Catalytic Transfer Hydrogenation of Ketones with $KHCr(CO)_5/HCO_2H/Et_3N$ Systems[+]

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In the presence of a HCO_2H/Et_3N (1:1) mixture, $KHCr(CO)_5$ is an efficient catalyst precursor for the transfer hydrogenation of ketones in THF at room temperature. $KHCr(CO)_5$ is also a stoichiometric reagent for the selective reduction of the carbon–carbon double bond of α,β-unsaturated ketones.

Introduction

Main-group hydrides, such as the well-known boron and aluminium hydrides, are widely used in organic synthesis as reducing agents for a large range of functional groups and derivatives have been designed which exhibit very useful chemoselectivities.[1] These reagents must be used in stoichiometric quantities. In contrast, transition-metal hydrides are much less widely used, even though a large number of easily accessible derivatives are available. These compounds are interesting alternatives because of the possibility of using them in catalytic amounts in the presence of molecular hydrogen or of a hydrogen transfer agent.[2] As an extension of our work on carbonylhydridoferrates,[3,4] we recently became interested in the chromium series, and we developed a very easy and reproducible preparation of $K^+[HCr(CO)_5]^-$.[5]

The reactivity of $[PPN]^+[HCr(CO)_5]^-$ {$[PPN]^+$ = bis(triphenylphosphoranylidene)ammonium} has been previously investigated by Darensbourg et al.[6–8] This reagent has been shown to reduce selectively acid chlorides into aldehydes without further reduction to alcohols.[7] $[PPN]^+[HCr(CO)_5]^-$ itself is also inactive towards ketones, but becomes an efficient reducing agent in the presence of one equivalent of acetic acid (H^+ assistance and in situ protonolysis).[8]

Two catalytic systems involving carbonylchromates and molecular hydrogen have also been reported for the hydrogenation of ketones. Firstly, the system $Cr(CO)_6$/MeONa in methanol is active at 100–120°C under 100 bar of H_2.[9] Secondly, the complex $[PPN]^+[Cr(CO)_5(OAc)]^-$ is an active catalyst precursor for the hydrogenation of ketones in THF at 125°C under 40 bar of H_2.[10] In these catalytic reactions, $[HCr(CO)_5]^-$ is believed to be the active species.

To the best of our knowledge, no report has been published of the use of carbonylchromium complexes as catalyst precursors for the reduction of ketones by hydrogen transfer from easy-to-handle hydrogen donors.[11] Such reactions do not require the use of high-pressure reactors.

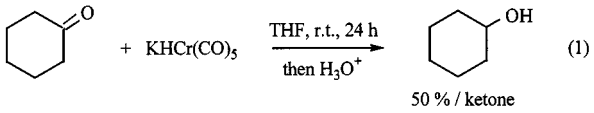
We report here that $K^+[HCr(CO)_5]^-$ (**1**) does react with ketones in THF at room temperature under *mild* conditions. Moreover, in the presence of the HCO_2H/Et_3N combination as a hydrogen transfer agent, *catalytic* reduction to the corresponding alcohols is achieved under atmospheric pressure at room temperature.

Results and Discussion

Stoichiometric Experiments

We have previously reported that $K^+[HFe(CO)_4]^-$ does not reduce normal ketones in the absence of a Brønstedt acid, either in THF or in methanol.[12] In contrast, we have now found that the chromium analogue **1** reacts with ketones to give the corresponding alcohol *in the absence of any Brønstedt acid*.

Treating cyclohexanone with **1** in THF at room temperature for 24 h resulted in 50% reduction (GC analysis) to cyclohexanol after hydrolysis of the reaction medium.



(1)

There is thus a significant difference in reactivity between $K^+[HCr(CO)_5]^-$ and $[PPN]^+[HCr(CO)_5]^-$ (vide supra). This phenomenon may be ascribed to K^+ assistance, as previously demonstrated for the hydrogenation of ketones with potassium hydrido(phosphane)ruthenate complexes.[13] From a more general point of view, and as previously observed for $[HFe(CO)_4]^-$,[4] the reactivity of $[HCr(CO)_5]^-$ seems to be strongly dependent on the associated cation, due to ion-pairing effects.[14] For example, it has been reported that $[PPN]^+[HCr(CO)_5]^-$ exchanges with MeOD (or D_2O) in THF at room temperature to give the corresponding deuteride $[PPN]^+[DCr(CO)_5]^-$[8] whereas $[Et_4N]^+[HCr(CO)_5]^-$ has been reported to react vigorously with MeOH at room temperature with H_2 evolution and formation of the dinuclear complex $[HCr_2(CO)_{10}]^-$[9] (however,

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the reaction with 1-phenylethanol requires heating to 75°C). Similarly, we observed that, at room temperature, $K^+[HCr(CO)_5]^-$ slowly reacts with cyclohexanol in THF with formation of the dinuclear $[HCr_2(CO)_{10}]^-$ species.

