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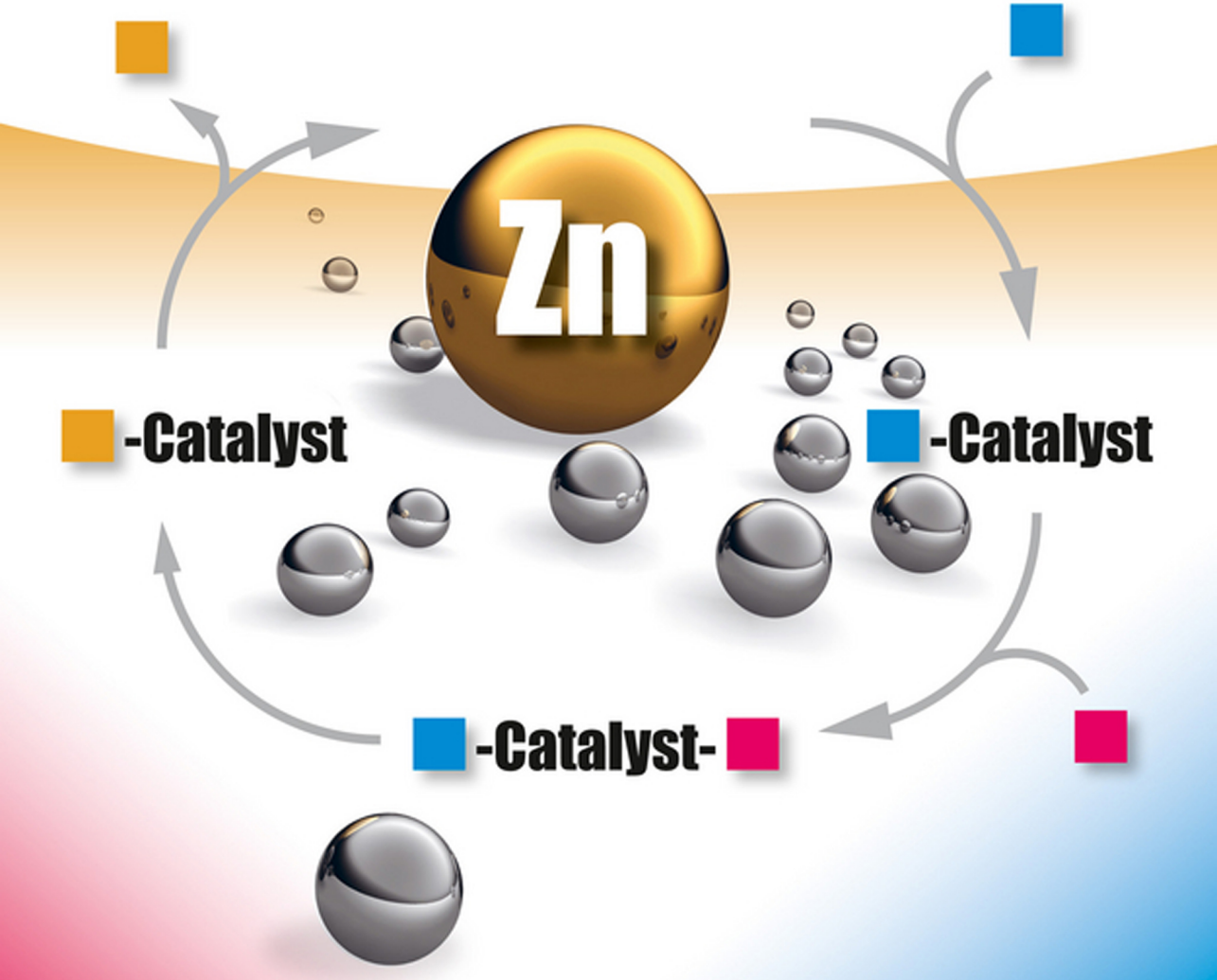
Zinc Catalysis

Applications in Organic Synthesis



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Zinc Catalysis

Applications in Organic Synthesis

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1
Introduction: Zinc Catalysts for Organic Transformations

Stephan Enthaler and Xiao-Feng Wu

The development of methods for sustainable, efficient, and selective synthesis of chemicals with higher values is one of the fundamental research objectives in modern chemistry. Especially, the reduction of waste and the reduction of energy demands are clearly the challenges for the future to use the steadily decreasing resources in a more efficient manner to create a sustainable society [1]. Among all of the chemical methodologies considered thus far, heterogeneous, homogeneous, and biocatalyses offer an efficient approach to achieve this goal, which is underlined by the high impact of catalysis on industrial processes including bulk, fine agrochemicals and pharmaceuticals (~90%) [2]. In particular, metal catalysts are among the most successful examples of practical catalysis. Nevertheless, the use of most of the metals (e.g., Pd, Rh, Ru, Ir) involved difficulties due to their low abundance, high price, or toxicity (Figures 1.1 and 1.2). For example, the current prices are 1460 € per mole of palladium, 2052 € per mole of iridium, 2484 € per mole of rhodium, and 150 € per mole of ruthenium [3]. Moreover, the current trend to establish a "greener" chemistry has initiated the search for more environmentally benign and sustainable alternatives [4]. Hence, current research is focusing, on the one hand, on replacement with cheaper and low toxic metals and, on the other, on the discovery of new protocols with such metals. In this regard, the application of zinc can be of great interest because of its general abundance (twenty-fourth (0.0076%) in the earth crust) and high concentration in ores [5]. For instance, one major mined source for zinc is the mineral *Sphalerite*, which contains significant amounts of zinc sulfide (~60% zinc concentration) and variable amounts of iron. In contrast to other metals, zinc is easily extracted from the minerals in high purity. Moreover, the zinc-containing minerals *Smithsonite* (zinc carbonate), *Hemimorphite* (zinc silicate), and *Wurtzite* (zinc sulfide) are of importance [6]. Currently, the identified world zinc resources are estimated at 1.8 billion metric tonnes, and several million tons are fixed in man-made materials, from which zinc can be potentially recovered [7]. On the basis of the abundance and accessibility of zinc, the current price for 1 mol is only 0.12€. An additional attractive aspect is the biological relevance of zinc as an essential trace element with a daily dose for humans of 12 – 15 mg, for instance, to keep several enzymes working [8]. Based on that, a lower toxicity compared to other metals has been found,

