboxylic acid and phthalimide was observed. In the case of internal and terminal alkynes on the same molecule, only the terminal alkyne was selectively reduced such as **93** into **94** with 87% yield (Scheme 30). Undesired dimers by-products, generated *via* the homo-addition of phenylacetylene were suppressed by the addition of 5 mol% hexamethylenetetramine. In both cases, the supposed mechanism goes through a hydrometalation followed by a reduction of the metal (II) to metal (0) by hypophosphorous acid.

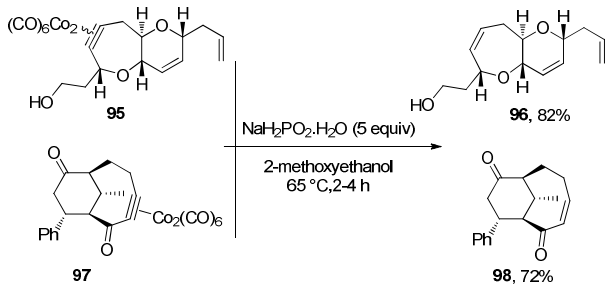


93 **94**, 87%

Scheme 30. Regioselective reduction of terminal alkynes to alkenes catalyzed by copper

4.2.3. Reductive decomplexation

Sodium hypophosphite monohydrate was used as a safe, effective and economical reagent in replacement of tri-*n*-butyl tin hydride for the reductive decomplexation of acetylene-biscobalt-hexacarbonyl. The cobalt complex of 7-membered ring alkyne **95** was converted into the corresponding olefin **96** with a large excess of NaH_2PO_2 monohydrate (5 equivalents) with a satisfactory yield of 82% (Scheme 31).[125] A total synthesis of ciguatoxin involving an acetylene-dicobalt-carbonyl complex was reported by the same research group.[126] Iwasawa then applied the same methodology on bridged-type cycloadducts **97** (Scheme 31).[127]



Scheme 31. Reductive decomplexation

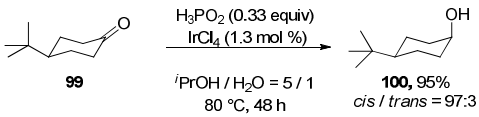
5. Reduction of C-heteroatom multiple bonds

5.1. Reduction of carbonyl derivatives

With a catalytic amount of metal, carbonyl derivatives were reduced either in alcohols or alkanes depending on the metal used and the structure of the substrate to be reduced.

Reduction catalyzed by Ir, Rh and Ru salts or complexes

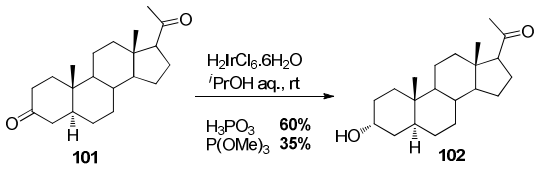
Carbonyl derivatives were selectively reduced in alcohols by hypophosphites in the presence of iridium[128] and ruthenium catalysts.[129] Henbest and Mitchell reported the reduction of carbonyl derivatives by phosphorous acid (or an easily hydrolyzed ester of this acid) with iridium chloride in aqueous isopropanol.[128] This method, often called the Henbest reduction, allows the reduction of cyclic ketones with good diastereoselectivity to the thermodynamically unfavored axial alcohols. Nonadecan-2-one is only reduced in 27% yield under the same conditions and benzophenone is unreactive. The reaction is also sensitive to steric hindrance.[128c] Hypophosphorous acid, under these conditions, was a good reductant with a better reduction rate than phosphorous acid. For example, 4-*tert*-butylcyclohexanone **99** was reduced quantitatively into the alcohol **100** with a *cis*/*trans* ratio of 97:3 by hypophosphorous acid and $IrCl_4$ (Scheme 32).



Scheme 32. Reduction of 4-*tert*-butylcyclohexanone by hypophosphorous acid / iridium chloride

Selectivity towards cyclic ketone reduction was applied to the synthesis of steroids due to excellent stereo- and chemoselectivities. Only the cyclic ketone was reduced and the main product was the axial alcohol **102**.[128b,130] The reaction tolerates amide and amine functions.[130c]

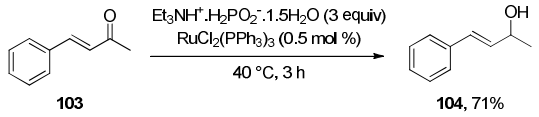
The use of phosphorous acid instead of trimethylphosphite increases the yield from 35 to 60% (Scheme 33).[130b]



Scheme 33. Application of Henbest reduction to steroid synthesis

In 1970, a study showed that the addition of acetic acid decreased the reaction rate while NaOH induced a 3-fold increase in the reaction rate. The iridium catalyst can be replaced by the Wilkinson's catalyst. Yields were comparable to those with the iridium catalyst but with better stereospecificities and regioselectivities.[131]

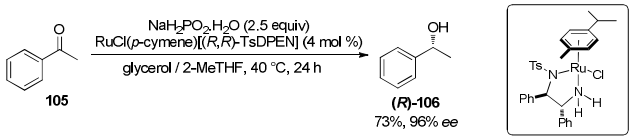
Khai and Arcelli developed a method for the reduction of ketones catalyzed by $RuCl_2(PPh_3)_3$ (1 mol%) in the presence of triethylammonium hypophosphite ($NEt_3H^+.H_2PO_2^-$) both as solvent and reducing agent at room temperature for 24 h.[129a] Under these conditions, aromatic and aliphatic ketones were chemoselectively reduced in good to excellent isolated yields (81-94%). Aromatic nitro-derivatives, halides, alkenes, nitriles and esters were not reduced. Deactivation of the $RuCl_2(PPh_3)_3$ catalyst was observed and subsequently resolved by supporting $RuCl_2(PPh_3)_3$ on carbon; therefore the question of the true catalyst homogeneous transition metal complex or metal particles still remains unsolved.[129b] Good stereoselectivity was obtained on cyclic ketones generally giving the axial alcohol as main product. Benzylideneacetone **103** was selectively reduced into the unsaturated alcohol **104** with 71% yield and 27% of the starting material was recovered (Scheme 34). The reduction of chalcone led to the allylic alcohol with 20% yield as well as the saturated ketone with 40% yield. In both cases, saturated alcohols were not observed.



