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Hydrogenation without a Transition-Metal Catalyst: On the Mechanism of the Base-Catalyzed Hydrogenation of Ketones

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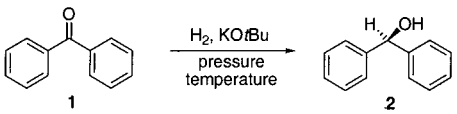
Abstract: The hydrogenation of unsaturated organic substrates such as olefins and ketones is usually effected by homogeneous or heterogeneous transition-metal catalysts. On the other hand, a single case of a transition-metal-free and purely base-catalyzed hydrogenation of ketones was reported by Walling and Bollyky some 40 years ago. Unfortunately, the harsh reaction conditions (ca. 200 °C, >100 bar H_2, potassium *tert*-butoxide as base) limit the substrate spectrum of this reaction to robust, nonenolizable ketones such as benzophenone. We herein present a mechanistic study of this process as a basis for future rational improvement. The base-catalyzed hydrogenation of ketones was found to be irreversible, and it shows first-order kinetics with respect to the substrate ketone, hydrogen, and catalytic base. The rate of the reaction depends on the type of alkali ion present (Cs > Rb ≈ K ≫ Na ≫ Li). Using D_2 instead of H_2 revealed a rapid base-catalyzed isotope exchange/equilibration between the gas phase and the solvent as a concomitant reaction. The degree of deuteration of the product alcohols did not indicate a significant kinetic isotope effect. It is proposed that both ketone reduction and isotope exchange proceed via similar six-membered cyclic transition states involving the $H_2(D_2)$-molecule, the alkoxide base, and the ketone (solvent alcohol in the case of isotope exchange). Mechanistic analogies are pointed out which apparently exist between the base-catalyzed hydrogenation of ketones studied here and the Ru-catalyzed asymmetric ketone hydrogenation developed by Noyori. In both cases, heterolysis of the hydrogen molecule appears to be assisted by a Brønsted-base (i.e., alkoxide), the latter being bound to the substrate ketone or the catalyst ligand, respectively, by a bridging Lewis-acidic alkali ion.

Introduction

Hydrogenation is one of the most important chemical processes, both in industry and in the synthesis-oriented research laboratory. Numerous heterogeneous and homogeneous transition-metal catalysts have been developed to remarkable perfection, with applications ranging from the mass production of hydrogenated bulk materials to the synthesis of enantiomerically pure chemicals by asymmetric hydrogenation.[1−5] On the other hand, a single transition-metal-free hydrogenation of an organic substrate − in this case of benzophenone (**1**) − was observed already some 40 years ago by Walling and Bollyky. At high temperatures and H_2-pressure, and in the presence of potassium *tert*-butanolate, the formation of benzhydrol (**2**) was reported (Scheme 1).[6] Clearly, the harsh reaction conditions (ca. 200 °C, strong base) limit the substrate spectrum to stable, nonenolizable ketones such as benzophenone. Nevertheless, a mechanism-based improvement of this hydrogenation procedure might eventually lead to milder reaction conditions and thus to broader applicability. With this in mind, we found it worthwhile to study the base-catalyzed hydrogenation in detail. In summary, a mechanistic proposal for this intriguing transformation could be derived on the basis of kinetic data, as well as on structural variations of substrate and base. As it turned out, some mechanistic similarities to the Ru-catalyzed asymmetric hydrogenation of ketones developed by Noyori et al. apparently exist.[5,7,8]

Scheme 1



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(1) Brown, J. M. Hydrogenation of Functionalized Carbon−Carbon Double Bonds. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, Heidelberg, 1999; pp 121−182.
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(6) Walling, C.; Bollyky, L. *J. Am. Chem. Soc.* **1964**, *86*, 3750−3752; **1961**, *83*, 2968−2969.
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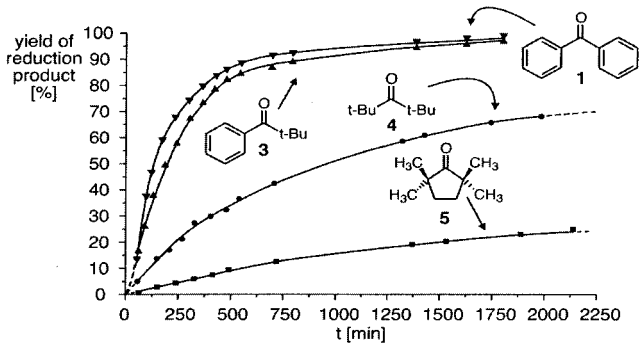


Figure 1. Time course of the base-catalyzed hydrogenation of various ketones. Reaction conditions: 210 °C, 135 bar H_2, *t*-BuOH, 20 mol % *t*-BuOK.