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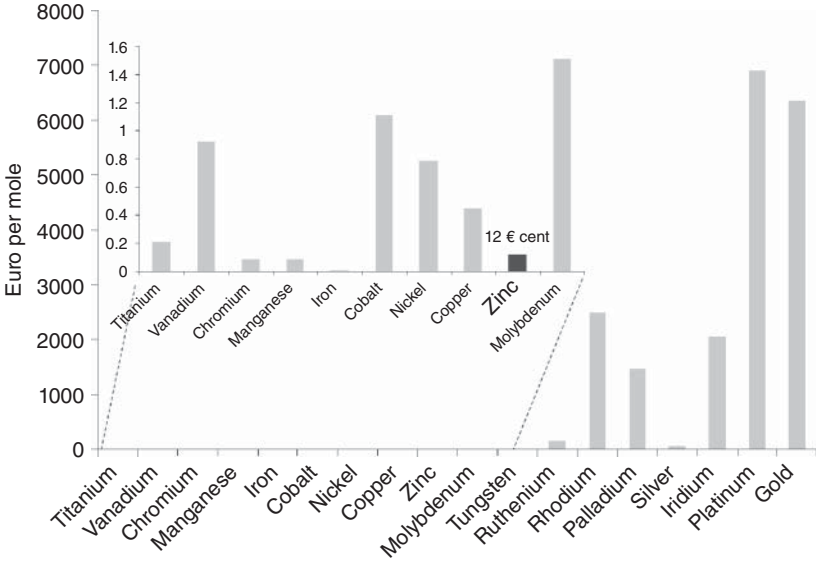

Figure 1.1 Comparison of metal costs [3].

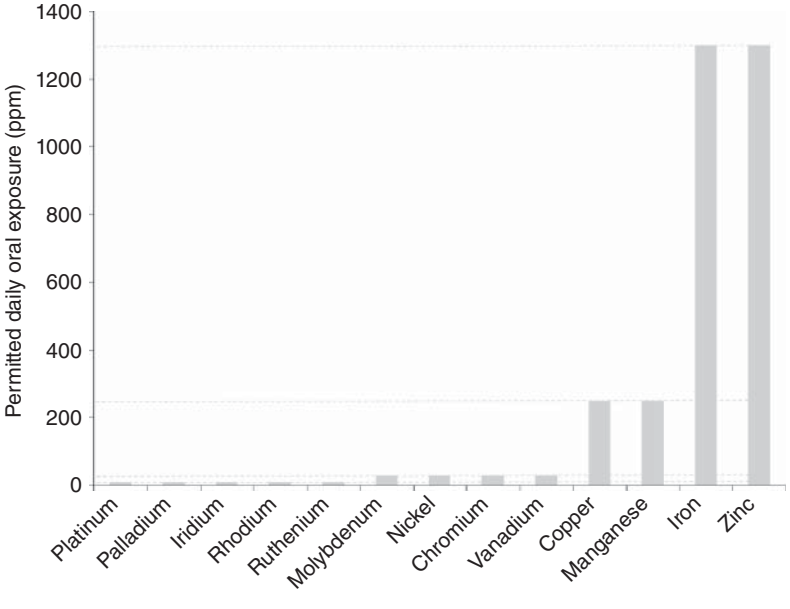

Figure 1.2 Concentration limits for metal catalysts and metal reagents (European Medicines Agency).

which makes it probably attractive for application in pharmaceutical synthesis (Figure 1.2, permitted daily oral exposure: 1300 ppm). Because of these advantages zinc has found numerous applications until now since the first documentation of brass, an alloy made of copper and zinc, dating back to the time of Aristotle (384–322 BC) and Cicero (106–43 BC). However, several centuries passed until the discovery of zinc as an independent metal [9]. The name "zincum" was possibly first written down by Paracelsus (1493–1541) in the sixteenth century, potentially derived from the German word "zinke," which could mean "spike," "jagged," or "tin-like" [10]. Subsequent development during the centuries resulted in its use for today's manifold purposes in galvanizing, alloys, brass, bronze, and others [11]. In contrast, the first attempts of organic chemistry to make use of zinc date back to 1849 when Edward Frankland (1825–1899) synthesized the first organometallic compound diethyl zinc. Since then, numerous stoichiometric applications of zinc have been accounted, for example, the Reformatskii reaction, Fukuyama reaction, and Negishi reaction, which are all breakthrough chemical transformations in organic chemistry. Surprisingly, in comparison to other metals, the application of zinc catalysis in organic chemistry was underdeveloped. Often, this situation is explained by the "transition" position of zinc in the periodic table, between transition metals and main group elements [12]. Based on the [Ar] $3d^{10}$ $4s^2$ electron configuration with filled d-shells the chemistry is different from that of the transition metals and is more related to main group chemistry. Because of this, zinc does not have a distinct redox chemistry compared to other transition metals; mainly Zn(0) and Zn(II) are known, while recently complexes with Zn(I) have been established [13]. Often, the question arose if "zinc is a boring element?" due to the straightforward and "predictable" chemistry [14]. Nevertheless, more recently the situation has changed, and the catalytic potential of zinc has been proved in several applications [15]. This book will therefore focus on a selection of recent achievements applying zinc in organic transformations including major accomplishment in the field of zinc-catalyzed reductions, oxidations, C–C, C–N, C–O bond formations, polymerizations, and applications of zinc in stoichiometric transformations such as cross coupling and the embedment of zinc in total synthesis.