Scheme 34. Reduction of benzylidene acetone by triethylammonium hypophosphite catalyzed by $RuCl_2(PPh_3)_3$

The enantioselective reduction of ethyl 4-chloroacetoacetate to ethyl 3-hydroxy-4-chlorobutyrate by $NEt_3H^+.H_2PO_2^-$ catalyzed by ruthenium BINAP was carried out with almost quantitative yield and 38% *ee*.[129b]

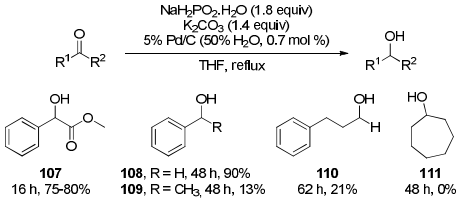
Recently, reduction under biphasic conditions using sodium hypophosphite as the reducing agent instead of the combination of triethylamine / phosphinic acid has been described by our group. $[RuCl_2(p\text{-cymene})]_2$ in association with bipyridine reduced aliphatic and aromatic ketones with a good chemoselectivity. An enantioselective version was developed with RuCl(*p*-cymene)[(*R*,*R*)-TsDPEN] in a biphasic solvent mixture of glycerol / 2-MeTHF (Scheme 35). This solvent mixture was important in order to reach high conversion and enantioselectivity ranging from 67 to 97% *ee* on aromatic and heteroaromatic ketones. However, only poor enantiomeric excess was obtained with aliphatic ketones.[132]



Scheme 35. Enantioselective reduction of ketone with RuCl(*p*-cymene)[(*R*,*R*)-TsDPEN]

Reduction catalyzed by palladium

Sodium hypophosphite in the presence of palladium on carbon and a stoichiometric amount of potassium carbonate reduced methyl benzoylformate and benzaldehyde to the corresponding alcohols **107** and **108** with good yields (Scheme 36).[17] However, acetophenone and aliphatic aldehydes were poorly converted into **109** and **110** after several days of reflux and aliphatic ketones were unreactive (**111** was not detected).



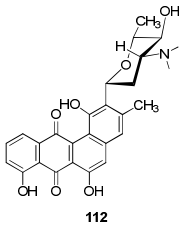
Scheme 36. Reduction of carbonyls by sodium hypophosphite catalyzed by Pd/C in the presence of a base

Reduction of quinone to hydroquinone was reported using phosphinic acid and Pd/C in different solvents (EtOH, THF, toluene).[133] In the absence of a catalyst, phosphinic acid or sodium hypophosphite reduced quinones very slowly in modest yields.

Reduction of aromatic ketone with sodium hypophosphite and palladium on carbon in the absence of base in a biphasic solvent (toluene / water), led to a mixture of the alcohol and the alkane product from competitive over-reduction.[134]

5.2. Reductive amination

The modified Leuckart-Wallach *N*-methylation was first described by Redmore in 1978 with phosphorous acid and aqueous formaldehyde. Dimethylation of benzylamine substrate was performed in 72% yield with two equivalents of formaldehyde. When only one equivalent of the carbonyl derivative was added a mixture of monomethylated and dimethylated products was observed.[135] These conditions were later used in the total synthesis of benzanthrin pseudoaglycone **112** which exhibits antimicrobial activity (Figure 1). The dimethylated intermediate was prepared from the corresponding amine in dioxane at 60°C with an excess of formaldehyde and NaH_2PO_3.[136]

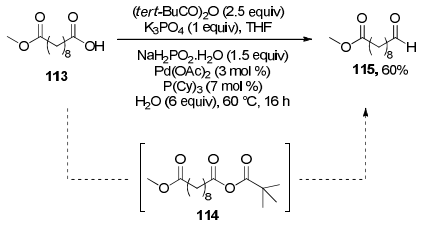


112

Figure 1. Structure of benzanthrin pseudoaglycone

5.3. Reduction of carboxylic acid derivatives

Gooßen and coworkers reported the reduction by sodium hypophosphite of carboxylic acids into aldehydes through the reduction of mixed anhydrides.[137] The reaction involves a catalyst generated *in situ* from palladium acetate (3 mol %) and tricyclohexylphosphine (7 mol %), pivalic anhydride, six equivalents of water and potassium phosphate as the base (Scheme 37). In this case, hypophosphorous acid, potassium and calcium hypophosphite are less efficient than sodium hypophosphite. This reaction can be applied to either aromatic or aliphatic carboxylic acids with good chemoselectivity towards ketones, esters, nitriles, methyl ethers, amides and conjugated double bonds.

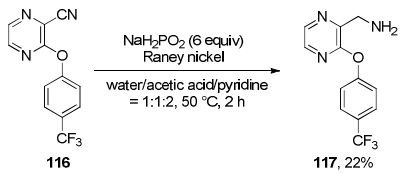


Scheme 37. Carboxylic acid reduction to aldehyde *via* a mixed anhydride

5.4. Reduction of nitriles

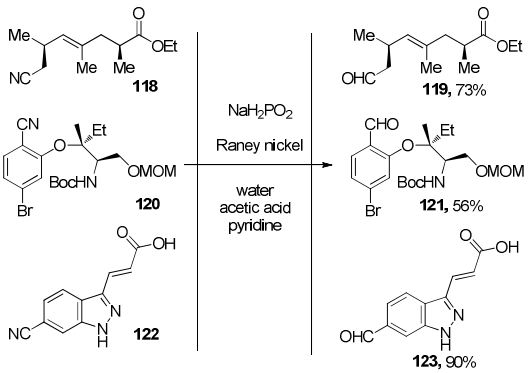
Among the unsaturated functions, nitrile can be reduced into either amine or aldehyde after the hydrolysis of the intermediate imine. The reduction in classical conditions under

hydrogenation or with hydrides mainly affords the amine. Selective access to the aldehyde is more difficult as the intermediate imine is more reactive than the nitrile, requiring working at very low temperature. However, the reaction with hypophosphites led mainly to the formation of aldehydes. The reduction into amine was mentioned as the result of the formation of an undesired product observed by Johnstone during the cleavage of aromatic ethers with sodium hypophosphite and palladium on charcoal.[19b] Another example using Raney Nickel of this application described the reduction of nitrile into amine with a low yield of 22% (Scheme 38).[138]



