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Efficient Rhodium-Catalyzed Hydrogenation of Aldehydes and Ketones

Mark J. Burk* , T. Gregory P. Harper, Jeffrey R. Lee, Christopher Kalberg
Department of Chemistry, Duke University, P.M. Gross Chemical Laboratory, Durham, NC 27706

Abstract: A cationic rhodium(I) catalyst bearing the air-stable and crystalline diphosphine 1,1'-bis-(diisopropylphosphino)ferrocene (**1**, DiPFc) allows the hydrogenation of aldehydes and ketones under mild conditions.

The preparation of alcohols through reduction of the carbon-oxygen double bond of aldehydes and ketones is one of the most fundamental and useful transformations in organic chemistry. In contrast to the multitude of effective stoichiometric reagents available for the reduction of aldehydes and ketones, very few general and efficient *catalytic* methods are known.[1] In terms of ease, efficency, and commercial viability, catalytic hydrogenation represents one of the most attractive procedures for reduction. Although several homogeneous hydrogenation catalysts have been reported for carbonyl reduction, these generally require high pressures, high temperatures, or the use of air-sensitive trialkylphosphine ligands that are not readily available.[2-5] While the advantages of hydrogenation over stoichiometric hydride reducing agents are apparent, no aldehyde or ketone hydrogenation catalyst has yet been developed into a useful synthetic tool for the practicing organic chemist.

We now report that the cationic rhodium complex [(COD)Rh(DiPFc)]$^+$OTf$^-$ bearing the air-stable and crystalline diphosphine 1,1'-bis(diisopropylphosphino)ferrocene[6] (**1**, DiPFc) behaves as a very efficient catalyst precursor for aldehyde and ketone hydrogenations. For example, benzaldehyde was smoothly converted to benzyl alcohol under mild conditions (25°C, 30 psi H_2, S/C 500, 3h) and in essentially quantitative yield. The hydrogenation of acetophenone occurred under similarly mild conditions (25°C, 60 psi H_2, S/C 450, 4 h), and again in essentially quantitative yield. In contrast, the analogous catalyst derived from 1,1'-bis(diphenylphosphino)ferrocene afforded less than 5% acetophenone reduction product under otherwise identical conditions. While 1,1'-bis(dialkylphosphino)ferrocene ligands previously have been used in olefin hydrogenations,[7] no report of their use in ketone hydrogenations has appeared.

Studies aimed at optimizing the efficiency of ketone hydrogenations revealed the influence of solvent, concentration, and pressure on the rate of acetophenone reduction. Protic solvents (i.e., MeOH, EtOH) appear to be required as incomplete conversion and catalyst inactivation were observed in solvents such as CH_2Cl_2, EtOAc, and THF. Complete conversion was observed only

at relatively high substrate concentration (≥ 0.65 M), probably due to the documented tendency of the catalyst to yield inactive hydride-bridged dimers in the absence of olefin or ketone substrates.[8] Increasing pressures led to higher rates as indicated by conversion/pressure relationships (73%/10 psi, 91%/30 psi, 95%/60 psi, 98%/90 psi) monitored over 3 h reaction time.

A wide variety of aldehydes and ketones were readily hydrogenated using the Rh-DiPFc catalyst under our standard conditions outlined above (Figure 1). Experimental details describing the hydrogenation procedure are provided as a footnote.[9] Simple acyclic ketones, cyclic ketones, β-keto esters, α-keto esters, and trifluoromethyl-substituted ketones were quantitatively converted to alcohols. For reasons that are unclear, the cyclic ketone indanone proved difficult to reduce, with ≤10 % conversion being observed over 24 h.

Aldehydes also were readily reduced to the corresponding alcohols in high yield over 3 h (Figure 1). In contrast to most known catalysts reported capable of hydrogenating aldehydes,[2] no catalyst deactivation through decarbonylation was apparent over the course of the reaction and complete conversion was observed in all cases reported.

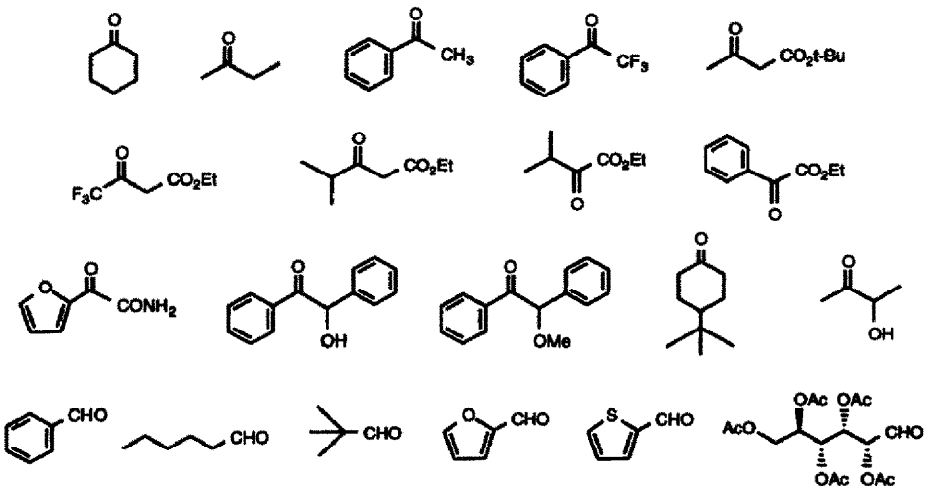
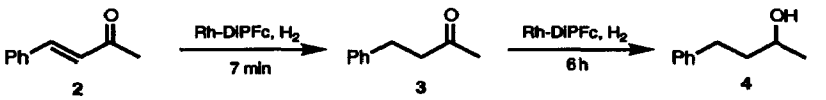


Figure 1. Range of aldehydes and ketones hydrogenated with Rh-DiPFc catalyst.

