Development and Evaluation of a Borohydride-palladium System for Selective Reduction of the C=C Bond of **α,β**-unsaturated Carbonyl Compounds

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This work has undergone a double-blind review by a minimum of two faculty members from institutions of higher learning from around the world. The faculty reviewers have expertise in disciplines closely related to those represented by this work. If possible, the work was also reviewed by undergraduates in collaboration with the faculty reviewers.

Abstract
Selective reduction of the carbon-carbon double bond of α,β-unsaturated carbonyl compounds is most commonly and reliably effected using a palladium metal catalyst together with molecular hydrogen from a pressurized tank. Sodium borohydride, like other hydrides, is ordinarily associated with reduction of the more polarized carbonyl of such compounds. However, we have developed an alternative means of employing sodium borohydride in combination with palladium metal to selectively reduce the carbon-carbon double bonds of these compounds. In this survey study, we introduce sodium borohydride as an alternative hydrogen source for such selective, palladium-catalyzed reductions. We also compare the results of this new, heterogeneous borohydride-palladium method with that of traditional palladium-catalyzed hydrogenation. A third method using only sodium borohydride with no palladium is included for comparison.

Keywords
chemistry, palladium, borohydride, catalyst, reduction, hydrogenation

Editor's Note: Dr. David B. Cordes, Associate Professor, Department of Chemistry, Pacific University, served as the faculty mentor for this work.

INTRODUCTION

To the alchemists of past centuries, the skillful and selective *transformation* of one substance into another might be but a single step in their efforts to prepare the Philosophers' Stone (Principe, 2013)**.** The Philosophers' Stone was, in turn, thought to promote the *transformation* of metals such as tin and lead into gold. Today, expanding the range and improving the quality of *functional group transformations* continues to occupy a primary place in the work of organic chemists. Of all the various organic reactions that have been described, it is fair to say that *reduction* is one of the most common and fundamentally important.

Catalytic reduction of carbon-carbon double and triple bonds with hydrogen gas was first demonstrated with a platinum metal catalyst in 1874, but was developed as a general method by Sabatier, who won the 1912 Nobel Prize for this work; see Figure 1 (Sabatier & Senderens, 1897; Wilde, 1874). Palladium, however, soon became the preferred metal catalyst. In fact, the unique properties of palladium combined with hydrogen so impressed early researchers that they referred to the combination as a unique metallic compound or alloy and called it *"hydrogenium"*.
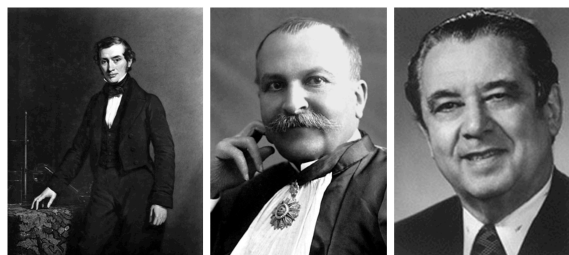

*Figure 1*. Palladium pioneers: Thomas Graham, Paul Sabatier, and Herbert C. Brown

Thomas Graham hypothesized that structural changes were occurring with new Pd-H bonds formed as the hydrogen was added and broken as the hydrogen departed (Graham, 1868, 1869). In the modern conception of the palladium-hydrogen system, it is understood that several distinct structural Pd-H phases may exist, sometimes simultaneously, depending on the hydrogen concentration, pressure, and temperature (Lewis, 1967). Since palladium retains much of its form and structural properties even as it absorbs very large volumes of hydrogen, these Pd-H phases are sometimes referred to as 'solid solutions' and 'palladium hydrides'.

There is general agreement on the basic steps for the palladium-catalyzed hydrogenation of alkenes and related compounds as described by Horiuti and Polyani in 1934 (Mattson et al., 2013; Polyani & Horiuti, 1934). Key steps involve adsorption of the unsaturated substrate to the metal surface by way of its C=C *pi*-bond system. With addition of hydrogen gas (H_2), absorption and dissociation of molecular hydrogen occurs both on the surface and, to some degree, in the subsurface volume of the metal to form so-called palladium-hydrides (Pd-H). These palladium hydrides are understood to be the active species in palladium-catalyzed hydrogenations.

Reagents such as sodium borohydride and lithium aluminum hydride represent an entirely different approach to chemical reduction as they harness the nucleophilicity of hydride ions (Nystrom & Brown, 1947; Schlesinger et al., 1953; Seyden-Penne, 1997). Hydride nucleophiles (:H⁻) attack electrophiles and positively polarized moieties such as the carbon atom of a carbonyl or imine. The mechanisms for both hydride reduction and palladium-catalyzed hydrogenation are depicted in Scheme 1.