If the reaction of **1** with cyclohexanone is conducted for longer reaction times (120 h), the reduction yield is not increased. After 24 h of reaction, ^{1}H-NMR analysis of the reaction medium (after evaporation of the solvent and redissolution in [D$_8$]THF) indicates that the starting complex **1** ($\delta_{CrH} = -7.05$) had been consumed and that the dinuclear hydrido anion $[HCr_2(CO)_{10}]^-$ ($\delta_{CrH} = -19.56$) is the only detectable hydride species. ^{13}C-NMR spectroscopy confirms the presence of $[HCr_2(CO)_{10}]^-$ ($\delta_{CO} = 222.4$ and 227.3) and suggests the presence of $[Cr_2(CO)_{10}]^{2-}$ ($\delta_{CO} = 243.8$ and 244.1).[15] The IR spectrum mainly exhibits the characteristic bands of $KHCr_2(CO)_{10}$ [2030 cm^{-1} (w), 1940 (vs) and 1882 (br.)], but also less intense bands at 2050 cm^{-1} (vw), 1919 (m), 1880 (br.) and 1766 (m) which may be ascribed to $[Cr_2(CO)_{10}]^{2-}$ or mixture of the latter with $[ROCr(CO)_5]^-$ (R = cyclohexyl) on the basis of literature data.[8][9] Unexpectedly, a ν_{OH} band corresponding to free cyclohexanol was also observed *before* hydrolysis of the reaction medium.

Control experiments indicated that the dinuclear hydride $KHCr_2(CO)_{10}$ reduces cyclohexanone in less than 5% yield after 72 h at room temperature in THF. It is thus reasonable to propose that **1** is the active species for the reduction. The first step of the reaction could occur by hydride transfer, generating an alkoxocarbonylchromate species (Equation 2).[9]

$$[HCr(CO)_5]^- + R^1R^2C{=}O \rightleftharpoons [R^1R^2CHOCr(CO)_5]^- \quad (2)$$

According to literature data, alkoxocarbonylchromates may further react with $[HCr(CO)_5]^-$, to give $[Cr_2(CO)_{10}]^{2-}$ (Equation 3)[9] and/or $[HCr_2(CO)_{10}]^-$ (Equation 4).[8]

$$[R^1R^2CHOCr(CO)_5]^- + [HCr(CO)_5]^- \longrightarrow R^1R^2CHOH + [Cr_2(CO)_{10}]^{2-} \quad (3)$$

$$[R^1R^2CHOCr(CO)_5]^- + [HCr(CO)_5]^- \longrightarrow [R^1R^2CHO]^- + [HCr_2(CO)_{10}]^{2-} \quad (4)$$

Quantitative conversion of the ketone thus requires another in situ evolution of the alkoxochromium complex, for example by protonation by HX (Equation 5) under conditions where $[HCr(CO)_5]^-$ does not decompose.

$$[R^1R^2CHOCr(CO)_5]^- + HX \longrightarrow R^1R^2CHOH + [XCr(CO)_5]^- \quad (5)$$

For a catalytic version, the carbonylhydridochromate $[HCr(CO)_5]^-$ has to be regenerated from $[XCr(CO)_5]^-$. This could be expected from the formato complex $[HCO_2Cr(CO)_5]^-$ which has been shown to undergo a rapid decarboxylation process according to Equation 6.[16]

$$[HCO_2Cr(CO)_5]^- \rightleftharpoons [HCr(CO)_5]^- + CO_2 \quad (6)$$

Formic acid itself cannot play the role of HX for the introduction of the formate moiety. Indeed, reaction of cyclohexanone with stoichiometric amounts of $KHCr(CO)_5$ in the presence of 1 equiv. of formic acid in THF resulted in less than 5% reduction to cyclohexanol after 24 h at room temperature (the same result was obtained by using acetic acid). These results are in contrast to the reported 95% yield reduction of cyclohexanone with $[PPN]^+[HCr(CO)_5]^-$/AcOH for 4 h in THF.[8] Both formic and acetic acids are too strong for the $KHCr(CO)_5$ base in THF, and preferentially lead to $KHCr_2(CO)_{10}$. However, when the strength of formic acid is moderated by the presence of triethylamine, the stoichiometric reduction of cyclohexanone (ketone/$KHCr(CO)_5$/HCO_2H/Et_3N in a 1:1:1:1 ratio) leads to a reduction yield of up to 65% after 24 h at room temperature. Using a 1:1:5:5 ratio of reagents resulted in a quantitative reduction to cyclohexanol after 6 h. By comparison, Noyori et al. recently reported the use of a different HCO_2H/Et_3N combination (5:2 azeotropic mixture[17]) for the ruthenium(II)-catalysed asymmetric transfer hydrogenation of ketones.[18]