Results

We first concentrated on the reproduction of the observation made by Walling and Bollyky (WB).[6] Thus, the catalytic reduction of benzophenone (**1**) to benzhydrol (**2**) in *tert*-butanol as solvent was followed as a function of time. In the presence of 20 mol % of potassium *tert*-butanolate and 135 bar H_2-pressure at 210 °C, a final yield of ca. 95% benzhydrol (**2**) was reached after ca. 25 h (Figure 1). This result is in good agreement with the data given by WB (98% after 25 h).[6] In addition, our capillary GLC analysis revealed the formation of minor quantities of diphenylmethane (2−4%). No reduction occurred in the absence of base or when hydrogen was exchanged for argon (at identical pressure). The latter controls (not reported by WB) unambiguously established that H_2 is indeed the reductant. We were delighted to see that other nonenolizable ketones such as pivalophenone (**3**), di-*tert*-butyl ketone (**4**), or 2,2,5,5-tetramethylcyclopentanone (**5**) could cleanly be hydrogenated as well, albeit at lower rates in the cases of the aliphatic substrates **4** and **5**. As will be discussed later, the higher reactivity of the phenone substrates **1** and **2** may be interpreted by cation−π interaction of the alkali ion and the phenyl residue(s) involved.

When the solvent *tert*-butanol was exchanged for diglyme, our experiments yielded results in contrast to those reported by WB. When rigorously purified diglyme was employed, no transformation of the substrate benzophenone (**1**) occurred at all.[9] In unpurified "off the shelf" diglyme, the substrate benzophenone (**1**) was largely converted to benzoic acid (ca. 50%, in addition to ca. 8% triphenylmethanol), independent of the presence or absence of hydrogen. The conversion of benzophenone (**1**) to these products could be induced in absolute diglyme by addition of catalytic amounts of the radical initiator AIBN. Apparently, a hitherto unknown radical chain conversion of the ketone occurs that requires both a base and a radical initiator.[10] Further experiments thus concentrated exclusively on *tert*-butanol as solvent.

Kinetic Studies, Variation of Hydrogen Pressure and Temperature. As expected, lowering of the hydrogen pressure from 135 bar (Figure 2, trace 1) to 45 bar (Figure 2, trace 2) resulted in a reduction of the reaction rate.[11] When the hydrogenation was started at 45 bar and the H_2-pressure was increased to 135 bar after ca. 12 h, the product formation was accelerated, and the reaction profile switched almost perfectly from the original 45 bar trace to the 135 bar curve (Figure 2, trace 3). However, subsequent release of pressure (after ca. 24 h) did not reverse the reaction (Figure 2, trace 3). This indication of *irreversibility* was further supported by the finding that treatment of the product benzhydrol (**2**) with potassium *tert*-butanolate under "45 bar conditions" did not give rise to significant quantities of benzophenone (≤5%).

Performing the hydrogenation of benzophenone in the presence of potassium *tert*-butanolate at different temperatures revealed that this process actually follows biphasic kinetics. At 100 °C, the product formation leveled off at ca. 15% conversion (Figure 3, trace 2). At 150 °C, a comparatively fast initial reduction was followed by a slow but steady increase of the benzhydrol concentration (Figure 3, trace 4). Finally, at 210 °C, the "normal" smooth and almost quantitative reduction of benzophenone (**1**) occurred (Figure 3, trace 5). The conversion achieved at 100 °C corresponds to somewhat less than one turnover of substrate per *tert*-butanolate (20 mol %). We assume that at this temperature, potassium *tert*-butanolate is the only