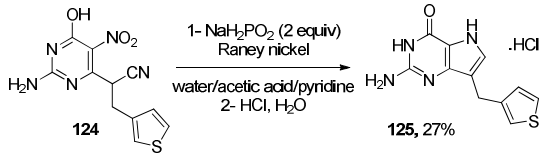
Scheme 38. Nitrile reduction into amine

By contrast, the utilization of hypophosphites was studied for the reduction of nitriles into aldehydes. In the sixties, Staskun was the first to report this transformation with hypophosphites and Raney nickel as catalyst in a water/acetic acid/pyridine solution (Scheme 39).[139] These conditions were thereafter widely applied to the reduction of aliphatic,[140] aromatic[141] and heteroaromatic[142] nitriles. As an example, Gosh used these conditions to reach compound **119**, intermediate in the total synthesis of (+)-Jasplakinolide, isolated from a marine sponge.[143] The chemoselectivity of this reaction is well represented by the reduction of compound **120** into **121** for which no dehalogenation was observed.[144] The presence of a protic function did not affect the reaction. Moreover, the reduction could be performed in the presence of a heteroaromatic ring for example the transformation of **122** to **123** with 90% yield.[145]

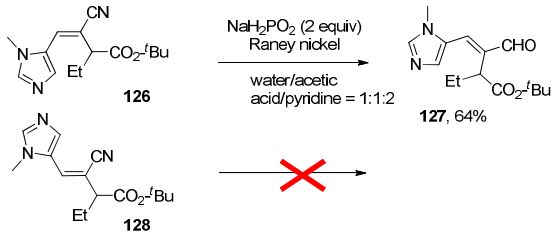


Scheme 39. Reduction of nitriles into aldehydes

The seminal work of Staskun[139] is one of the most used reduction methods with hypophosphite derivatives for the direct transformation of a nitrile into an aldehyde. The power of this method was illustrated by Staskun in a review gathering synthetic applications until 2008.[20] In general, aldehydes are obtained with moderate to good yields with an excellent chemoselectivity towards alkene, alcohol, ester, amide, amine, sulfoxide and carboxylic acid, with the exception of nitro-derivatives which are reduced under these conditions. This peculiar reactivity was exploited by Hicks to directly form a pyrrole fused ring *via* a reductive cyclization (Scheme 40).[146] However, this reduction is very sensitive to steric hindrance. In fact, in the study of the synthesis of (+)-Pilocarpine, Rapoport reported the lack of reactivity of the (*Z*)-*tert*-butyl-3-cyano-2-ethyl-4-(1-methyl-5-imidazolyl)-3-butenoate **128** in comparison with the *E* isomer **126** which is efficiently reduced into compound **127** (Scheme 41).[147]



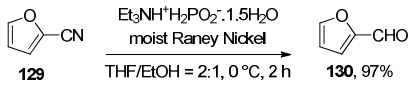
Scheme 40. Tandem reduction



Scheme 41. Steric limitations to the reduction of nitrile into aldehydes

The final treatment of the above reduction could be modified in order to avoid the formation of by-products due to the high reactivity of the aldehyde. So in 1973, Moffatt developed the use of *N,N'*-diphenylethylenediamine specifically with sugar chemistry to avoid the formation of furan derivatives.[148] In the same way, when tosylhydrazine was added in the reaction mixture the corresponding tosylhydrazone was isolated.[149] Finally, Hoye described the reductive amination of a nitrile with a chiral amine by performing the reaction under hydrogen.[150]

Another source of hypophosphite, $NEt_3H^+.H_2PO_2^-$, was employed by Khai and Arcelli in 1989,[129a] displaying higher solubility in classical organic solvents (reactions performed in THF/EtOH) contrary to sodium hypophosphite (Scheme 42).



Scheme 42. Reduction of nitrile to aldehyde with $Et_3NH^+H_2PO_2^-$

Under the above conditions, nitro-derivatives and oximes were reduced but esters, ketones and aldehydes were not.

6. Deoxygenation

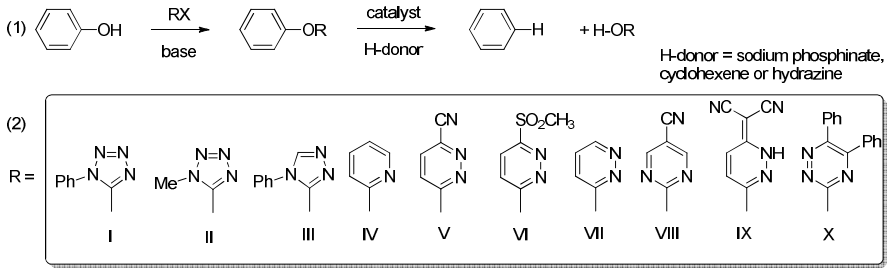
6.1. Deoxygenation of carbon compounds

Deoxygenation of an organic substrate required hard conditions as formely described by Clemmensen and Wolff-Kishner. It is also a very important reaction for the valorization of bio-sourced starting materials. In fact, cellulose and hemicellulose, sugar, starch, lignin and organic tannins are poly-oxygenated substrates and require deoxygenation in order to obtain usable chemical building blocks. Deoxygenation appears to be a key reaction if fossil fuel starting material is to be replaced by renewable material.