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2
Zinc-Catalyzed Reductions of Unsaturated Compounds

Yuehui Li, Kathrin Junge, and Matthias Beller

2.1
Introduction

Catalytic reductions represent an important class of synthetic methodologies and have attracted the long-lasting interest of academic and industrial researchers in the last few decades [1]. In general, saturated compounds are formed in a straightforward manner by the addition of hydrogen to the unsaturated substrates. Specifically, alcohols, alkanes, and amines are produced via reduction of C=C, C=O, and C=N bonds. With the aid of catalysts, high efficiency and selectivity can be obtained in the presence of a suitable reductant. In this regard, the activation of the reducing reagent and the control of chemo-, regio-, and stereoselectivity by appropriate transition metal catalysts are essential. To date, most reduction methodologies were developed using precious metals such as Ru, Rh, Ir, Pt, and Pd. Owing to economic and ecologic constraints, nonprecious metals such as Ni, Cu, Fe, and Zn come more into the limelight of catalysis. Zinc, as an essential mineral and constituent of enzymes, is of fundamental biochemical importance for plants, animals, and humans. In fact, the redox properties of Zn are known for a long time, although research on Zn-catalyzed reductions has been scarce [2]. In this chapter, we summarize the use of Zn-based homogeneous catalysts in hydrogenations, transfer hydrogenations, and hydrosilylation reactions of C=O and C=N bonds. In addition, a few examples of related reductions of olefins and sulfoxides are highlighted.

2.2
Hydrosilylation of Unsaturated Compounds

Already in the 1960s and 1970s efforts were undertaken to utilize cheap and benign zinc salts (Zn, 0.07 € mol^{-1}) for hydrosilylation of unsaturated compounds [1, 2]. However, more recently, this topic has been rediscovered and significant improvements regarding more active and highly selective catalysts for the reduction of various functionalized substrates using silanes were reported (Scheme 2.1).

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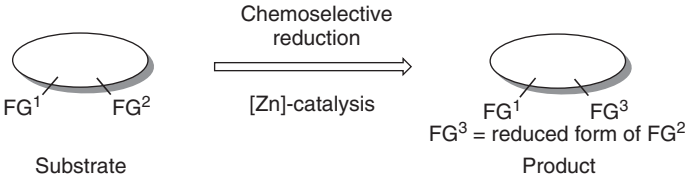
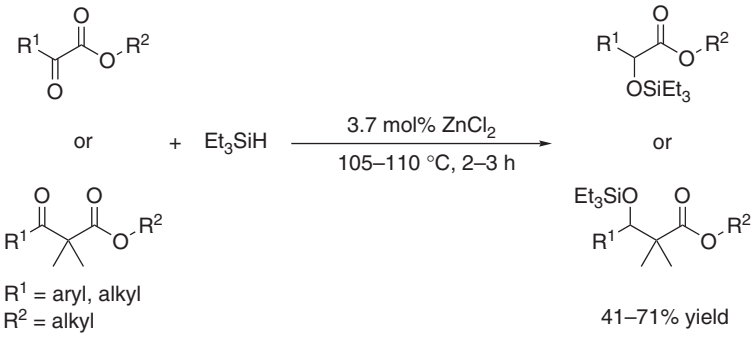


Scheme 2.1 Catalytic efficient hydrosilylation of unsaturated compounds (FG = functional group).

2.2.1

Nonchiral Hydrosilylation of Carbonyl Bonds

As early as in the 1960s, Calas *et al.* [3] investigated the use of $ZnCl_2$ to promote the reduction of acetals (to ethers), nitriles (to *N*-silyl imines or amines), amides or imidates (to amines), and lactones (to silyl ethers) with trialkylsilanes at elevated temperatures. It was proposed that typical Lewis-acid-catalyzed hydrosilylations took place. In 1978, Lapkin *et al.* reported the chemoselective hydrosilylation of α- and β-ketoesters. In the presence of 3.7 mol% of $ZnCl_2$, moderate to good yields were obtained using 1 equiv of triethylsilane (Scheme 2.2) [4].