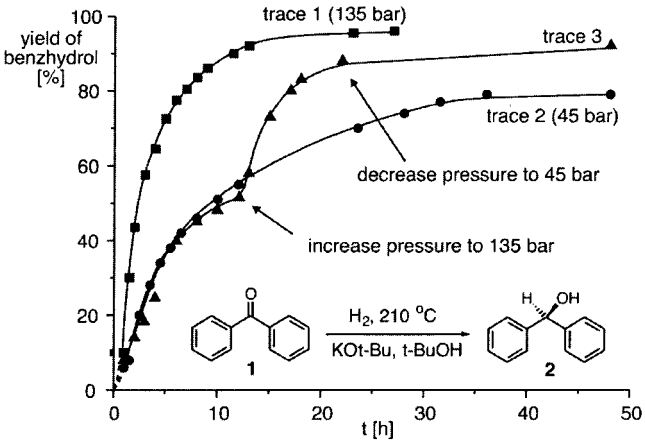


Figure 2. Base-catalyzed hydrogenation of benzophenone (**1**) at various pressures.

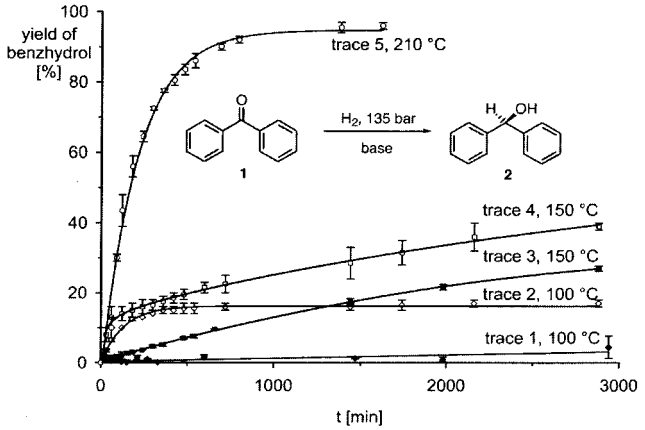


Figure 3. Effect of temperature and type of base (20 mol % in all cases) on the base-catalyzed hydrogenation of benzophenone (**1**). Traces 1,3, $KOCHPh_2$; traces 2,4,5, KO*t*-Bu.

(9) For example, WB reported a 52% yield of benzhydrol (**2**) after 18 h at 170 °C, 100 bar H_2 pressure, 20 mol % of *t*-BuOK (ref 6).

(10) For example, the radical initiator could oxidize the hemiacetal anion which may be formed in small quantities from benzophenone (**1**) and *tert*-butanolate to an alkoxyl radical. Intramolecular H-abstraction from a *tert*-butyl methyl group (similar to a Norrish type II reaction), β-fission with loss of isobutene, and extrusion of a phenyl radical furnish benzoic acid and propagate the radical chain. This mechanistic assumption also explains the formation of triphenylmethanol, that is, the addition of a phenyl moiety to benzophenone.

(11) Final yields of benzhydrol (**2**): 135 bar, 95%; 90 bar (not shown), 90%; 45 bar, 79%.

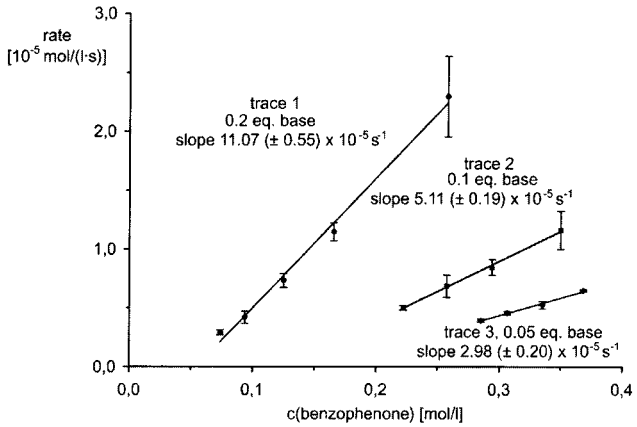


Figure 4. Reaction rates as a function of benzophenone and base concentrations (210 °C, 135 bar H_2).