6.1.1. Deoxygenation of phenols into arenes

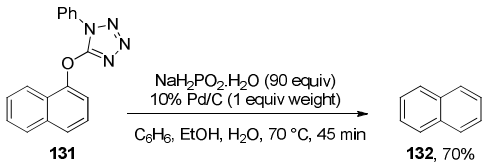
Deoxygenation of phenols can be carried out in a stepwise process consisting of the synthesis of phenol ether with specific heterocycles or strong electron-withdrawing groups by classical alkylation, followed by the hydrogenolysis of the ether by a reducing agent (Scheme 43, (1)). For example, phenol ethers were completely converted into the corresponding arenes in the presence of a hydrogen donor (sodium phosphinite, cyclohexene or hydrazine) and a mass equivalent of 10% Pd/C catalyst. The other screened metals (Ru, Rh, Pt, Re) were completely ineffective. The reduction was strongly dependent on the nature of the R substituent of the ether. The best results were observed with a strong electron-withdrawing 2-phenyltetrazolyl substituent **I** (Scheme 43, (2)).[151]

A complete study was developed by the same group two years later. It focused specifically on the nature of 10 different electron-withdrawing substituents in order to more efficiently distribute the electronic density of the lone pair on the oxygen far from the phenol group. As possible substituents I, II, III and X displayed the same kinetics for the reduction, thus confirming the efficiency of the 2-phenyltetrazolyl group, but also opened the way not only to tetrazole scaffolds but also to triazole and triazinones (Scheme 43).



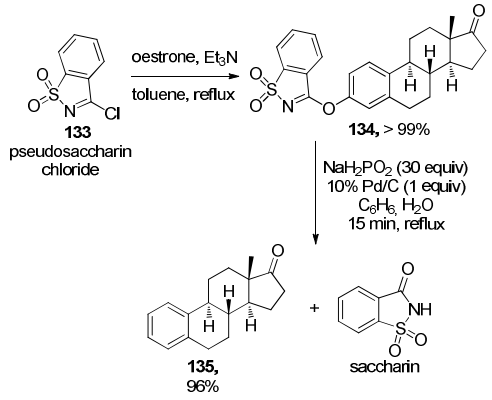
Scheme 43. Evaluation of different substituents on the reductive cleavage of ethers

As an example of the previously described general scheme, the 2-phenyltetrazolyl ether of 1-naphthol was stirred in a mixture of benzene / ethanol / water (7 / 3 / 2) in the presence of a large amount of 10% Pd/C and sodium hypophosphite at 70 °C. In 45 min, naphthalene **137** was obtained with 70% yield (Scheme 44).



Scheme 44. Cleavage of ether to naphthalene

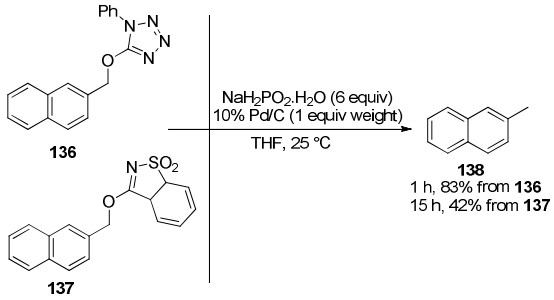
As the cost of the 5-phenyltetrazolyl group is a serious limitation to further industrialization, Johnstone investigated the synthesis of aryl ether by reaction with readily-available pseudosaccharin chloride **133** (obtained by chlorination of saccharin), and applied the hydrogenolysis methodology leading to oestratrienone **135** (Scheme 45).[152]



Scheme 45. Oestratrienone synthesis

More recently, the scope of the reaction was extended to 2-naphthalenemethanols, converted into their corresponding tetrazolyl or benzisothiazolyl derivatives, which were subjected to hydrogenolysis (Scheme 46). With tetrazolyl substituent (**136**), the 2-

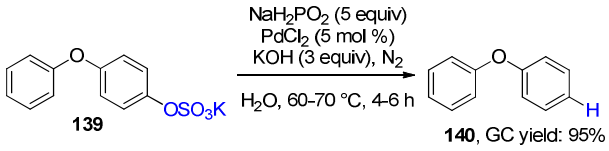
methylnaphthalene **138** could be obtained in 1 h at 25°C with a very good yield of 83%, whereas the benzisothiazolyl substituent (**137**) behaved differently since a longer reaction time was required leading to only 42% of the same isolated compound.[153]



Scheme 46. Comparison of reactivity of tetrazolyl and benzisothiazolyl derivatives

Mechanistic studies of arene formation by heterogeneous reductive cleavage of aryloxytetrazolyl ethers have been realized through kinetic experiments highlighting the rapid consumption of the benzyl ether followed by a linear formation of the corresponding arene (the nature of the substituent on the aromatic ring has no consequence on the rate of reaction). As expected from previous observations, the complexation of the tetrazole part of the molecule to the catalyst surface is a determining step in the mechanism. Other parameters, such as pH and steric hindrance of the substrate can also have an influence on the kinetics.[154] The importance of biphasic solvents, in comparison to single phase solvents, was emphasized by controlling access of the substrate and reducing reagent to the catalyst.[155]

The reductive cleavage of the C-O bond in monoarylsulfate was described by Beletskaya with sodium hypophosphite (5 equiv) in basic medium (KOH, 3 equiv) catalyzed by $PdCl_2$ in water. After 6 h, complete conversion of **139** was observed and 95% GC yield was obtained (Scheme 47).[156] Although both the yield and ecological impact of this reaction appear much greater than the previous methods, the scope and limitations of the sulfate reductive cleavage have not, to our knowledge, been investigated.



