

ORGANO TIN NUCLEOPHILES IV.¹
PALLADIUM CATALYZED CONJUGATE REDUCTION WITH TIN HYDRIDE

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Abstract: Highly chemoselective conjugate reduction of α,β -unsaturated carbonyl compounds is now possible by using tributyl tin hydride with $\text{Pd}(\text{P}\phi_3)_4$; an optimization study puts forth the importance of added radical scavenger and proton source in these reductions.

Chemoselective hydrogenation of activated double bonds such as α,β -unsaturated carbonyl functions, has been a long desired synthetic transformation. The arsenal of relevant synthetic tools has been strikingly enriched within the last two decades. In terms of chemoselectivity and regio- and stereocontrol, metal hydrides and in particular transition metal hydrides, offer a number of advantages over the more traditional methods of catalytic hydrogenation² and dissolving metal reduction methods.³ The most significant metallic hydrides used are those of iron,⁴ copper,⁵ rhodium,⁶ and to a lesser extent cobalt,⁷ ruthenium,⁸ iridium,⁹ and palladium.¹⁰ The ability to perform conjugate reduction on highly functionalized molecules in a controlled fashion poses a continuing challenge.

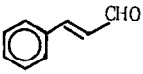
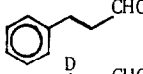
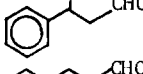
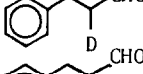
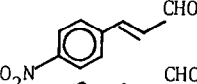
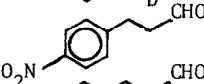
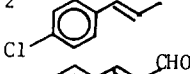
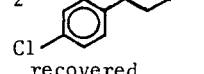
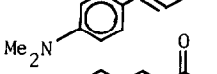
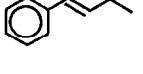
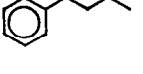
Herein is reported a new highly chemoselective palladium catalyzed conjugate reduction methodology, based on trialkyl tin hydride as an hydride donor and water as a proton donor. The reaction of nucleophiles covalently bound to trialkyl tin with soft electrophilic centers such as π -allyl palladium species has been previously reported,^{1,11} Our recent finding that tributyl tin hydride serves as an efficient hydride donor¹² to π -allyl palladium complexes, suggested that an analogous transfer of hydride to activated olefin-palladium complexes followed by concomitant protonation, should result in net conjugate reduction of Michael acceptors.

Indeed, addition of tributyl tin hydride to a stirred THF solution of an α,β -unsaturated carbonyl compound containing ~3 mole % $\text{Pd}(\text{P}\phi_3)_4$ at room temperature, followed by $\text{H}_2\text{O}/\text{CH}_2\text{Cl}_2$ work-up, resulted in excellent yield of the α,β -reduced carbonyl species. Results are shown in Table I.

The striking sensitivity of the reducing system to the electronic density at the double bond, as demonstrated in Table I, holds a great potential in terms of chemoselectivity.

Since the reaction involves a number of organometallic species which may lead to undesirable side reactions and decomposition products, an optimization study was carried out. The role and relative importance of five different factors were evaluated, based on 8 x 8 matrix of the factorial plane of experiments¹³ as depicted in Table II.

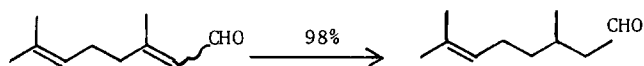
Table I. Conjugate reduction with $\text{Bu}_3\text{SnH}/\text{Pd}(\text{P}\phi_3)_4$

Starting material	Bu_3SnH (addition rate 1 eq./h)	Product (Yield)
	1.5 eq.	 (>99%)
"	1.5 eq. (Bu_3SnD)	 (>99%)
"	1.5 eq. (work up with D_2O)	 (>99%)
	1.7 eq.	 (98%)
	3 eq.	 (70%)
	4 eq.	recovered starting material (0%)
	1.7 eq.	 (>99%)

The semi-quantitative correlation between the product's yield and these first chosen parameters (eq. 1) revealed the beneficial roles of added radical scavenger, higher temperature and slow hydride addition rate. Added triphenyl phosphine, on the other hand, suppresses the reaction presumably by over-stabilizing the palladium catalyst. There is a small solvent effect in favor of benzene. Apparently, no significant correlation exists between temperature and radical scavenger or between temperature and hydride addition rate. Based on the above consideration, a step-wise sequence of the modified simplex method¹⁴ (Table III) led to an essentially quantitative yield after the resulting dozen experiments.