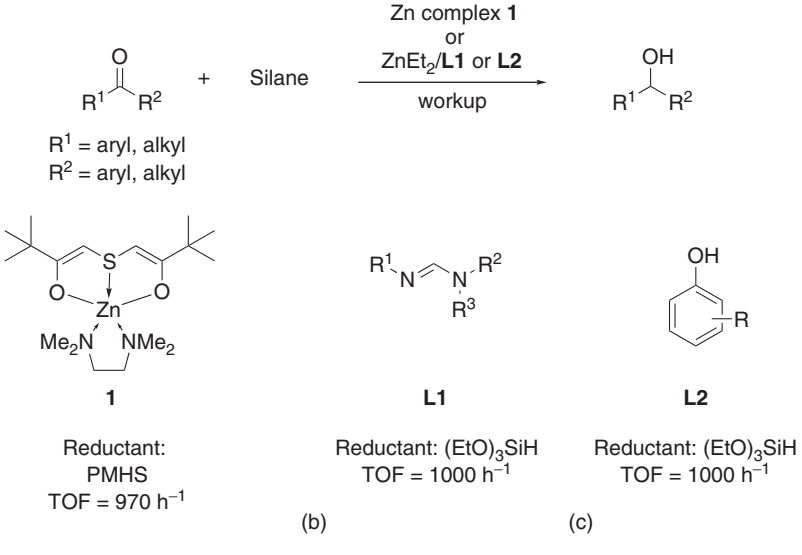


Scheme 2.2 Zinc-catalyzed hydrosilylation of α- and β-ketoesters.

Important works on zinc-catalyzed hydrosilylation of ketones were reported in 1987 by the group of Lukevics and by Mimoun in the late 1990s [5, 6]. Both systems focused on asymmetric reductions and the details are discussed in Section 2.2.2. Based on this initial work in the field of asymmetric hydrosilylations, several research groups became interested in the investigation of the reaction mechanism and the development of new ligands for more efficient zinc catalysis. For example, in 1999 Mimoun reported the $Zn(2\text{-ethylhexanoate})_2$-catalyzed hydrosilylation of aldehydes, ketones, epoxides, and esters using cheap PMHS (polymethylhydrosiloxane) as the reductant in the presence of a catalytic amount of $NaBH_4$ [7]. Very high yields were obtained for almost all substrates. It was found that the use of this specific zinc dialkoxide is critical for the reactivity (e.g., almost no reaction occurs when using zinc(II) acetate). Meanwhile, an excellent

functional group tolerance toward olefins was observed. Thus, triolein (glyceryl trioleate) was reduced almost quantitatively to give the corresponding oleyl alcohol. Furthermore, it was proposed that the interchange between zinc hydride and zinc alkoxide is important to activate PMHS to pentacoordinated hydrosilicates.

In 2003, Carpentier *et al.* reported the zinc-catalyzed hydrosilylation of ketones and imines in a methanol–toluene solvent mixture applying PMHS as the reductant. In the presence of 2 mol% precatalyst good to excellent yields (76–99%) were obtained for both aromatic and aliphatic ketones. The crucial role of the protic solvent for achieving high reactivity was discussed [8]. Later in 2010, the Driess group published the use of preformed zinc-*O,S,S′*-ligand precatalysts for the efficient hydrosilylation of ketones. TOF up to 970 h^{-1} were obtained by applying complex **1** (0.1 mol%) (Scheme 2.3a). The catalyst was made via direct acid–base reaction of the ligand with dimethylzinc in a 1 : 1 molar ratio followed by the coordination with a diamine auxiliary ligand (e.g., tetramethylethylenediamine (TMEDA)). To understand the reactivity in more detail, NMR experiments were also carried out [9]. Recently, Enthaler *et al.* [10] reported the application of versatile formamidines as ligands for the zinc-catalyzed hydrosilylation of ketones. A strong ligand acceleration effect was observed for the combination of **L1** and $ZnEt_2$ (Scheme 2.3b). It was discovered that $ZnEt_2$/**L1** (R^1 = Me, R^2 = Me, R^3 = 2,4,6-$Me_3C_6H_2$) showed the best reactivity (yields 18–87%). For a number of aromatic and aliphatic ketones, excellent yields were obtained (76–98% isolated yield). However, ortho-substituted aromatic substrates (e.g., 2,6-dimethylacetophenone and its derivatives) showed no reactivity. Mechanistically, it is interesting that the hydride character of the silanes (determined by NMR spectroscopy) showed no correlation with the reactivity. The same

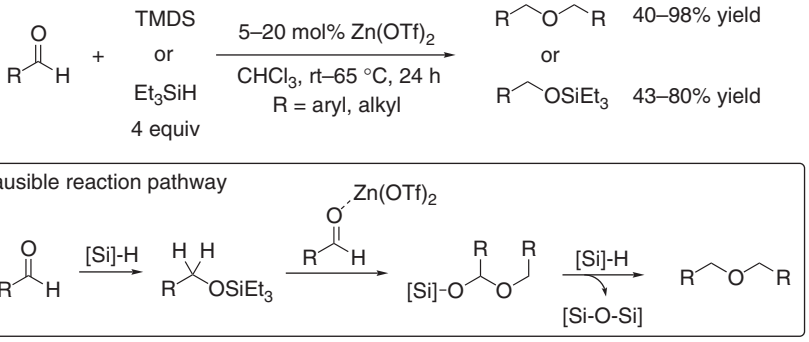


Scheme 2.3 (a–c) Zinc-catalyzed hydrosilylation of ketones with different ligand classes.

group also reported modified zinc precatalysts for the hydrosilylation of ketones (Scheme 2.3c) based on different phenol ligands **L2** [11]. Compared to the former method, similar reactivities and a broad functional group tolerance were achieved. Notably, the proposed mechanism suggested coordination of the zinc complex with the ketone substrate to activate the substrate molecule. Following this, the hydride of the silane was directly transferred to the carbonyl group [5].