In this study, we examined the chemoselectivity of several methods for the reduction of α,β-unsaturated carbonyl compounds. Their properties and reactivity vary dramatically depending on the presence of structural and electronic features such as
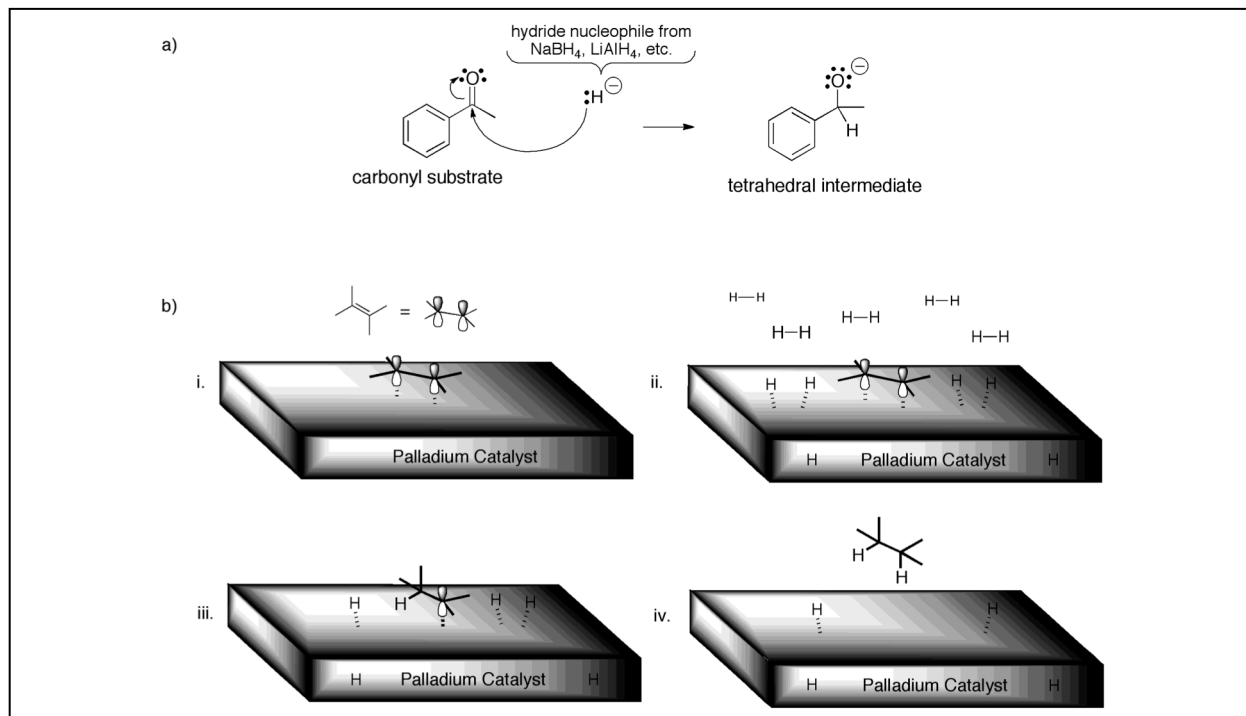
Scheme 1. Representative mechanisms for reduction/hydrogenation: a) hydride reduction of a ketone to tetrahedral intermediate; b) Horiuti-Polyani mechanism for alkene reduction to an alkane with a traditional Pd-H_2 system.

aromatic rings and donating or withdrawing groups conjugated with or in proximity to the α,β–unsaturated carbonyl system (Al-Rifai, Rucker, & Amslinger, 2013; Amslinger, 2010). Selective reduction of these compounds is required to gain access to the great variety of their saturated and partially saturated analogs. A notable example is the NAPDH-dependent biochemical reduction of testosterone to the potent analogue dihydrotestosterone by the 5α-reductase enzyme, as shown in Scheme 2 (Bull et al., 1996).
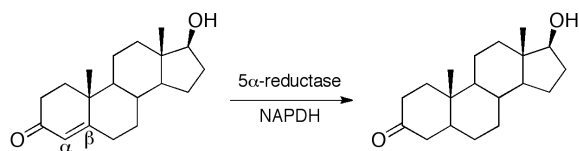
Scheme 2. Selective reduction of testosterone to dihydrotestosterone by the NAPDH-dependent 5α-reductase enzyme.