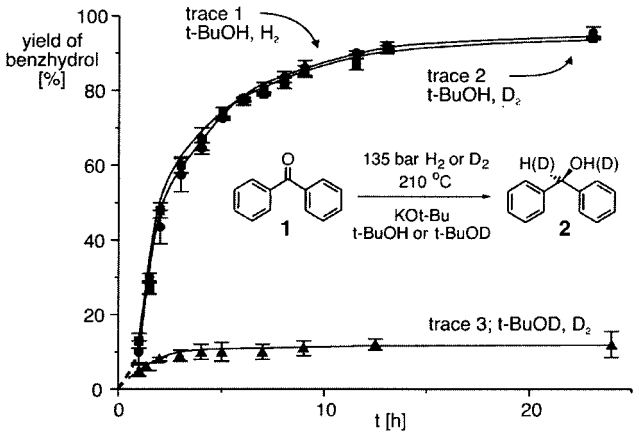


Figure 5. Isotope effect in the base-catalyzed hydrogenation of benzophenone (**1**).

catalytically active base. At higher temperature, the product benzhydrolate becomes effective in heterolyzing H_2 as well, and catalytic turnover results. This assumption is in agreement with the lower basicity of benzhydrolate as compared to that of *tert*-butanolate.[12] Obviously, the biphasic behavior poses serious problems for a kinetic analysis of the overall process. We therefore resorted to using benzhydrolate as the base right from the start of the reactions. As expected, only very slow conversion occurs under these conditions at 100 °C (Figure 3, trace 1). At 150 °C, clean monophasic reduction of benzophenone sets in, at a rate identical to that of the slow region of the biphasic curve observed in the presence of KO*t*-Bu (trace 3).[14]

Kinetic Orders in Benzophenone, Hydrogen, and Base. With the monophasic reaction conditions in hand, we proceeded to the determination of the kinetic orders of substrates and catalyst. In Figure 4, reaction rates are plotted against the corresponding concentrations of substrate, that is, benzophenone (**1**).[15] For trace 1, 20 mol % of base was employed, whereas traces 2 and 3 summarize the analogous experiments done with 10 and 5% of potassium benzhydrolate, respectively. Figure 4 nicely illustrates the linear relationship between substrate concentration and reaction rate; that is, the reduction is first order in benzophenone (**1**).

Furthermore, the rate constants found at base loadings of 20, 10, and 5 mol % (Figure 4, slopes of traces 1, 2, and 3) are proportional to the base concentrations. In other words, the reduction is also first order in base.[16] Finally, the dependence of the reaction rate on the hydrogen pressure was studied at 135, 90, and 45 bar (210 °C, 20 mol % of potassium benzhydrolate). Quite similar to the effect of lowering the base concentration (Figure 4), lowering of the hydrogen pressure resulted in a proportional decrease of reduction rate (graph not shown). Consequently, the reaction appears to be first order also in hydrogen.

Effect of the Alkali Ion on the Rate of Hydrogenation. For comparison, the hydrogenation of benzophenone (**1**) was carried out in the presence of lithium, sodium, potassium, rubidium, and cesium benzhydrolate, respectively (20 mol % in all cases). At 210 °C and 135 bar H_2, K and Rb proved equally active (relative initial rate = 100), whereas the Cs base was even slightly faster (ca. 105). Sodium benzhydrolate proved much less active (relative initial rate ca. 50), followed by lithium (relative initial rate ca. 7). In the case of cesium, the reduction of benzophenone (**1**) was complete after 7 h. When the latter reaction mixtures were analyzed after 24 h at 210 °C and 135 bar H_2, a minor amount of diphenylmethane was found as well (ca. 1%). Some reduction of benzophenone (**1**) to benzhydrol (**2**) also occurred in the presence of 20 mol % KOH (22% after 24 h), whereas KOAc was completely inactive.

Exchange of Hydrogen for Deuterium. When hydrogen was exchanged for deuterium, the kinetic course of the hydrogenation of benzophenone (**1**) was indistinguishable from that in the presence of H_2 (Figure 5, traces 1, 2). In the isolated product benzhydrol (**2**), ^{1}H- and ^{13}C NMR indicated D-incorporation at CH(D)-OH of ca. 60%, and not quantitative, as originally expected. This result pointed to a concomitant base-catalyzed exchange between the gas phase and the protic solvent. Such exchange phenomena are well documented in the literature.[17] To test the validity of our assumption, the deuterium content of the solution was monitored by ^{1}H NMR, in the presence (Figure 6, trace 1) and absence (Figure 6, trace 2) of the substrate benzophenone (**1**). As shown in Figure 6, rapid isotope exchange between the gas phase and the solution occurs, independent of the presence/absence of the substrate ketone. After ca. 2 h at 210 °C and 135 bar [ca. 1/10 of the time needed for the full conversion (i.e., hydrogenation) of benzophenone (**1**)], equilibrium is reached at a *t*-BuOD/*t*-BuOH ratio of ca. 6:4. We furthermore analyzed the isotopic composition of the gas phase by means of low-temperature GC at equilibrium conditions.[18] The molar ratio of H_2:HD:D_2 was found to be 1.0:2.1:3.04 (±0.05). Finally, the reduction of benzophenone (**1**) with D_2