Notably, a remarkable ligand-free approach was presented by Konod, Aoyama, and coworkers [12] Interestingly, a strong solvent effect was observed in the $Zn(OAc)_2$-catalyzed hydrosilylation of ketones. In the presence of 2 equiv of $PhSiH_3$ at room temperature, under the same conditions, the solvent *N*,*N*-dimethylformamide (DMF) gave quantitative yields, although there are only traces of the product in other solvents, such as acetonitrile, tetrahydrofuran (THF), 1,4-dioxane, ethyl acetate, toluene, and methanol.

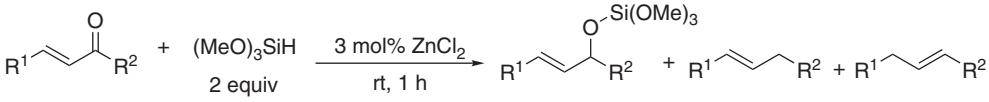
Interestingly, when aldehydes are used as substrates, silyl ethers or symmetric ethers can be obtained through zinc-catalyzed hydrosilylation reactions. By switching the silane from 1,1,3.3-tetramethyldisiloxane (TMDS) to Et_3SiH, silyl ethers were obtained instead of symmetric ethers for the reduction of aromatic aldehydes. In the case of aliphatic aldehydes, the symmetric ethers were produced in good yields with the combination of $Zn(OTf)_2$ and triethylsilane. After control experiments, the reaction pathway was proposed to proceed through the formation of the silyl ether as the key intermediate followed by its attack on the activated aldehyde to form the silylated hemiacetal. After a second reduction with another silane molecule, the corresponding symmetric ether was obtained. Accordingly, when the benzene ring of the substrate is electron deficient, the subsequent addition step cannot happen with the formation of silyl ethers as the major products (Scheme 2.4) [13].



Scheme 2.4 Zinc-catalyzed hydrosilylation of aldehydes to ethers.

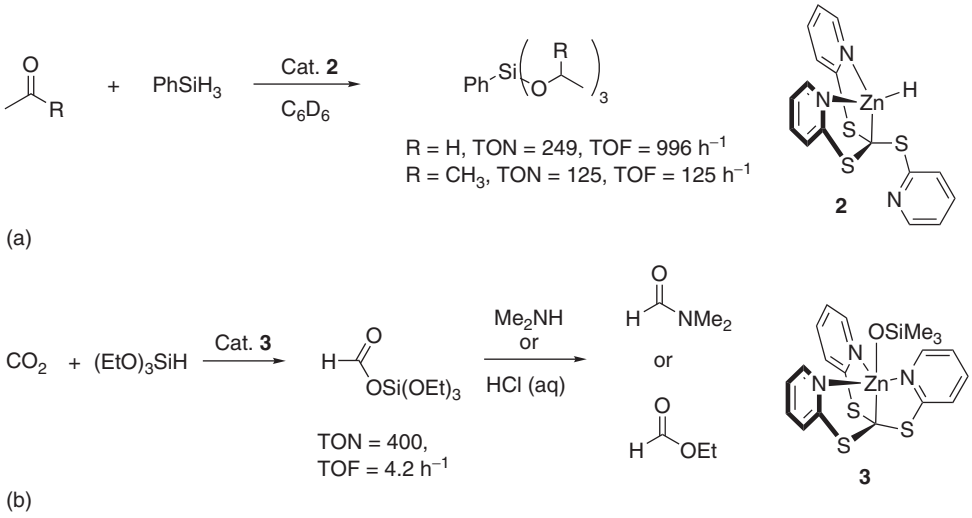
The selective 1,2-reduction of α,β-unsaturated ketones to olefins represents an important chemical transformation in organic chemistry. This task can be achieved by zinc-catalyzed hydrosilylation, which was reported by Mimoun *et al.* [6, 7] in 1990s. This topic was recently investigated in detail by Lai and coworkers [14]. Among the different tested zinc salts and silanes, $ZnCl_2$ and $(MeO)_3SiH$

showed the best reactivity for all substrates. Quantitative yield of the desired product can be obtained after 5 min. However, isomerization of the C=C bond occurred (Scheme 2.5).



Scheme 2.5 Zinc-catalyzed hydrosilylation of α,β-unsaturated ketones.

