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ZINC CHLORIDE-MEDIATED CONJUGATE REDUCTION WITH SILICON HYDRIDES AND PALLADIUM(0) CATALYST

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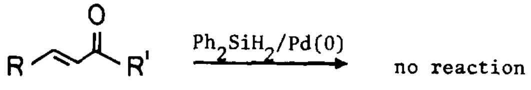
Abstract. The chemistry of diphenylsilane/Pd(0), a system previously known to reduce only allylic heterosubstituents, has been radically altered by addition of catalytic amounts of zinc chloride, enabling efficient conjugate reduction of α,β-unsaturated ketones and aldehydes.

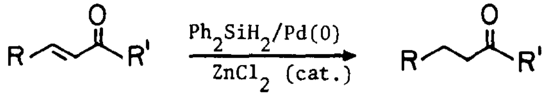
In the absence of a catalyst, silicon hydrides are generally poor reducing agents,[1] a characteristic which makes them potentially attractive for chemoselective reductions. A judicious selection of the silane, reaction conditions and catalyst holds a great promise for improved chemoselectivity, as well as regio- and stereocontrol. For example, ionic hydrogenations,[2] involving hydride transfer to an electron-deficient center are usually achieved with an acid catalyst and/or the assistance of a nucleophilic silanophile.[3] Moreover, hydrogen atoms may be transferred from silicon hydrides via radical processes[4] induced by radical initiators. More importantly, selective reductions and hydrosilation reactions are also catalyzed by transition metals.[1,5]

We have recently demonstrated the transition metal approach by introducing novel reducing systems comprising various silicon hydrides and a soluble palladium(0) catalyst[6] which allow chemoselective allylic reductions under very mild conditions. We have also observed, remarkably, that easily reducible functionalities such as Michael-acceptors are unaffected by those systems (Equation 1). We report now that addition of catalytic amounts of zinc chloride to the above-mentioned silane/Pd(0) system substantially changes its reducing properties. This new three-component system is now capable of efficient conjugate reduction of α,β-unsaturated ketones and aldehydes (Equation 2).

(1)

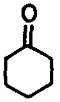
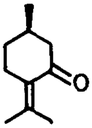
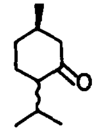
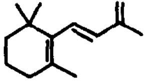
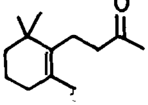
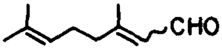
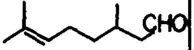
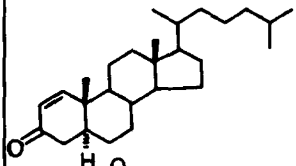
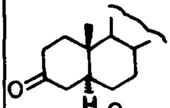
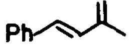
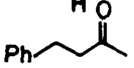
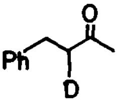
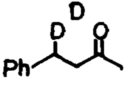
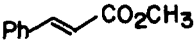
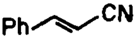


(2)



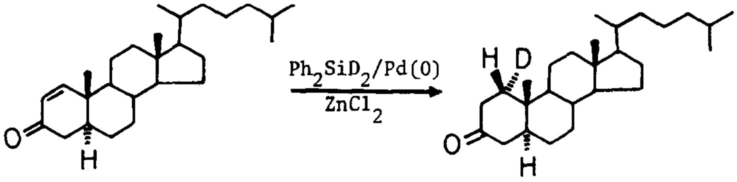
In addition to the generality of the method (see Table) and the mild reaction conditions used, the very simple and convenient experimental procedure makes this reduction superior to most other known procedures for conjugate reduction, including our previously reported tin hydride/Pd(0) approach.[7] Interestingly, the method is highly selective for unsaturated ketones and aldehydes which can be cleanly reduced in the presence of α,β-unsaturated esters and nitriles (e.g. entries 9 and 10 in the Table). A typical reduction is carried out according to the following procedure: $Pd((PPh)_3)_4$ (0.01-0.03 mmol) is added to a chloroform (filtered over active alumina) solution (3-5 ml) containing one mmol of the enone substrate, diphenylsilane (1.1-1.5 mmol), and 0.1-0.5 mmol of zinc chloride (Merck, #8816). The solution is stirred at room temperature (inert atmosphere is not required). Upon completion (reaction is monitored by either TLC or GC), the mixture is filtered through a short silica gel column using CH_2Cl_2 as eluent, and the products are purified by distillation or by chromatographic methods.