(12) The pK_a of benzhydrol (**2**) is ca. 2−3 units lower than that of *tert*-butanol: ref 13.
(13) (a) Arnett, E. M.; Small, L. E. *J. Am. Chem. Soc.* **1977**, *99*, 808−816. (b) Reeve, W.; Erikson, C. M.; Aluotto, P. F. *Can. J. Chem.* **1979**, *57*, 2747−2754.
(14) In practice, potassium benzhydrolate was prepared in situ by dissolving equivalent amounts of benzhydrol (**2**) and potassium *tert*-butanolate in *tert*-butanol.
(15) At a given conversion, the slope of a time/conversion curve is equal to the reaction rate at the concentration of substrate still present at this point. Experiments were run at least in duplicate, and the error bars represent deviations from the mean value.
(16) Similarly, doubling the amount of base to 40 mol % resulted in a further increase of the reaction rate. However, the high reaction rate, as compared to the time needed for the thermal equilibration of the autoclave, prohibited a kinetic analysis under these conditions.
(17) Klingler, R. J.; Rathke, J. W. *Prog. Inorg. Chem.* **1991**, *39*, 113−180.
(18) GC on Fe-doped alumina at liquid nitrogen temperature, see Experimental Section for details.

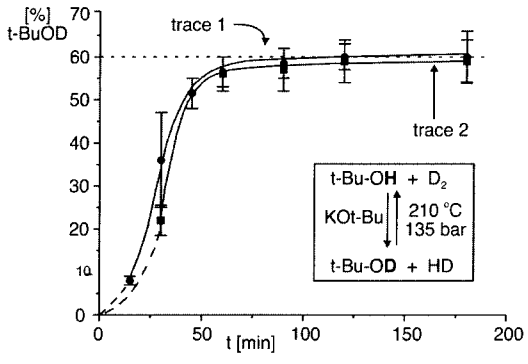
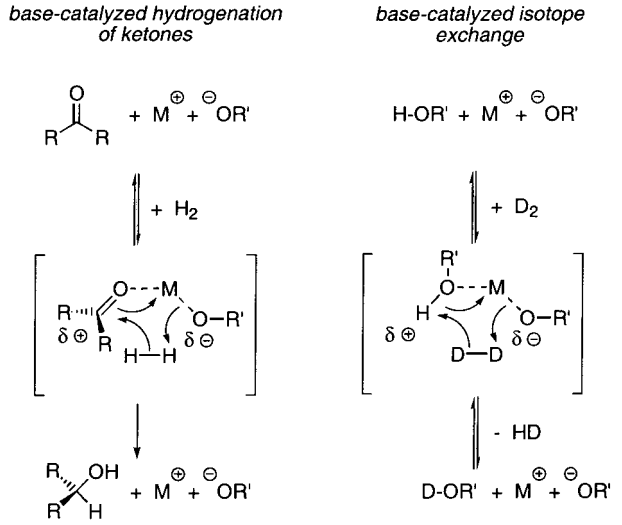


Figure 6. Base-catalyzed isotope exchange between the gas phase and the solvent. Trace 1, in the presence of benzophenone (**1**); trace 2, no benzophenone (**1**).