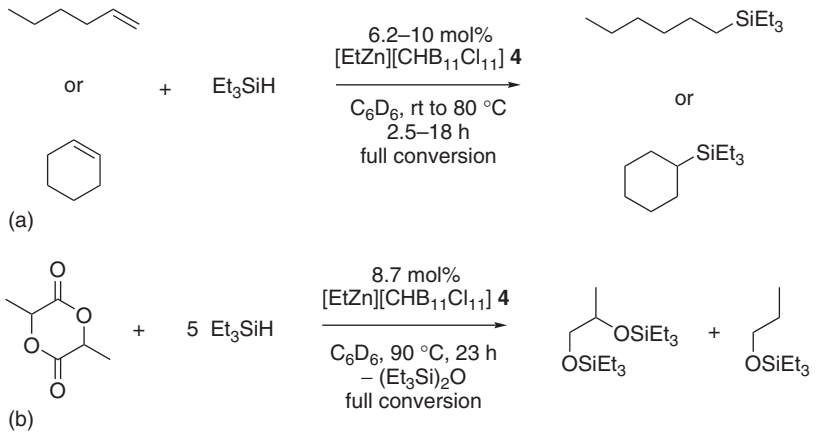
[Tris(2-pyridylthio)methyl]zinc hydride {[κ^3-Tptm]Zn, **2**} was used by the Parkin group as catalyst for hydrolysis of Si–H bonds (see Chapter 4). In addition, complex **2** can be an efficient catalyst for the hydrosilylation of ketones and carbon dioxide (Scheme 2.6). For the reduction of acetaldehyde and acetone catalyst, TOF up to 996 h^{-1} was obtained. The reduction of CO_2 to formic acid is an actual topic in carbon dioxide chemistry [15]. Under neat conditions, a TOF of 4.2 h^{-1} was obtained using 0.25 mol% of {[κ^4-Tptm]Zn($OSiMe_3$), **3**} in the presence of 1 equiv of triethoxysilane, producing the corresponding $(EtO)_3SiO_2CH$. By aminolysis or alcoholysis of $(EtO)_3SiO_2CH$, the desired amides or esters are produced [16].



Scheme 2.6 Zinc-catalyzed reduction of acetone, acetaldehyde (a), and CO_2 (b).

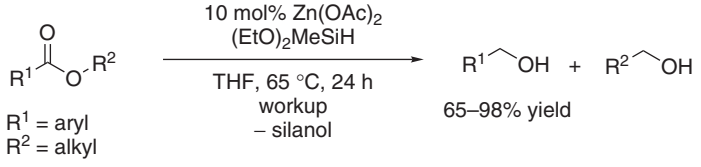
In 2011, Wehmschulte *et al.* reported the synthesis and application of a novel cationic ethylzinc compound $[EtZn(\eta^3\text{-}C_6H_6)][CHB_{11}Cl_{11}]\dot{c}C_6H_6$ (**4**$\dot{c}C_6H_6$) for the hydrosilylation of olefins, benzophenone, and lactide. The high Lewis acidity of the metal center was believed to be responsible for the good reactivity. Besides, this tight ion pair of a $EtZn(\eta^3\text{-}C_6H_6)$ cluster cation

and the chlorinated carborate anion can also catalyze hydroamination reactions (Scheme 2.7) [17].



Scheme 2.7 (a, b) $[EtZn(\eta^3\text{-}C_6H_6)][CHB_{11}Cl_{11}]\dot{c}C_6H_6$ (**4**)-catalyzed hydrosilylation.

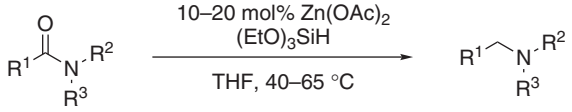
In 2011, zinc-catalyzed reduction of esters to alcohols was reported by our group [18]. Using inexpensive $(EtO)_2MeSiH$ as the reductant, various esters gave good to excellent yields. It is noteworthy that many reducible functional groups such as nitrile, nitro, olefin, alkyne, indole, and heterocyclic groups were well tolerated under these conditions (Scheme 2.8).



FG tolerance: nitrile, nitro, olefin, alkyne, indole, heterocycle

Scheme 2.8 Chemoselective Zn-catalyzed hydrosilylation of esters.

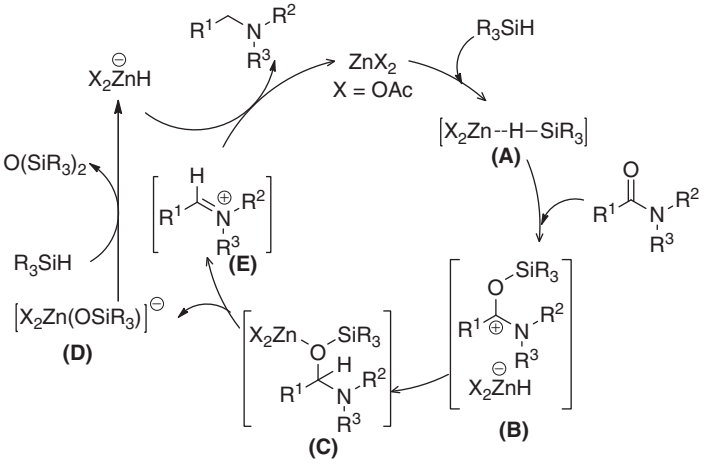
Chemoselective reduction of amides is also possible by using appropriate zinc-catalyzed hydrosilylations. By applying commercially available zinc salts, an efficient protocol was developed to reduce tertiary amides to the corresponding amines with excellent functional group tolerance. Particularly, the direct production of functionalized amines can be realized using this method without the protecting and deprotecting steps. More specifically, the amide group was selectively reduced in the presence of ketone, alkene, hydrazine, ester, nitrile, and nitro groups (Scheme 2.9). In many cases, the corresponding amines were obtained in high yields. Notably, the tolerance to more active ketones facilitates good potential application of this method for the synthesis of functionalized amines [19]. In general, triethoxysilane shows comparable



Scheme 2.9 Zinc-catalyzed chemoselective hydrosilylation of organic amides.