While reduction of the C=C bond is thermodynamically and kinetically favorable (Bond, 1962), non-selective reduction and the formation of unwanted side-products will often be a problem. Selectivity for reduction of a bifunctional molecule largely depends on the rate constants for the competing reactions in question, but it can also depend on competition between functional groups for adsorption onto active catalytic sites (Rylander, 1994). Possible products for the reduction of α,β-unsaturated carbonyl compounds, illustrated for chalcone, are shown in Scheme 3.
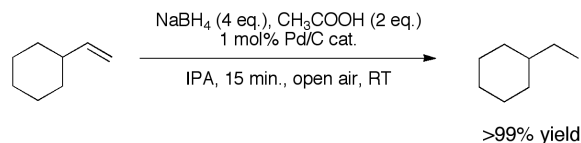
While hydrogen gas in combination with a Pd catalyst reliably reduces the C=C bond of many α,β-unsaturated compounds, hydride reagents tend to show selectivity for the reduction of the more polar carbonyl function (Meyer, 1981). High selectivity for the reduction of the C=O bond of α,β-
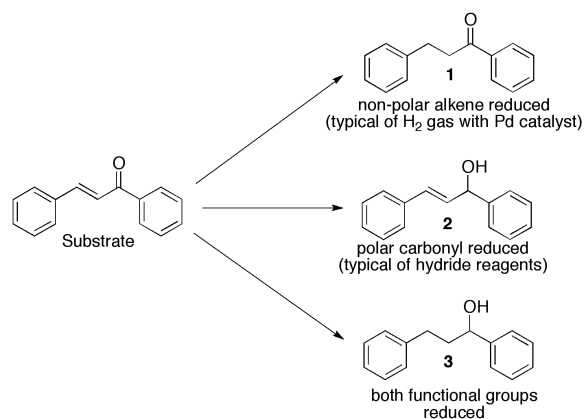
Scheme 3. Some possible fates for reduction of α,β–unsaturated compounds as illustrated for the reduction of chalcone.

Scheme 4. Palladium-catalyzed reduction of vinyl cyclohexane to ethyl cyclohexane using sodium borohydride.

unsaturated ketones and aldehydes is most notably achieved by Luche reduction in which the carbonyl is activated by a Ce^{3+} catalyst (Gemal & Luche, 1981). Many other strategies for the selective reduction of the C=O bond have been described, but only a handful of hydride-based methods for selective C=C bond reduction have been introduced (Aramini, Brinchi, Germani, & Savelli, 2000; Hutchins, Rotstein, Natale, Fanelli, & Dimmel, 1976; Keinan & Greenspoon, 1986; Ranu & Samanta, 2003, Mahoney & Stryker, 1989).

In a modification of a procedure first described by Herbert Brown (Brown & Brown, 1962a, 1962b), our group first reported a heterogeneous reaction system in which sodium borohydride is used in combination with a palladium-on-carbon (Pd/C) catalyst to rapidly reduce alkenes and alkynes to the corresponding saturated alkanes (Tran, Huynh, Friz, Whitney, & Cordes, 2009). We found that addition of acetic acid dramatically improved reaction times and yields for unsaturated substrates resistant to Brown's original method. A general stoichiometry that proved efficient for most substrates was 1:4:2 (substrate: borohydride: acetic acid). The reaction served as a mild, yet general method for the nearly quantitative reduction of a wide

variety of alkenes and alkynes. A typical reaction is shown in Scheme 4.

Literature reports and our observations suggest that this reaction takes place by way of catalytic hydrogenation on the metal surface using hydrogen that has been produced *in situ* from the decomposition of borohydride (Osby, Heinzman, & Ganem, 1986; Satyanarayana & Periasamy, 1984). It is known that palladium metal catalyzes the hydrolysis of sodium borohydride at the metal surface to liberate hydrogen which may then reside within or on the surface of the metal catalyst in the form of palladium-hydrides (Pd-H) (Brown & Brown, 1962b; Demirci & Garin, 2008; Guella, Zanchetta, Patton, & Miotello, 2006; Kaufman & Sen, 1985; Titova, Belykh, Belonogova, & Shmidt, 2009). As the alkene or alkyne will also be adsorbed on the metal surface, this would help to explain the extraordinarily rapid nature of the reduction. Acidic conditions are generally appreciated as favorable towards catalytic hydrogenation of the C=C bond (Rylander, 1994), but the acetic acid plays another role. Additional hydrogen is produced from reaction of the acetic acid with the borohydride, a combination known to produce an acetoxyborohydride (Gribble, 1996, 2006). This nucleophilic species may react further with acidic protons to form more highly substituted acetoxyborohydride species as it produces additional H_2 gas in the process (Scheme 5).