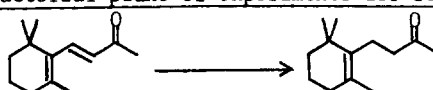
$$(\text{eq. 1}) \quad \text{Yield (\%)} = 20.7 + 10.4X_1 + 5.3X_2 - 11X_3 - 8.9X_4 - 3.5X_5 + 1.9^2X_1X_2 - 2.4^2X_1X_3$$

Under the optimized set of conditions, conjugated trisubstituted olefins were also reduced as demonstrated by the quantitative reduction of citral:



Interestingly, both Z and E isomers of the commercial 1:1 mixture were reduced at the same rate as judged by the G.C. analysis.

Tributyl tin hydride, being a typical free-radical reducing agent,^{15,16} has exhibited hydride donor properties only in two general cases: either in highly polar medium containing ZnCl_2 ,¹⁷ SiO_2 ,¹⁸ or in combination with highly electrophilic partners.¹⁹ The beneficial role played here by addition of a radical scavenger, the inertness of the benzyl chloride to the reaction conditions,²⁰ the need for only one equivalent of Bu_3SnH ¹⁸ and the absence of CIDNP effects when the reaction was followed by NMR,²¹ suggest the present hydrogenation to be another rare example of tin hydride acting as an hydride donor. A plausible mechanism involves palladium

Table II. Factorial plane of experiments for reduction of β ionone^a


Exp. No.	X ₁	X ₂	X ₃	X ₄	X ₅	X ₁ X ₂	X ₁ X ₃	Yield (%)
1	+	-	-	+	-	+	+	5.4
2	+	+	-	+	+	-	-	29.6
3	+	-	+	-	+	-	+	25.7
4	+	+	+	-	-	+	-	65.8
5	+	-	-	+	+	+	-	5.6
6	+	+	-	+	-	-	+	21.0
7	+	-	+	+	-	-	-	4.4
8	+	+	+	+	+	+	+	7.7

a) In each experiment a 5 ml solution containing 1 mmole β ionone and 0.03 mmole $\text{Pd}(\text{P}\phi_3)_4$ was subjected to the following conditions:

	-	+
X ₁ (temperature):	0°	23°C
X ₂ (2,6-di- <i>t</i> -butyl-4-methylphenol):	-	0.06 mmole
X ₃ (triphenylphosphine):	-	0.24 mmole
X ₄ (addition rate of Bu_3SnH):	1 mmole/h	6 mmole/h
X ₅ (solvent):	benzene	THF

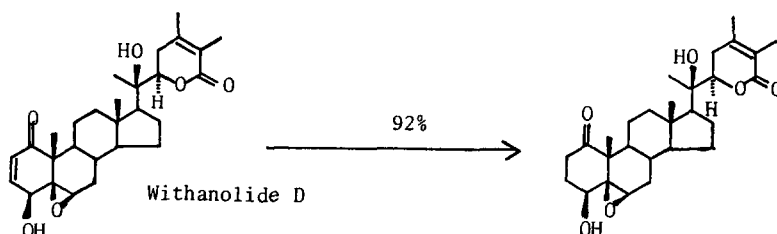
Table III. Simplex optimization of β ionone reduction^a

exp. no.	temp.	radical scavenger	solvent/proton source	yield
9	40°	0.48 eq.	benzene	70.3%
10	60°	0.72 eq.	benzene	29.7%
11	30°	0.42 eq.	THF/H ₂ O (2.8 eq.)	83.8%
12	30°	-	THF/H ₂ O 2.7 (eq.)/ NH ₄ Cl (2 eq.)	>98%

a) In each experiment Bu_3SnH was added at a rate of 1 eq./hr to a 5 ml solution of 1 mmole β ionone and 0.03 eq. $\text{Pd}(\text{P}\phi_3)_4$.

catalyzed hydrostannation to form an intermediate enol stannane which decomposes under protic conditions to the parent carbonyl compound.²²

The expected importance of steric factors was demonstrated by the resistance of Δ^4 -cholestenone or even $\Delta^{1,4}$ -cholestadienone to this reducing system, whereas withanolide **D**²³ was chemoselectively reduced in excellent yield:



Further scope and limitation studies, as well as *in situ* utilization of the intermediate enol stannane¹ are in progress.

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