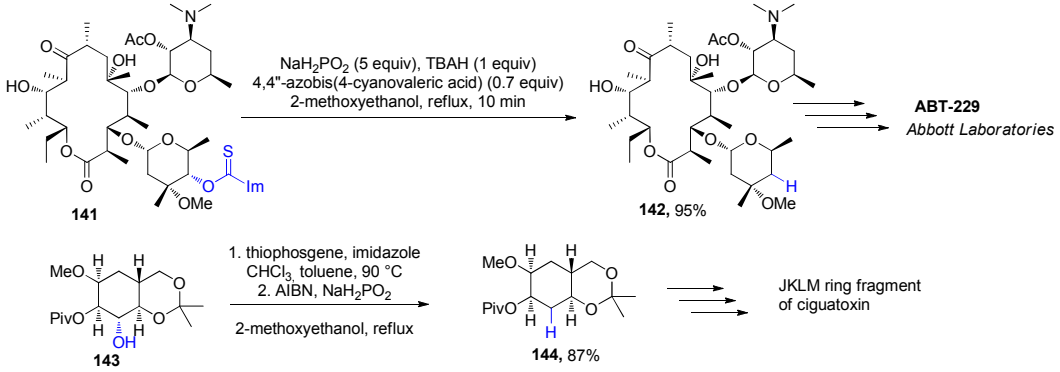
Scheme 47. Reductive cleavage of monoaryl sulfate

6.1.2. Radical deoxygenation

Radical deoxygenation usually requires activation of the hydroxyl function such as thiocarbonyl followed by generation of an alkyl radical and a reductive step.[157] One of the

most known radical deoxygenations is the Barton-McCombie reaction where an *O*-alkylthiocarbonyl derivative is often associated with Bu_3SnH as the reductant.[158] Due to regulatory requirements and the toxicity of tin, other alternatives have been developed including the use of silanes, phosphites, hypophosphorous acid and its organic salts.

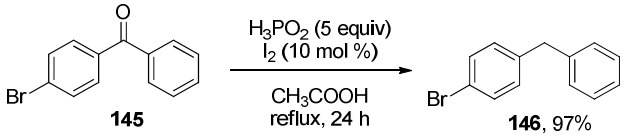
In 1992, Barton and coworkers reported the deoxygenation of thionocarbonate and xanthate derivatives by hypophosphorous acid / tertiary amine (triethylamine, tri-*n*-butylamine, DABCO, *N*-ethylpiperidine) in the presence of AIBN in refluxing dioxane.[77] Anhydrous or wet conditions can be used with ether solvents (dioxane,[77] 1,2-dimethoxyethane[78]) and alcohols. Primary, secondary and tertiary alcohols were reduced in high yields to alkanes as well as bromides, iodides and primary amines *via* isonitriles. Alkenes were also reactive under these conditions.[83,84] An organic base was used to protect acid-sensitive functions. Acetal, sugar,[77] fluoride,[78] nucleoside derivatives[78] and *tert*-butyldimethylsilyl ether[159] and ester[159] were tolerated. For example, a kilogram-scale radical deoxygenation was optimized leading to the synthetic precursor **142** of ABT-229, an erythromycin derivative identified as a potent motilin receptor agonist[160] after a complete study investigating the effect of solvents, phase-transfer agents, inorganic hyposphosphite salts and radical initiators (Scheme 48). Other radical initiators are also efficient as described in the deoxygenation step involved in the synthesis of the JKLM ring fragment of ciguatoxin.[161] A similar experimental procedure was reported for the synthesis of triciferol in 10 steps for vitamin D_2.[159] Later, the same research group focused on the extension of the reaction in water[162] and they observed competition with *S*-methyldithiocarbonate hydrolysis. The addition of a phase transfer catalyst, cetyltrimethylammonium bromide (CTAB), was necessary for the solubility, as well as water-soluble radical initiator 4,4'-azobis(4-cyanovaleric acid) (ABCVA).



Scheme 48. Radical deoxygenation

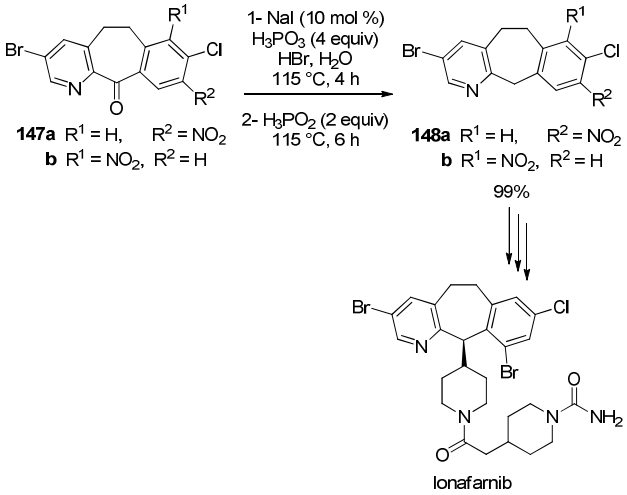
6.1.3. Reduction of carbonyl derivatives to methylenes

Phosphinic acid with a catalytic amount of I_2 in acetic acid reduced diarylketones to methylenes in good yields.[163] One of the main advantages, in comparison to classical methods, is the tolerance towards aromatic halides: *p*-bromodiarylketone **145** was reduced to the corresponding methylene **146** with 97% yield (Scheme 49). Phenols were also well tolerated while double bonds were partially reduced.[118] Acetophenone was reduced with only 11% yield to ethylbenzene and 89% of the starting material was recovered.



Scheme 49. Reduction of ketone to methylene with H_3PO_2 / I_2

Slightly modified conditions using NaI as the iodine source in HBr / water solvent have been used in the key step of the synthesis of a potential anticancer agent lonafarnib (Scheme 50).[164] The reaction performed on the mixture of regioisomers **147a** and **147b** led to the reduction of the aromatic nitro- and diaryl-ketone selectively without chloride or bromide hydrogenolysis or iodine exchange.