Two years later, our group applied this palladium-borohydride reduction system to the selective reduction of α,β-unsaturated
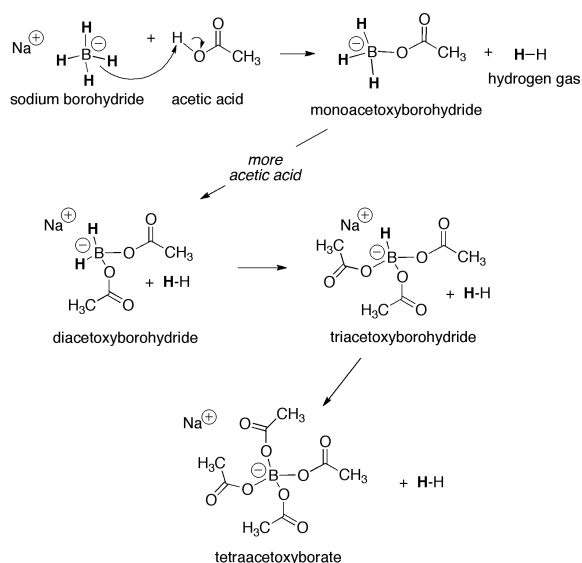
Scheme 5. Reaction of sodium borohydride and acetic acid to form variously substituted, nucleophilic acetoxyborohydride species.

carbonyl compounds and related compounds and obtained good results for selective reduction of the C=C bond of several substrates (Russo, Amezcua, Huynh, Rousslang, & Cordes, 2011). An example of such selective reduction is shown for the reduction of 4-phenyl-3-buten-2-one in Scheme 6.
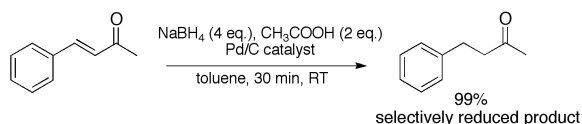
Scheme 6. Selective reduction of 4-phenyl-3-buten-2-one with the sodium borohydride-palladium system.

In these experiments, the 1:4:2 (substrate: borohydride: acetic acid) stoichiometry that we had been using earlier for alkene reduction was determined to be largely optimal for most of our unsaturated substrates (Amezcua, 2013). However, we were curious about the effects of other variables and, so, conducted a systematic study to explore more fully the effects of solvent, catalyst loading, and temperature.

RESULTS AND DISCUSSION

I. Determination of the Effects of Solvent, Catalyst Loading, and Temperature on Selectivity for the Reduction of Chalcone

a) Solvent Study

Often studied in the context of S_N1 and S_N2 reactions, solvent choice can have a major effect on the outcome of a reaction by stabilizing or destabilizing various reactants, transition states, and products. Solvents can also affect both rate and selectivity through competition for active catalytic sites and by altering hydrogen solubility (Rylander, 1994). In some systems, as in transfer hydrogenation, the solvent may even be involved directly as a hydrogen donor.

Our initial study was conducted to understand the effects of solvent polarity on the chemoselectivity of these reductions. When we first applied the palladium-borohydride system to the reduction of α,β-unsaturated carbonyl compounds, we used isopropyl alcohol since this solvent had worked well with alkenes and alkynes. Further study revealed that non-polar solvents tended to give better results, so we decided to conduct a more thorough solvent study using chalcone as the model substrate. We tested six different protic and aprotic solvents across a range of polarities: toluene, isopropyl alcohol, dichloromethane, dimethylformamide, tetrahydrofuran and acetonitrile. Results are shown in Table 1.

Often, the effects of solvent on selectivity are most evident at the extremes of the solvent dielectric constant. We observed this classic response, with selective reduction of the C=C bond increasingly favored in non-polar solvents. Toluene gave the best results. We believe this is because the hydride ion is not soluble in toluene as it is in polar solvents. Hydride ion, thus, is unavailable as a nucleophile for attack on
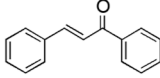
entry	Solvent (Dielectric Constant (ε))	% Unreacted Substrate	1 - % Desired Product Saturated Ketone C=C bond reduced	2- % Unsaturated Alcohol C=O bond reduced	3 -% Saturated Alcohol Fully Reduced
1	$CH_3C{\equiv}N$ acetonitrile (37.5)	1	24	0	76
2	dimethylformamide (36.7)	1	1	20	77
3	isopropyl alcohol (17.9)	2	19	5	74
4	CH_2Cl_2 dichloromethane (8.93)	40	54	0	6
5	tetrahydrofuran (7.58)	46	35	5	14
6	toluene (2.38)	20	77	0	3