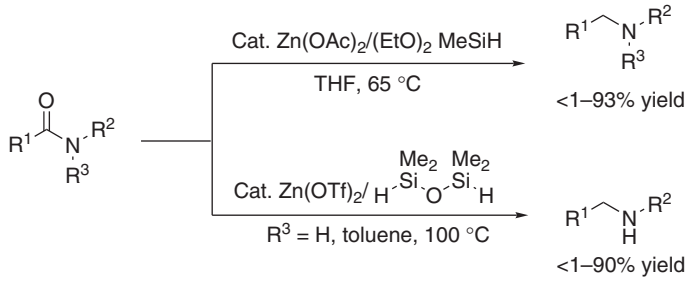
reactivity, but its application should be avoided due to the possible generation of SiH_4.

A reaction mechanism was proposed based on IR and NMR experiments: First, zinc(II) acetate interacts with triethoxysilane at room temperature to form an activated species **A.** Next, the organic amide reacts with the activated silane in **A** and generates the corresponding *N,O*-acetal species **C** via transition state **B.** Release of the anionic zinc complex **D** led to the iminium species **E.** Finally, another equivalent of the silane converts the iminium ion to the product and the siloxane (Scheme 2.10).



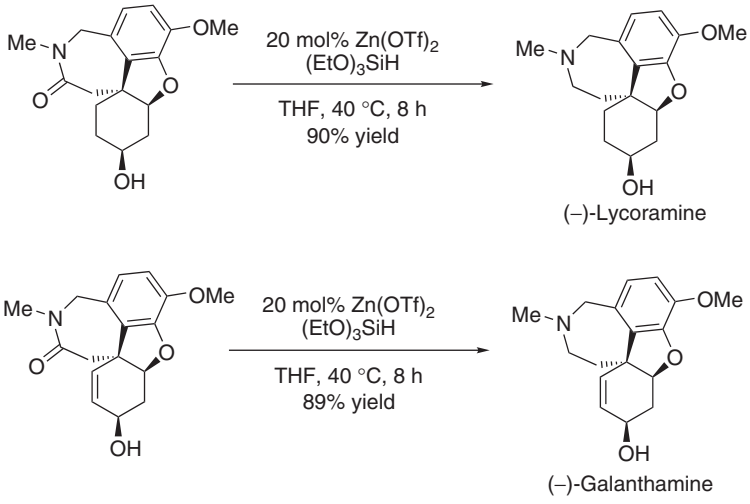
Scheme 2.10 Proposed reaction mechanism for zinc-catalyzed chemoselective hydrosilylation of organic amides.

Later, this procedure was successfully transferred to the zinc-catalyzed reduction of secondary amides to amines (Scheme 2.11). By using different zinc salts and silanes, convenient and general methods were developed for the reduction of both tertiary organic amides {$Zn(OAc)_2$/$(EtO)_2MeSiH$} and the chemically more inert secondary organic amides {$Zn(OTf)_2$/TMDS}. Meanwhile, it was observed that under such conditions ketone groups were reduced and the reactivity was suppressed in the presence of −SMe group or the aniline moiety. In addition, in both cases dehalogenation does not occur, which is in contrast to the previously reported method applying triethoxysilane [20].



Scheme 2.11 Zinc-catalyzed chemoselective hydrosilylation of organic amides.

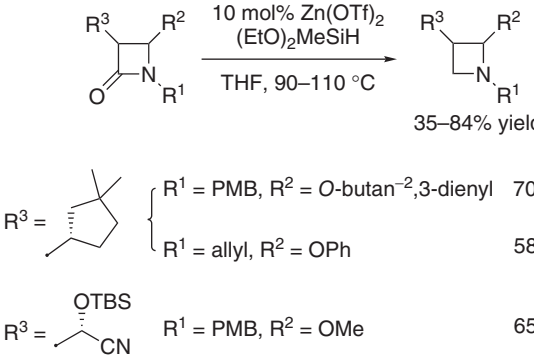
In 2012, Zhou *et al.* successfully applied this methodology, developed by our group, for the total synthesis of (−)-galanthamine (a drug used for the treatment of Alzheimer's disease) and (−)-lycoramine (cholinesterase inhibitor) (Scheme 2.12). In both cases, the reduction of amides was used as the final step of the 12- or 10-step synthesis, giving very high yields of the desired products. In more detail, the reduction of the amide moiety was carried out at 40 °C in the presence of 5 equiv of triethoxysilane, while hydroxyl, ether, and olefin groups were not affected. Notably, high efficiency and chemoselectivity is the key to the success of this application [21].



Scheme 2.12 Zinc-catalyzed chemoselective hydrosilylation of amides.

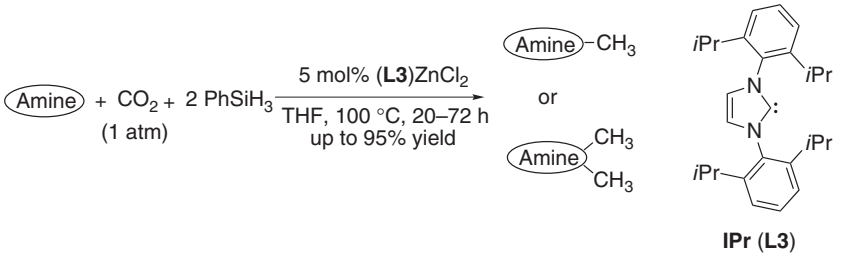
Moreover, the azetidine skeleton exists widely in biologically active compounds, such as penaresidin A (protein kinase C inhibitory activity). Direct synthesis of this four-membered ring is difficult owing to the ring strain. An efficient approach is the reduction of 2-azetidinones (β-lactams). Commonly, metal hydrides are