Table: Conjugate reductions with $Ph_2SiH_2/ZnCl_2/Pd(0)$.

Entry	Starting material	Ph_2SiH_2 (equiv.)	$ZnCl_2$ (equiv.)	$Pd(PPh_3)_4$ (equiv.)	Time (hours)	Product	Yield (%)
1		1.0	0.36	0.018	1		100[a]
2		1.55	0.4	0.018	6		90[a]
3		2.5	0.35	0.02	2		96
4		1.48	0.11	0.012	1.5		96[a]
5		1.6	0.5	0.03	1		100
6		1.3	0.3	0.009	2		100[a]
7	"	1.3	0.3[b]	0.009	2		100[a]
8	"	1.3[c]	0.3	0.009	2		100[a]
9		2.0	0.25	0.05	24	no reaction	-
10		2.0	0.25	0.05	24	no reaction	-

All reactions were carried out at room temperature in 5 ml chloroform with 1 mmol substrate. All products were fully characterized by comparison with authentic samples. a) Yield was determined by G.C. b) $ZnCl_2$ was dried by melting under high vacuum. D_2O was added to the reaction mixture. c) Ph_2SiD_2 was employed (prepared from $LiAlD_4$ reduction of Ph_2SiCl_2).

At this point, discussion of reaction mechanism must be speculative. It is clear that all three components (silane, Pd catalyst and $ZnCl_2$) are essential for the reduction, as no reaction takes place when one of them is omitted. It seems likely that our process involves a multi-step catalytic cycle which is analogous to the widely accepted mechanism of Pt-catalyzed hydrosilation of olefins[5] - a mechanism involving hydropalladation of the double bond to give an intermediate palladium enolate which decomposes in the presence of moisture to the saturated carbonyl. This is supported by the regioselectivity of deuterium-incorporation experiments (entries 7,8 in the Table and Equation 3), indicating a net transfer of hydride from silane to the β-carbon of the substrate and a proton transfer from water to the α-carbon. Experimental support for the postulated intramolecular transfer of hydride from palladium to the coordinated olefin is provided by the stereochemical course of the reduction of cholest-1-en-3-one, 1, with Ph_2SiD_2 (Equation 3). The observed stereoselective incorporation of deuterium at the less hindered α-face of the steroid, leading to 1α-d cholestanone, 2 mimics the stereoselectivity noticed in catalytic hydrogenation of such systems.[8] Structural assignment of 2 is based on ^1H NMR where H_2 absorbed at δ 2.39 ppm (doublet of doublets, J=15.3, 6.1 Hz) while the corresponding absorption of nondeuterated cholestanone appeared as triplet of doublets at 2.39 ppm (J=15.1, 6.2 Hz), in agreement with known data on related compounds.[9]

(3) 

1 2

It appears that the role played by $ZnCl_2$ is not merely that of an acid,[10] for despite the fact that the reaction also works with $MgBr_2$ or $SnCl_4$, very slow reduction (5-6 times slower) occurs in the presence of stronger Lewis acids such as $TiCl_4$ or $FeCl_3$ or in the presence of acetic acid while essentially no reaction takes place in the presence of NH_4Cl (with or without added water). Moreover, Et_3SiH, which is more nucleophilic than Ph_2SiH_2 and which has proven useful for conjugate reductions[11] in the presence of $TiCl_4$, was found to be completely inert in our case. Therefore one may speculate that hydride is indirectly transferred from silicon to palladium via an intermediate "Zn-H" or "Zn-H-Si" species. Such an hypothesis may be supported by the formation of Ph_2SiClH upon mixing Ph_2SiH_2 and $ZnCl_2$ in DMSO-d^6 (in the absence of a Pd catalyst). Addition of D_2O to this sample causes a vigorous evolution of hydrogen gas.

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10. We have found[7a] that the conjugate reduction of α,β unsaturated ketones and aldehydes with $Bu_3SnH/Pd(0)$ is substantially promoted by the presence of wet NH_4Cl. Similar observations were later reported by Guibe[7c] who used acetic acid or $ZnCl_2$ for the same purpose.

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