Table 1. Solvent study for reaction of chalcone: sodium borohydride, acetic acid (1:4:2) using 1.0 mol% Pd/C catalyst. Reactions conducted at room temperature. Results are shown for 30 minutes reaction time.

the carbonyl and little or no unsaturated alcohol is produced. Our observations support the hypothesis that, in toluene, the borohydride is not the active species and that it instead decomposes through interaction with palladium to form surface and subsurface palladium-hydrides (Pd-H) as the active species as well as excess hydrogen gas (H_2). As solvent polarity and borohydride solubility increases, however, the reaction system tends to give the fully reduced saturated alcohol. The data also suggests that in non-polar solvents, the olefinic bond is reduced first, but that over extended reaction times reduction of the carbonyl becomes competitive to give the fully reduced product.

b) Catalyst Loading

In earlier research, we found that Pd catalysts outperformed all common metal catalysts (Pt, Cu, Ni, Zn, etc.) when evaluated with sodium borohydride for reduction of unsaturated carbon-carbon bonds. In the current study, we tested catalyst loadings of Pd/C to determine an optimal level of catalyst loading for our reactions. While monitoring both selectivity and conversion of chalcone reduction, we tested loadings typically observed for traditional hydrogenation (0.5%, 1.0%, 2.5%, 5.0%). Results are shown in Table 2.

With respect to the gross effects of palladium catalyst loading, the results using palladium in combination with sodium borohydride are generally the same as those observed when conducting traditional hydrogenation: higher loadings provide more rapid, but less selective reduction. We found 2.5% catalyst loading to be optimal for reduction of chalcone. We used this 2.5% loading for all subsequent measurements. Results are depicted graphically in Figure 2.

c) Temperature Study

Temperature is well-known to affect both rate and selectivity with higher temperatures associated with increasing rates of conversion. At higher temperatures, catalyst activity is sometimes diminished and a loss of selectivity observed. We had

entry	Pd/C (mol %)	% Unreacted Substrate	1 - % Desired Product Saturated Ketone C=C bond reduced	2- % Unsaturated Alcohol C=O bond reduced	3 -% Saturated Alcohol Fully Reduced
1	0.5	72	28	0	0
2	1.0	49	51	0	0
3	2.5	0	99	0	1
4	5.0	0	94	0	6

Table 2. Catalyst loading study: substrate, sodium borohydride, acetic acid (1:4:2) using varying Pd/C catalyst loading in toluene at room temperature. Results are shown for 30 minutes reaction time.
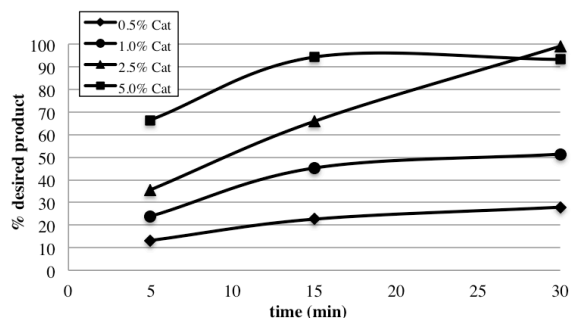

Figure 2. Catalyst loading study: substrate: sodium borohydride, acetic acid (1:4:2) using varying amounts of Pd/C catalyst in toluene.

anticipated that varying reaction temperature would give us some sense about how to improve the selectivity of the reaction for our desired products and would also, possibly, give us insight into the reaction mechanism. Results are shown in Table 3.

Saturated carbonyl compound **1** was always the main product of the reaction, however, changes in reaction temperature did alter both the overall conversion and selectivity of the reaction. As expected, lowering the reaction temp to -77 ^{o}C precluded formation of the fully reduced product within the 30-minute reaction time. However, despite the improvement in selectivity for the saturated carbonyl product, the overall conversion was

entry	Reaction Temperature (^{o}C)	% Unreacted Substrate	1 - % Desired Product Saturated Ketone C=C bond reduced	2- % Unsaturated Alcohol C=O bond reduced	3 -% Saturated Alcohol Fully Reduced
1	-77	94	6	0	0
2	0	71	29	0	0
3	25	34	63	0	2
4	75	14	69	0	17

Table 3. Temperature study: substrate, sodium borohydride, acetic acid (1:4:2) using 1.0 mol% Pd/C catalyst loading in toluene. Results are shown for 30 minutes reaction time.