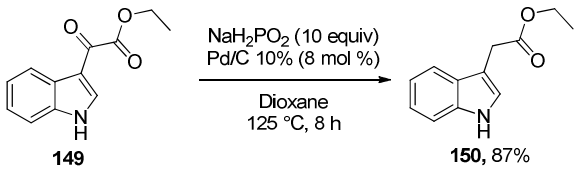
Scheme 50. Key reduction step using H_3PO_3 / H_3PO_2 / NaI in lonafarnib synthesis

Benzhydrols are also reduced by *in situ* generated HI from different sources. With the mixture of I_2 / hypophosphorous acid, benzhydrols are reduced at lower temperature than diarylketones.[165] Other sources of iodine have been used with hypophosphorous acid such as HI[166] and NaI.[167] This method has also been used for the aromatization of highly conjugated benzhydrols in numerous publications[168] and patents.[169]

The reduction by hypophosphite as a hydride donor, reductive agent alone without addition of radical initiator or metal catalyst, has been pursued since at least 1910.[170] Different functions have been tested. However, only the triphenylcarbinol was reduced in triphenylmethane[171] with a good yield of 93% and recently exemplified.[172]

Currently, sodium hypophosphite has been used for the reduction of graphene oxide containing oxygenated functions such as carboxylic acids, epoxides, alcohols and ethers to graphene.[173] The reaction was carried out either in basic (pH = 11) or acidic conditions using HCl or H_2SO_4 in the presence of a catalytic amount of SO_2.

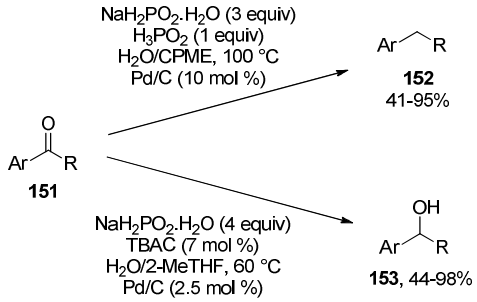
With palladium on carbon, deoxygenation was favored on the glyoxylic esters of indoles and pyrroles to the corresponding acetates (Scheme 51),[174] with better yields in dioxane than in 2-methyl-1-propanol The reaction suffers from strong limitation to activated ketoesters and ketoamides bearing an electron-rich aromatic. Otherwise, the ketone is selectively reduced to the corresponding alcohol, the major side product.



Scheme 51. Reduction of glyoxylic ester of indole into the corresponding acetate

These conditions were applied to the synthesis of potentially biologically-active molecules bearing an indole or/and pyrrole ring.[175] Polar functions such as phenol and amide were tolerated while benzyl protecting groups may be cleaved.[88,89]

General conditions to selectively reduce aromatic ketones to either alcohols or alkanes were developed using hypophosphites with palladium on carbon (Scheme 52).[176] Compared to the previous conditions described, the scope was broadened allowing the reduction of aromatic ketones. Aliphatic ketones remained unreactive. The conditions tolerated the presence of ester, ether and CF_3. In addition, protic functions such as OH, NH_2 and CO_2H did not inhibit the reaction. Other functions such as alkene, halide, and aromatic nitrile and nitro groups were partially or completely reduced.



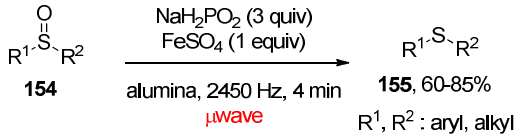
Scheme 52. Commutative reduction of ketones either to alkanes or alcohols

The key parameters for the selectivity towards alkanes are the use of acidic conditions, hydrophobic solvent, high palladium loading and temperature. Selectivity to the alcohol was reached using a phase transfer catalyst (TBAC, 7 mol %), a palladium loading of 2.5 mol %.

6.2. Deoxygenation of sulfur compounds

Dimethylsulfoxide was reduced into dimethylsulfide with 98.5% yield by hypophosphorous acid catalyzed by diselenide.[90]

In 2005, Meshram reported the reduction of sulfoxides into sulfides with sodium hypophosphite in the presence of iron (II) sulfate supported on aluminum oxide under microwave (Scheme 53).[177] Allylic or conjugated double bonds, nitro groups and chlorides were not modified under these conditions.



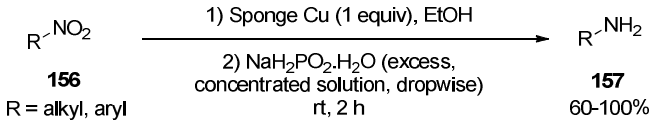
Scheme 53. Reduction of sulfoxides to thioethers under microwave irradation

6.3. Deoxygenation of nitrogen compounds

6.3.1. Reduction of nitro derivatives

6.3.1.1. Amine synthesis

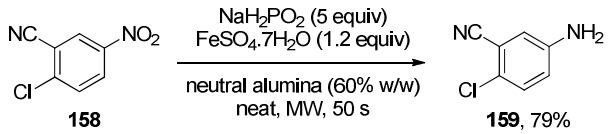
To the best of our knowledge, Mailhe and Murat[178] were the first to report the reduction of the nitro group in the presence of sodium hypophosphite and copper (Scheme 54). The authors reported the formation of copper in sponge form, also called Wurtz hydride, obtained *in situ* by the reaction between sodium hypophosphite and copper sulfate in ethanol. These conditions allowed the preparation of amines and anilines. The halides were not reduced and phenol did not impair the reaction.



Scheme 54. Reduction of nitro by copper and sodium hypophosphite

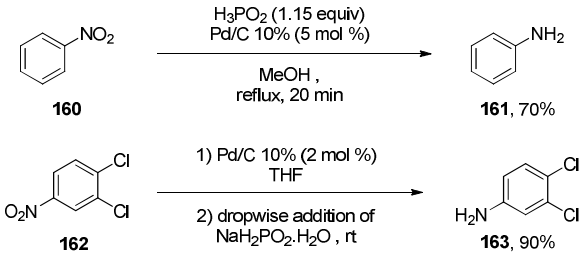
A few publications report the reduction of nitro aromatic derivatives into anilines using Raney nickel as catalyst and either sodium hypophosphite or triethylammonium phosphinate as reductant. For example, 3-nitro-4-diethylaminocoumarin was efficiently reduced into 3-amino-4-diethylaminocoumarin [179] by sodium hypophosphite in the presence of nickel. These conditions were not developed because of the presence of a difficult-to-separate impurity of unidentified structure.