Diastereoselective hydrogenation of several chiral ketones using the Rh-DiPFc catalyst was examined. For example, benzoin and 3-hydroxy-2-butanone were reduced to 5/1 and 2/1 syn/anti diol product mixtures, respectively. Similarly, the methoxy ether of benzoin was reduced to a 2/1 syn/anti product mixture. Hydrogenation of 4-*tert*-butylcyclohexanone afforded the *trans*-and *cis*-alcohol products in an 86:14 ratio. Assignment of product stereochemistry was based on comparison of ^{1}H and ^{13}C NMR spectra and GC retention times with those of authentic alcohols.

The Rh-DiPFc catalyst also has been found to be an excellent catalyst for the reduction of other unsaturated groups such as olefins (including tetrasubstituted olefins), imines, and N-acylhydrazones. In an effort to briefly explore the issue of chemoselectivity, hydrogenation of benzalacetone (2) was examined (eq 1). We found that hydrogenation of the C=C double bond occured rapidly, and with complete chemoselectivity, over 7 min at 60 psi H_2 to provide the saturated ketone (3). Further reduction to the saturated alcohol (4) occurred over 6 h.



(eq 1)

The present hydrogenations were equally effective with isolated catalyst or *in situ* catalyst generated through the addition of DiPFc (1.05 eq) to $[(COD)_2Rh]^+OTf^-$ (commercially available from Strem Chemicals, Inc.) in methanol. No hydrogenation was observed with $[(COD)_2Rh]^+OTf^-$ in the absence of DiPFc ligand. Like the DiPFc ligand, the isolated solid Rh-DiPFc catalyst is fairly stable to oxygen and moisture. Catalyst left exposed to the atmosphere for 2 days showed no loss of catalytic activity in the reduction of acetophenone. This feature should greatly increase the general utility of the Rh-DiPFc catalyst system. While the solid catalyst is generally impervious to oxygen (prolonged storage under nitrogen is recommended), relatively rapid reaction with oxygen occurs in solution and leads to catalyst deactivation. Accordingly, suitably degassed MeOH should be used for hydrogenation reactions involving the Rh-DiPFc catalyst.

Relative to olefin hydrogenations,[10] the mechanism of ketone hydrogenations remains relatively obscure. Our ability to hydrogenate 1,1,1-trifluoroacetophenone and ethyl benzoylformate indicates that the hydrogenation does not proceed through an enol tautomer. No incorporation of deuterium into the carbon skeleton of the product was observed when the hydrogenation was performed in CD_3OD. Coordinative unsaturation at Rh appears to be required as the addition of 1 eq of PPh_3 to the Rh-DiPFc catalyst completely inhibited the reaction.

We previously have noted that no efficient hydrogenation catalyst possessing a diphosphine with a two-carbon bridge has yet been reported.[11] This may be due to a requirement that the diphosphine ligand accomodate various coordination geometries, or span the equatorial sites of an intermediate trigonal bipyramid, during the catalytic cycle. Alternatively, loss of one arm of the chelating diphosphine may be required, although kinetic results of Tani and Otsuka suggest that this process is unlikely even when butano-bridged diphosphines are used in ketone hydrogenations.[5b] On the basis of our studies, as well as those of others,[2-5] we believe that two features of diphosphine ligands have emerged as important in terms of catalytic efficiency in ketone hydrogenations: 1.) backbone flexibility; and 2.) electron-rich (di- or trialkyl-substituted) phosphorus atoms. The DiPFc ligand possesses both properties, which may explain the high activity of this catalyst system.

We have outlined the utility of a readily accessible rhodium hydrogenation catalyst bearing the electron-rich diphosphine DiPFc (1). The Rh-DiPFc catalyst proved highly efficient for reduction of a variety of aldehydes and ketones under mild conditions. Given the simplicity of the process and the ease of workup, wide application of this catalyst for carbonyl reductions may be expected. We currently are extending these studies beyond the Rh-DiPFc catalyst to chiral (dialkylphosphino)-ferrocenes for asymmetric ketone hydrogenations.

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9. General Hydrogenation Procedure: A Fisher-Porter bottle was charged with ketone (2.02 mmol), preformed or *in situ* generated [(COD)Rh(DiPFc)]$^+$OTf$^-$ (4.5 x 10^{-3} mmol, 0.22 mol %), and degassed MeOH (3 mL) under nitrogen. After five vacuum/H_2 cycles to remove air from the hydrogen lines, the reaction was pressurized to 30-60 psi H_2. The reaction was allowed to proceed until no further H_2 uptake was observed (≤ 6 h). The reaction was then concentrated, the residue was passed through a short plug of silica to remove catalyst, and the filtrate was concentrated to provide the product alcohol directly. In all cases reported, complete reduction to alcohol was confirmed by TLC, GC, ^{1}H and ^{13}C NMR spectroscopy.
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