significantly lowered as well. This can be understood in terms of slower reaction rates and, perhaps, more competitive binding of the C=C function in the catalyst active site than the C=O function. At a temperature of 75 °C, selectivity for the desired product was reduced as carbonyl reduction became increasingly favored. We observed a high conversion rate at this elevated reaction temperature. The distribution of products and the lack of any unsaturated alcohol **2** strongly suggests that the fully reduced saturated alcohol product **3** is produced from stepwise reduction in which the C=C bond is reduced first. Having obtained a good balance between conversion and selectivity, we decided to use a reaction temperature of 25 °C for the reduction of all α,β-unsaturated carbonyl compounds in the study.

d) Optimized method

The final optimized method derived from the three studies uses toluene as a solvent with the catalyst loaded at 2.5 mol% and a reaction temperature of 25 °C. We used these optimized conditions and the stoichiometry of 1:4:2 (substrate: sodium borohydride: acetic acid) (Scheme 7) and compared our method to two related reduction methods.
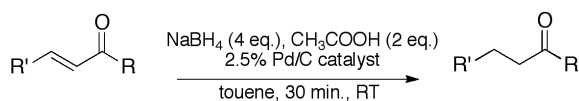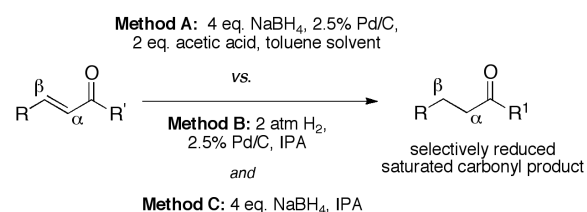
Scheme 7. Optimized reaction of α,β-unsaturated carbonyl compounds by the Pd-borohydride system.

II. Comparison study for selective reduction of α,β-unsaturated carbonyl compounds

a) Evaluation of the system for selective reduction of various α,β-unsaturated carbonyl compounds

We compared our optimized borohydride-palladium reduction method (Method A) with traditional palladium catalyzed hydrogenation in IPA at 2 atm H_2 (Method B). We also included results from reductions using sodium borohydride in IPA solvent (Method C). The three methods were evaluated for the selective reduction of both cinnamyl and non-cinnamyl type α,β-unsaturated carbonyl compounds (Scheme 8) and results of the study are shown in Table 4.

Scheme 8. Optimized reaction of α,β-unsaturated carbonyl compounds by the Pd-borohydride system.

In general, we found that traditional palladium-catalyzed hydrogenation using hydrogen gas under pressure (Method **B**) is a superior method for selective C=C reduction of most substrates. Our optimized borohydride-based approach (Method **A**), however, is competitive in some cases, especially for cinnamyl-type compounds. In the case of the cinnamyl-type compounds, it is believed that the aromatic ring proximal to the C=C bond may assist in the C=C bond in outcompeting the C=O bond for attachment to the catalyst surface. For the non-aromatic cyclohexane type substrates, the poor conversion and selectivity may be explained by the steric bulkiness of these compounds and their inability to adsorb their C=C functions on the catalyst surface (Torres, Ledesma, Jablonski, de Miguel, & Scelza, 1999; von Arx, Mallat, & Baiker, 1999). As expected, sodium borohydride by itself tends to reduce only the carbonyl function, sometimes with surprisingly good selectivity for the unsaturated alcohol.
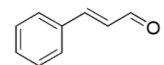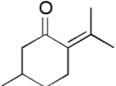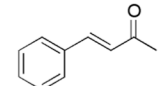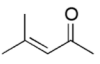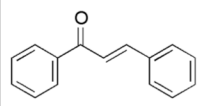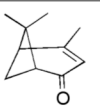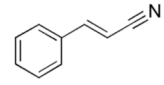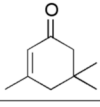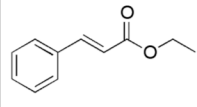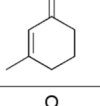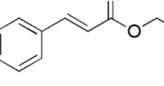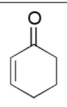
Compound	Method	% Product 1	% Product 2	% Product 3	Compound	Method	% Product 1	% Product 2	% Product 3
(cinnamaldehyde)	A	39	0	16	(pulegone)	A	40	0	0
	B	37	0	63		B	>99	0	0
	C	0	>99	0		C	0	81	0
(benzylideneacetone)	A	95	0	5	(mesityl oxide)	A	97	0	3
	B	>99	0	0		B	>99	0	0
	C	0	95	5		C	0	98	2
(chalcone)	A	98	0	0	(verbenone)	A	89	0	0
	B	54	0	45		B	>99	0	0
	C	0	0	>99		C	0	88	12
(cinnamonitrile)	A	88	0	0	(isophorone)	A	5	0	0
	B	>99	0	0		B	>99	0	0
	C	0	0	0		C	0	81	0
(ethyl cinnamate)	A	99	0	1	(3-methyl-2-cyclohexenone)	A	59	0	13
	B	>99	0	0		B	>99	0	0
	C	1	0	0		C	0	87	13
					(2-cyclohexenone)	A	75	0	23
						B	98	0	2
						C	0	30	70