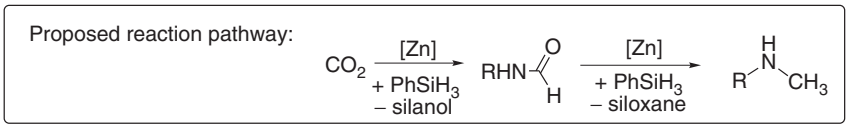
used for this type of reaction, but the functional group tolerance is very limited. Recently, Alcaide, Almendros and coworkers presented the chemoselective zinc-catalyzed reduction of β-lactams for the preparation of functionalized azetidines (Scheme 2.13). Although temperatures above 90 °C were required, a good functional group tolerance to dienyl, olefinyl, and nitrile groups was observed [22].



Scheme 2.13 Zinc-catalyzed chemoselective hydrosilylation of β-lactams (PMB = 4-$MeOC_6H_4$).

In 2013, the domino reduction of CO_2 to formamides and further on to methylated amines was reported by Cantat *et al.* [23] (Scheme 2.14). This reductive methylation reaction was catalyzed by zinc–carbene complexes using phenylsilane as the reductant. Many primary amines were smoothly transformed to the corresponding methylated products (up to 95% yields). Notably, 1 atm of CO_2 was required. **IPr**$ZnCl_2$, which is easily prepared from $ZnCl_2$ and **L3** (**IPr**), showed the best catalyst performance. Under optimized reaction conditions (5 mol% **IPr**$ZnCl_2$, 2 equiv $PhSiH_3$, and CO_2 (1 atm) in THF), various primary amines were examined to prove the generality of this methodology. The results of control experiments and *N*-methylaniline derivatives suggest that formylation of the amines followed by reduction of the formamides is the dominant pathway.





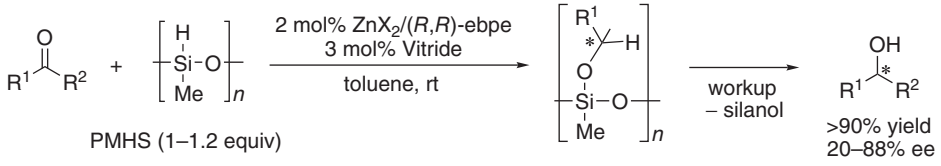
Scheme 2.14 Zinc-catalyzed methylation of amines from CO_2.

Other than hydrosilylation using hydrosilanes as the reductant, Zn-catalyzed reductive silylation was also reported by the Noyori group in the presence of metal hydrides. Here, commercial lithium hydride as the reductant was activated with a catalytic amount of a zinc(II) salt or zinc(0) powder in the presence of chlorotrimethylsilane. Aldehydes and aromatic or aliphatic ketones were reduced to silyl ethers in high yields. In this reaction system, a Zn(II) species is proposed to be the active catalyst [24]. Similarly, there was a series of studies by the Caubère group on the use of zinc(II) salts for the activation of sodium hydride with chlorotrimethylsilane for the reduction of ketones and aldehydes [25].

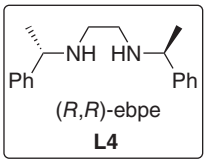
2.2.2
Asymmetric Hydrosilylation of C=O Bonds

Owing to its mild conditions, nonprecious metal-catalyzed asymmetric hydrosilylation of ketones represents a useful method for producing chiral secondary alcohols, which are widely used intermediates [2b]. The first example of an asymmetric zinc-catalyzed hydrosilylation of ketones was reported in 1987 by the Lukevics group [5]. The authors synthesized *N*-benzyl-*N*-methylephedrinium dibromodichlorozincate and used this catalyst for hydrosilylation of acetophenone and 3-acetylpyridine in the presence of Ph_2SiH_2 giving TONs of 90 and 150, respectively. Although no enantioselectivity was observed for the reduction of acetophenone, (*S*)-1-(3-pyridyl)-ethanol was obtained with 46% ee for the reduction of 3-acetylpyridine.

A more general and efficient asymmetric hydrosilylation of carbonyl compounds was reported by Mimoun *et al.* 10 years later, using ZnR_2 (R = Et, Me, or H) and chiral diimine or diamine ligands in the presence of inexpensive PMHS. Good reactivity and selectivity were obtained with C_2-symmetric secondary diamines (e.g., **L4**) and 1-phenyl ethanol was produced with up to 88% ee. Using 2 mol% of a zinc precursor, 2 mol% of the chiral ligand, and 1–1.2 equiv of PMHS, reduction reactions proceeded smoothly and the alcohol products were obtained with >90% yields and 70–88% ee values. Other than $ZnEt_2$ or $ZnMe_2$, a zinc carboxylate can also be used as an efficient catalyst precursor in the presence of a hydride activator such as Vitride (Scheme 2.15). Notably, the authors showed the



- ✔ Good reactivity and enantioselectivity
- ✔ Scale up to 1 kg
- ✔ High purity of product easily seperated by distillation
- ✔ Chiral ligand recovered efficiently and reused



Scheme 2.15 Zinc-diamine-catalyzed chemoselective hydrosilylation of ketones (Vitride = sodium bis(2-methoxyethoxy)aluminumhydride).