Control experiments indicated that the formate ion alone [which could have been useful for displacing the unsaturated "Cr(CO)$_5$" moiety from the alkoxochromate, thus preventing $[HCr(CO)_5]^-$ consumption (Equations 3 and 4)] is not sufficient to promote the observed reactivity. Indeed, the association $KHCr(CO)_5/HCO_2K$ reduces cyclohexanone in the same yield than **1** alone (50%, 24 h at room temperature).

Catalytic Experiments

The system $KHCr(CO)_5/HCO_2H/Et_3N$ (1:5:5 ratio) was tested for the catalytic reduction of cyclohexanone. In the presence of stoichiometric amounts of HCO_2H/Et_3N as a hydrogen transfer agent, cyclohexanone is almost quantitatively (95%) reduced to cyclohexanol with 20% $KHCr(CO)_5$ after 24 h at room temperature in THF. Using lower amounts of **1** is also possible (10% $KHCr(CO)_5$: 83% yield after 24 h; 5% $KHCr(CO)_5$: 70% yield after 24 h) but complete conversion of cyclohexanone is achieved only after several days.

Performing the catalytic reaction at 0°C resulted in a decrease in reaction rate. However, if after 24 h at 0°C the temperature is raised to room temperature, the expected catalytic activity is restored. For reactions conducted at 60°C, the cyclohexanol yield is lower than 50% (24 h) and no longer evolves, suggesting that the catalytically active species have been destroyed competitively.

The above system was tested for the catalytic reduction of some representative ketones at room temperature (Table 1). For comparison, the experiments were stopped after 24 h.

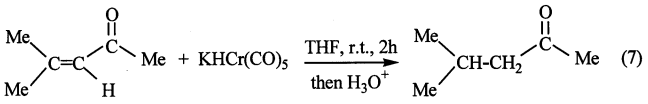
As expected from literature data on the reduction of ketones with hydridometallates,[8,9,19] cyclohexanones are more rapidly reduced than methyl ketones. In the case of 4-*tert*-butylcyclohexanone, the preponderant formation of the *trans* alcohol has previously been explained by the steric demand of the "$OCr(CO)_5$" group of the alkoxocarbonylchromate formed in the first step of the reaction (Equation 2).[9] This explanation also stands for the present system.

Table 1. Catalytic reduction of ketones with 20% $KHCr(CO)_5$ in the presence of HCO_2H/Et_3N[a,b]

	conversion (%)[c]	products[d] (yield%)[c]
2-hexanone	38	2-hexanol (38)
acetophenone	25	1-phenyl ethanol (25)
3-methyl-2-butanone	45	3-methyl-2-butanol (45)
cyclohexanone	95	cyclohexanol (95)
4-*tert*-butylcyclo-hexanone	80	4-*tert*-butylcyclohexanol (80)[e]
mesityl oxide	20	4-methyl-2-pentanone (20)

[a] Reactions conducted with 100 mg of $KHCr(CO)_5$ (0.43 mmol) in THF (10 mL) for 24 h at room temp. – [b] Ketone/$KHCr(CO)_5$/HCO_2H/Et_3N = 1:0.2:1:1. – [c] Determined by GC analysis with internal standards. – [d] Identified by GC retention times and GC-MS analysis. – [e] *cis*/*trans* ratio = 33:67.

The selective reduction of the carbon–carbon double bond of mesityl oxide to give 4-methyl-2-pentanone (Table 1) is noteworthy. This specificity of $KHCr(CO)_5$ has been confirmed by a stoichiometric experiment (*in the absence the HCO_2H/Et_3N combination*) leading to 4-methyl-2-pentanone in > 95% yield after 2 h at room temperature (Equation 7).



(7)

For this reaction, $KHCr(CO)_5$ is more reactive than $KHFe(CO)_4$ but exhibits the same chemoselectivity. Indeed, it has been shown that *under the same conditions*, $KHFe(CO)_4$ reduces mesityl oxide to give 4-methyl-2-pentanone in less than 25% yield after 24 h [literature data indicate that, in the presence of excess $Fe(CO)_5$, $NaHFe(CO)_4$ reduces mesityl oxide to 4-methyl-2-pentanone in 96% yield after 24 h *at 60°C* in MeOH[20]].