Table 4. Comparison study. Method **A** – our optimized Pd-sodium borohydride method; Method **B** – traditional Pd-catalyzed hydrogenation with 2 atm H$_2$; Method **C** – sodium borohydride only. Results are shown for 30 minutes reaction time.

b) Electron Donating and Electron Withdrawing Effects

In order to explore the sensitivity of our method to electronic effects, six *para*-substituted chalcone derivatives were synthesized by Claisen-Schmidt condensation and reduced using our optimized sodium borohydride-Pd system (Scheme 9).

Results indicate that electron withdrawing cyano groups significantly lessen the reactivity, especially when near to the carbonyl. Conversely, the presence of electron-donating methoxy groups significantly accelerates the reaction (Table 5).

Such reactivity is consistent with the suspected mechanism. If a nucleophilic hydride were involved in either a *1,2* or *1,4* nucleophilic conjugate addition, then the
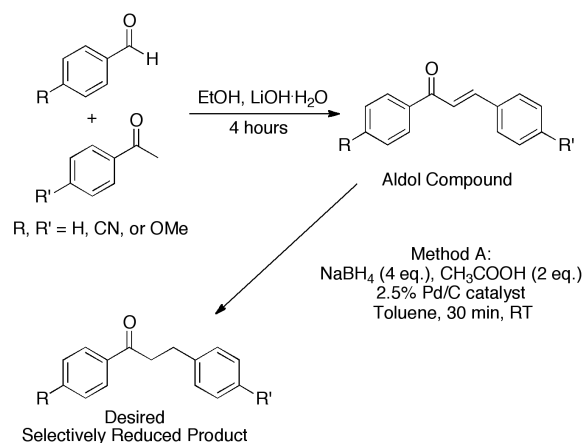
Scheme 9. Synthesis and reduction of chalcones substituted with electron donating and withdrawing groups.

electron withdrawing groups should increase reactivity by positively polarizing the carbonyl and β-carbon atoms. Instead, the significant decrease in activity with
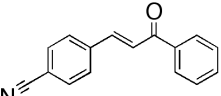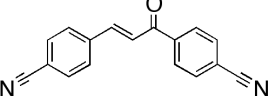
Aldol Compound (with donating groups)	% Desired Product (saturated ketone)
	34
	57
	52
	14
	3
	8

Table 5. Results for reduction of chalcones substituted with electron donating and withdrawing groups. (The saturated ketone was the sole product of these reaction.)
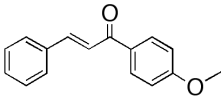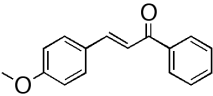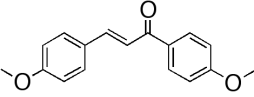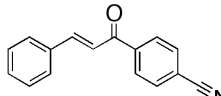
withdrawing groups and increase when donating groups are present suggests that greater electron density proximal to the C=C bond assists with its selective adsorption and reduction on the metal surface.

CONCLUSIONS

We prepared a generally optimized palladium-borohydride system for the selective reduction of chalcone and other α,β-unsaturated carbonyl compounds. Investigations into the optimal reaction parameters used chalcone as a model compound. These experiments revealed that non-polar solvents, such as toluene, work well at low catalyst loadings and room temperature to promote rapid and highly selective reduction of the C=C bond. We

speculate that the reaction operates through the palladium and acetic acid-catalyzed decomposition of borohydride to form hydrogen gas that in turn reduces the C=C bond of the α,β-unsaturated carbonyl system via palladium hydride active species along the lines of a classical Horiuti-Polyani mechanism.