A recent study by Meshram in 2000[180] reported the solvent-free reduction of aromatic nitro derivatives in the presence of sodium hypophosphite and more than a stoichiometric quantity of iron sulfate under microwave irradiation (Scheme 55). The main advantage of these conditions is the chemoselectivity: halide, nitrile, ketone, amide, carboxylic acid, aniline and phenol are well tolerated. For example, **158** is reduced selectively into **159** without reduction of the nitrile and chloride function in 79% yield. However, even if the price and toxicity of iron sulfate are low, its stoichiometric use makes it unacceptable for an industrial purpose.



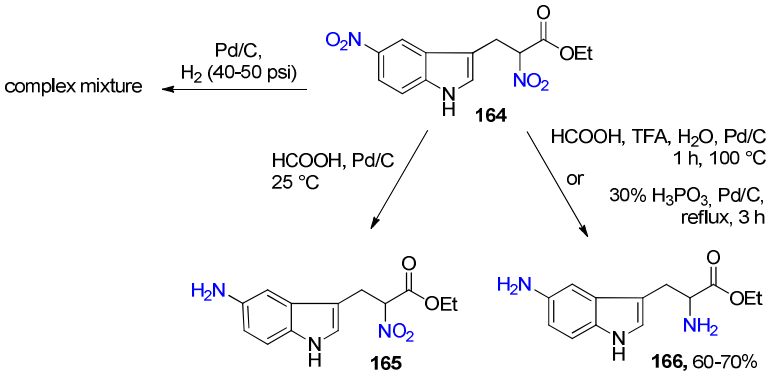
Scheme 55. Microwaves promoted reduction of substituted nitrobenzene

Until now, the metal catalyst the most used to reduce nitro-derivatives into amines was palladium, which was more efficient than platinum or rhodium with hypophosphorous acid or phosphorous acid.[181] Johnstone reported the use of palladium on charcoal with hypophosphite derivatives.[181] Hypophosphorous acid in methanol or sodium hypophosphite in THF reduced the nitro compounds. The chemoselectivity was good and the presence of acidic conditions did not affect the conversion (side product rising from de-halogenation was not observed) (Scheme 56).



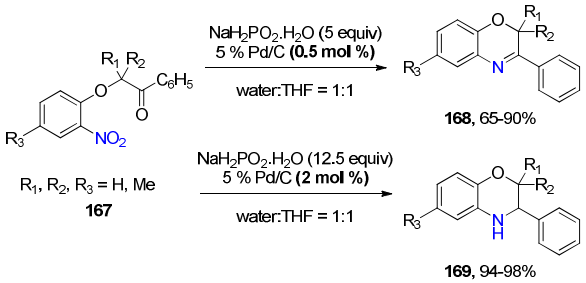
Scheme 56. Nitro aromatic reduction catalyzed by Pd/C

The interest of this method was illustrated through the reduction of dinitrotryptophan **164** (Scheme 57).[182] Classical hydrogenation conditions (Pd/C, 40-50 psi) afforded a complex mixture according to the authors. When the reduction was carried out with formic acid and Pd/C at room temperature only the product of reduction of the nitro on the indole ring **165** was observed. When the reaction was pushed to 100 °C, a complex mixture was obtained. The authors hypothesized that formic acid was not acidic enough to protonate the formed amine which would consequently react with the ester. Indeed, when the reaction was run in TFA, formic acid and water mixture, amine **166** resulting from the reduction of both nitro was formed cleanly in 60-70% yields. Comparable results were observed when the reduction of compound **164** was performed in phosphorous acid with Pd/C.



Scheme 57. Reduction of aromatic and aliphatic nitro catalyzed by Pd/C

The Johnstone conditions[181] were applied to the reduction of different target molecules.[183] Under the developed conditions, the nitro reduction allowed subsequent cyclisation with ketone in **167** affording either benzoxazine **168** or dihydrobenzoxazine **169** depending on the loading of the palladium catalyst and quantity of NaH_2PO_2 (Scheme 58).[184]

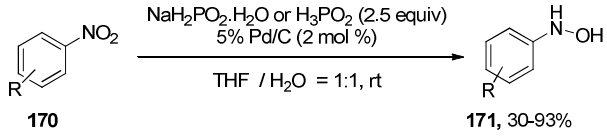


Scheme 58. Nitro aromatic reduction catalyzed by Pd/C

Access to non-natural tryptamines was recently reported through the reduction of aliphatic nitro groups to amines in the presence of a biphasic solvent system (2-MeTHF/H_2O) with a mixture of sodium hypophosphite / phosphinic acid / palladium on carbon.[185] These conditions were generally applied on aliphatic and aromatic nitro compounds.

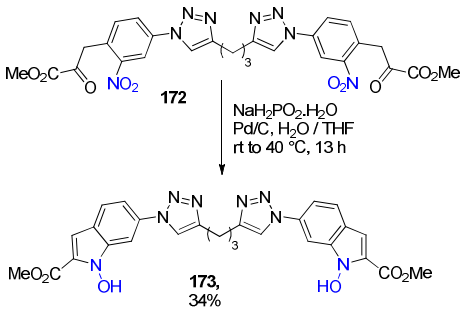
6.3.1.2. Hydroxylamine synthesis and Bamberger rearrangement

In 1978, Johnstone reported the reduction of aromatic nitro **170** to hydroxylamine **171** with phosphinic acid or its sodium salt with a palladium on charcoal or rhodium catalyst in a two-phase solvent system, THF/water (Scheme 59).[186]



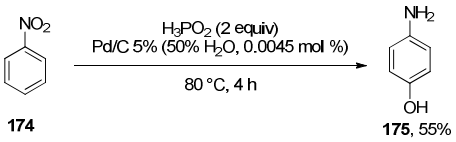
Scheme 59. Reduction of aromatic nitro to hydroxylamine