In control experiments, it has been shown that $KHCr_2(CO)_{10}$ (1 equiv.) also selectively reduces mesityl oxide under the conditions of Equation 7, but 4-methyl-2-pentanone was formed in less than 10% after 2 h. Thus, for this reaction, $KHCr(CO)_5$ is also much more reactive than $KHCr_2(CO)_{10}$. This order of reactivity between the mono- and dinuclear carbonylhydridochromates is in contrast to what has been reported in the iron series where $NaHFe_2(CO)_8$ is at least 26 times more reactive than mononuclear $NaHFe(CO)_4$ for the reduction of α,β-unsaturated ketones.[2,20,21]

Finally, exploratory experiments were conducted on a possible enantioselective catalytic system based on the chiral amine, quinine, instead of Et_3N. The system $KHCr(CO)_5$/(–)-quinine/HCO_2H (1:5:5 ratio.) reproducibly reacts with acetophenone (5 equiv.) in a catalytic manner to yield 1-phenylethanol in 45% yield and 10% ee (120 h in THF at room temperature).

Work is in progress to obtain a better mechanistic understanding of the observed reactivity of $KHCr(CO)_5$ (in particular, a catalytic cycle is to be sought) and to extend its use as reagent or catalyst in organic synthesis.

Experimental Section

General: All reactions were performed under argon using standard Schlenk tube techniques. THF was distilled under argon from Na/benzophenone. – NMR: Bruker AC 200 or AMX 400 apparatus. – IR: Perkin–Elmer 1725X FT-IR spectrometer with CaF_2 windows (0.5 mm). – GC: Hewlett–Packard HP 5890 apparatus equipped with a 30-m capillary Rt-β-DEXm chiral column. – GC MS: Hewlett–Packard HP 6890 apparatus (EC Wax, 30-m capillary column) equipped with an HP 5973 M ion detector. – $KHCr(CO)_5$[5] and $KHFe(CO)_4$[22] were prepared from the corresponding $Cr(CO)_6$ or $Fe(CO)_5$ and technical KOH, according to the reported procedures. $KHCr_2(CO)_{10}$ was prepared as follows. A solution of 86% KOH (0.290 g, 4.55 mmol) in 7.5 mL of absolute ethanol was added to 20mL of a CH_2Cl_2 solution of $Cr(CO)_6$ (0.500 g, 2.27 mmol). After stirring for 10 min, the solution was concentrated to 4 mL. Water (5 mL) was added and the solution stirred for 0.5 h at room temp. THF (2 × 10 mL) was added and each time concentrated to dryness to remove any trace of water. The resulting solid was dissolved in THF (20 mL), the solution filtered under argon, and concentrated to dryness to leave an orange solid (0.434 g, 90% yield). – IR (THF) $\tilde{\nu}$ = 2030 cm^{-1} (w), 1940 (s) and 1878 (vs). – ^1H NMR (CD_3CN, 200 MHz): δ = –19.56 (s).

Stoichiometric Reductions of Ketones: The general procedure is exemplified for the reduction of cyclohexanone. A solution of cyclohexanone (223 μL, 2.16 mmol) and nonane (138 mg, 1.08 mmol) in THF (10 mL) was cannulated to solid $KHCr(CO)_5$ (500 mg, 2.16 mmol). After stirring for 24 h at room temp., the solution was treated with 1 N HCl (10 mL) and diethyl ether (10 mL) was added. The aqueous phase was then extracted with diethyl ether (2 × 10 mL) and the ethereal phase analysed by GC. For complementary experiments (see text), additives (HCO_2H, AcOH, HCO_2K, or HCO_2H/Et_3N mixtures) were dissolved in the THF solution containing cyclohexanone before it was cannulated to solid $KHCr(CO)_5$.

Catalytic Reduction of Ketones: The general procedure is exemplified in the case of cyclohexanone. Triethylamine (300 μL, 2.16 mmol) and technical (95–97%) formic acid (82 μL, 2.16 mmol) were added to a solution of cyclohexanone (223 μL, 2.16 mmol) and nonane (138 mg, 1.08 mmol) in THF (10 mL). The resulting solution was then cannulated into a Schlenk flask containing solid $KHCr(CO)_5$ (100 mg, 0.43 mmol) and a stirring bar. The flask was closed with a glass stopper and the solution magnetically stirred at room temp. Aliquots (0.5 mL) were hydrolysed with dilute HCl (0.5 mL), extracted with diethyl ether (0.5 mL) and analysed by GC.

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