The optimized reduction system was applied to the reduction of a series of cinnamyl and non-cinnamyl type α,β-unsaturated carbonyl compounds. For purposes of comparison, we compared the results obtained with our system to those using traditional Parr-style catalytic hydrogenation with a Pd/C catalyst. We also obtained results for reduction of these compounds using simple sodium borohydride with no catalyst. The three methods were evaluated for selective reduction of the α,β-unsaturated carbonyl substrates. We found that our system was particularly effective for the selective reduction of cinnamyl-type compounds, less so for cyclohexanone and other non-aromatic α,β-unsaturated carbonyl compounds. Generally speaking, traditional Parr-style catalytic hydrogenation showed superior selectivity for reduction of the C=C bond and usually gave a single pure product. In some cases, however, our borohydride-palladium system gave competitive and, in one case, superior results. When hydrogen gas tanks are not available or when high pressure catalytic hydrogenation is precluded for fear of side reaction, then this borohydride-palladium method may be a excellent alternative.

EXPERIMENTAL

Note on Pd/C Catalysts: It is important to note that, from batch to batch, supported catalysts such as Pd/C have long been recognized for variations in both activity and selectivity. Variability is thought to depend

on factors such as catalyst preparation and the formation of catalytic 'active centers' (Chaston & Sercombe, 1961). Significantly, the activity and selectivity of supported Pd catalysts are also known to be sensitive to catalyst poisoning and deactivation during storage in industrial and research laboratory atmospheres. (Young, Hartung, & Daniels, 1952) While we consistently used a Pd/C catalyst that was nominally prepared with 10% Pd by weight, we did employ catalysts from different manufacturers (Aldrich and Alfa Aesar) and did use these catalysts after they had been opened and then stored in our lab for many months. We believe that this explains the variability in results for the reduction of chalcone from one experiment to another. Nevertheless, we did use a single Pd/C catalyst source for each different study and are confident that results within each experiment (solvent study, catalyst loading study, temperature study, comparison study) are valid.

Representative Procedure for Method A (borohydride-palladium system): A 25 mL round-bottomed flask with stir bar is flushed with inert gas and charged with Pd/C catalyst (2.5 mol %), the substrate (1 mmol), and 5 mL of toluene. The flask is clamped over a mechanical stirrer and the contents are stirred. Acetic acid (2 mmol) is added in a single portion via pipette. Powdered sodium borohydride, $NaBH_4$, (4 mmol) is added in a single portion directly to the stirring heterogeneous solution (Note: Addition of the $NaBH_4$ causes the rapid evolution of small hydrogen gas bubbles). The contents of the reaction flask are left to stir in the open air at room temperature. Aliquots are removed at 30 minutes and 1 hour for analysis. Workup is conducted by quenching the aliquot with several mLs of 0.1 M HCl until no hydrogen evolution is observed. The solution is then made basic using $NaHCO_3$ (Note: pH is tested using red

litmus paper). 5 mLs of hexanes are added and the sample is shaken, then the organic layer is removed. The hexanes extraction is repeated two more times, for a total of 15 mLs. The organic layer is then dried with $MgSO_4$ and filtered through a filter pipette. Each sample is analyzed by GC/MS.

Representative Procedure for Method B (catalytic hydrogenation with palladium and hydrogen gas): A small hydrogenation flask is filled with nitrogen gas and charged with Pd/C catalyst (2.5 mol %), the substrate (1 mmol), and 10 mL of isopropyl alcohol. The flask is then loaded in a Parr shaker-style hydrogenator, placed under 2 atms of hydrogen gas, and the contents of the flask shaken for 30 minutes. Workup and analysis are as described for Method A.

Representative Procedure for Method C (just sodium borohydride in IPA): A 25 mL round-bottomed flask with stir bar is charged in open air with the substrate (1 mmol), and 5 mL of isopropyl alcohol. The flask is clamped over a mechanical stirrer and the contents are stirred. Powdered sodium borohydride, $NaBH_4$, (4 mmol) is added in a single portion directly to the stirring heterogeneous solution The contents are left to stir in the open air at room temperature. Workup as described for Method A.

Procedure for Synthesis of substituted chalcones: A 25 mL round-bottom flask with stir bar is charged in open air with the ketone (5 mmol), 6 mL ethanol, and LiOH•H_2O (10 mmol) as a basic catalyst. The flask is clamped over a mechanical stirrer and the contents stirred. The aldehyde is added dropwise and the contents are stirred for four hours and left to chill overnight. Products are diluted with ~7 mL HCl solution (1%), filtered through a vacuum, and washed with brine. (Note: 4'

cyanochalcone was prepared using 6 mL of 6 M NaOH is used in place of LiOH. The products are filtered and washed with brine or EtOH. Products are purified by recrystallization in EtOH and characterized by m.p. and GC-MS analysis.

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