These conditions were selective and led to the formation of hydroxylamine[187] except when the aromatic core is substituted by the following groups: 4-isopropyl-3-methyl-, 4-methyl-, 4-methoxy-, or 2,5-dimethoxy-. With these strong electron-donating groups, the corresponding anilines were obtained. This method has found several applications in syntheses.[188] For example, partial reduction of a nitro group on bis *N*-substituted triazoles **172**, with concomitant cyclization afforded the bis(*N*-hydroxyindole) **173** in a modest 34% yield (Scheme 60).[189] The smooth conditions with sodium hypophosphite prevented the over-reduction of the nitro group, which often generated difficulty during the purification step due to large amounts of *N*-H indole side products.[190]



Scheme 60. Reduction of nitro to hydroxylamine followed by cyclisation

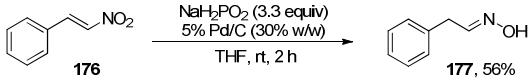
The possibility to selectively prepare hydroxylamine was exploited by Sasson in 1994 with the Pd/C catalyzed Bamberger rearrangement of nitrobenzene **174** to *para*-aminophenol **175**.[191] Phosphinic acid acts both as hydrogen donor and strong acid (Scheme 61). Aniline was observed as a by-product as well as bis-(4-amino-phenyl) ether 2% and *ortho*-aminophenol 1%.



Scheme 61. Bamberger rearrangement

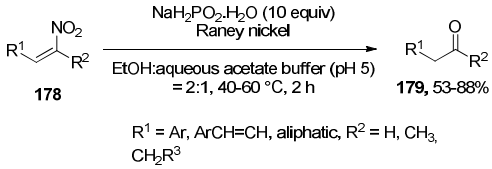
6.3.1.3. Reduction of nitroalkenes

In 1986, Kabalka described the reduction of unsaturated nitro compounds to oximes in the presence of palladium on charcoal with sodium hypophosphite (Scheme 62).[192] Partial de-hydrobromination was observed under these conditions. This transformation was later employed in a multistep synthesis to prepare dimethylhistamine in 1989 by Davey.[193] The corresponding ketoxime was obtained in 83% yield.



Scheme 62. Reduction of unsaturated nitro into oxime

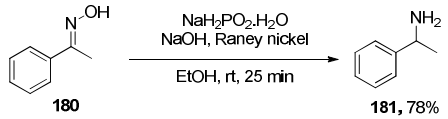
When the palladium is substituted by Raney nickel, a ketone is formed (Scheme 63).[194] The intermediate oxime is transformed in the corresponding carbonyl derivative, also referred to as the Nef reaction.[195]



Scheme 63. Reduction of unsaturated nitro derivatives into carbonyl compounds

6.3.2. Reduction of oximes

In 1966, Staskun reported the reduction of oximes to amines using sodium hypophosphite monohydrate in the presence of Raney nickel and sodium hydroxide in ethanol (Scheme 64).[196]

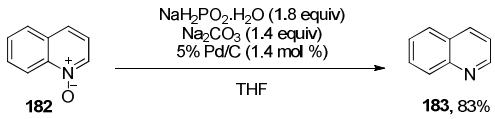


Scheme 64. Oxime reduction

These conditions allowed the formation of the corresponding amines with moderate to good yields (52-89%) even in the presence of bromo substituent. In this paper, the author also reported the de-oximation to the carbonyl compound when the oxime was heated at reflux in alkaline solution with Raney nickel.

6.3.3. Reduction of N-oxides

Boyer reported the reduction of aromatic and aliphatic *N*-oxides by sodium hypophosphite with Pd/C under basic conditions (Scheme 65).[17] Quinoline and morpholine *N*-oxides were efficiently reduced to amines in 83 and 90% yield, respectively. This method, compared to the deoxygenation of *N*-oxides with PPh_3, avoids the formation of triphenylphosphine oxide which is difficult to remove from the crude mixture. These conditions also allowed the reduction of alkylazide to amine.



Scheme 65. Reduction of *N*-oxides

N-Oxides were selectively reduced in acidic conditions by Kaczmarek, in the presence of ketones, esters, nitriles or bromides in high yields (up to 71%).[197] The reaction was carried out in acetic acid without additional water than the one present in sodium hypophosphite salt.

7. Conclusion

Reductive properties of hypophosphite derivatives have been known for more than a century but the number of publications dedicated to their application in organic synthesis is relatively small (< 300). Its major application is still limited to the reduction of metal salts, for example for nickel or chromium plating. In our opinion, this short review illustrates the great potential of hypophosphite derivatives. The advantages and disadvantages can be classified as follows in Table 4.

Table 4. Advantages and disadvantages of hypophosphite derivatives

Advantages	Disadvantages
Stable, not dangerous	Low E factor
Low toxicity of the reagent	One hydrogen per 106 g/mol (for $NaH_2PO_2.H_2O$)
Low toxicity of the by-product	
Available on a large scale at a relatively low price	Two hydrides with two different reactivities; most of the time only one is useful
Usable with phase transfer catalysts	Mostly insoluble in organic solvents
Able to reduce metal salts	Little data available on the mechanism and side reactions are often not known
Can be used in both acidic and basic conditions	Difficult to control the pH during the reaction

It has already been shown that such non-hazardous reducing agents are, in various conditions, able to dehalogenate, deoxygenate, and desulfurize with good yields, and to selectively reduce CC, CN and CO multiple bonds as well as nitro derivatives. In only a few cases, the original properties of such reagents allow development on an industrial scale.

Some asymmetric reductions were performed with success using known organometallic complexes. One of the reasons to be optimistic about the development of these reagents lies in the large variety of conditions and catalysts which can be used with hypophosphites. This hydride donor could also be used with or without catalyst. Reactions could be performed either *via* radical, ionic or transition metal catalyzed mechanism. Reduction using hypophosphites could be carried out either in neutral condition or in the presence of strong

acids or with strong bases. It is possible to use polar or non-polar organic solvents or water as well.

Finally, the selectivity can be modified by using the appropriate heterogeneous or homogeneous catalyst. If only a few transition metals have been tested until now, the potential seems very large. This is obviously of great importance if we consider the recent numerous applications found with silicon hydrides such as PMHS and TMDS using a large panel of different catalysts. The future is even more favorable when considering the relatively low cost of this type of reagent.

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