was repeated in *t*-BuOD as solvent. Under these conditions, the isotope exchange between the gas phase and the solution is degenerate, and only D_2 can react. As shown in Figure 5 (trace 3), the reduction becomes extremely slow under these conditions. This result indicates that H_2/HD effect the formation of benzhydrol in the D_2/*t*-BuOH system. Control experiments, that is, subjecting Ph_2CD-OH to the strongly basic reaction conditions, revealed that the deuterium label at the benzhydrylic carbon atom is not stable and undergoes exchange with the solvent. This exchange phenomenon frustrated a simple distinction − based on the deuterium incorporation in the product benzhydrol (**2**) − whether or not there is a kinetic isotope effect k_{H_2}/k_{HD}. However, in the purely aliphatic and less CH-acidic 2,2,4,4-tetramethyl-3-propanol [the reduction product of di-*tert*-butyl ketone (**4**, Figure 1)], no isotope exchange at the 3-position occurs under the reaction conditions. When the ketone **4** was treated with D_2 in *t*-BuOH under identical conditions, NMR analysis of the product carbinol revealed D-incorporation of ca. 50%, that is, a value compatible only with the *absence* of a kinetic isotope effect k_{H_2}/k_{HD}.

Finally, the question of asymmetric induction in the base-catalyzed ketone hydrogenation was addressed. If a chiral base is employed as catalyst, face selection in the formal hydride transfer to a prochiral ketone may be expected. The irreversibility of the process is clearly an advantage, but the high reaction temperatures required so far are not. In preliminary experiments, we found that the hydrogenation of prochiral pivalophenone (**3**) in the presence of 20 mol % of potassium *R*-1-phenylethanolate at 140 °C and 135 bar H_2 for 24 h gave ca. 50% of the product alcohol and a reproducible ee of 12% (major enantiomer: *R*-2,2-dimethyl-1-phenyl-1-propanol).[19] Control experiments in the absence of hydrogen established that there was no competing Meerwein−Ponndorf−Verley reduction of the substrate ketone by the chiral secondary alkoholate used as base. To the best of our knowledge, this is the first example of asymmetric induction in a purely base-catalyzed hydrogenation. The relatively low ee observed prompted us to investigate whether concomitant racemization of the chiral base or the chiral product alcohol may obscure an intrinsically higher enantioselectivity. However, the 1-phenylethanol liberated from the base after the reaction (by acidification) had very close to the same ee as the 1-phenylethanolate employed as base (base, 85% ee; recovered 1-phenylethanol, 83% ee). Similarly, when enantiomerically enriched phenyl-*tert*-butylcarbinol (58% ee) was subjected to the reaction conditions, the recovered material did not show a significant loss of enantiomeric purity (55% ee). Consequently, the low enantioselectivity observed in our experiment must be attributed to insufficient discrimination of the diastereomeric transition states that lead to the two product enantiomers. The high reaction temperature probably accounts for the low effect of the subtle differences in transition-state energy.

Scheme 2



Discussion

For the sake of clarity, the most important features of the base-catalyzed hydrogenation of ketones shall be summarized again:

(i) Reversibility: The reaction is irreversible.

(ii) Kinetic orders: The reaction is first order in ketone, hydrogen, and base.

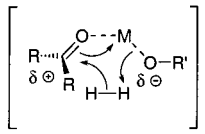
(iii) Effect of alkali ion: In the series of alkali benzhydrolates as catalytic bases, the rate of the hydrogenation decreases in the order Cs > Rb ≈ K ≫ Na ≫ Li.

(iv) Deuterium versus hydrogen: The product alcohols are partially deuterated. The source of deuterium is HD, resulting from a rapid, base-catalyzed isotope exchange between the gas phase and the solution.

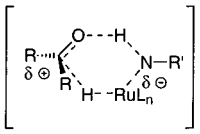
All of these experimental observations can be accommodated by the mechanism shown in Scheme 2. The key features for both ketone hydrogenation and isotope exchange are (i) the binding of substrate and base to the alkali cation, and (ii) the joint action of a Brønsted-base and a Lewis-acid (the ketone carbonyl-C or the alcohol proton, respectively) on the H_2 molecule. For both reactions, a cyclic, six-membered transition state can be formulated. This representation might suggest that H−H bond cleavage is the rate-determining step, but our experimental evidence speaks against that. In the presence of D_2 instead of H_2, the incorporation of D at the benzhydrylic position clearly proceeds via intermediate HD, and both the observed rates and the extent of deuterium labeling indicate that there is no significant discrimination of H_2 over HD. In other words, the reaction does not show a significant kinetic H/D effect which in turn speaks against H−H fission as the rate-determining step. A comparison with the low relative rate observed in the D_2/*t*-BuOD experiment appears problematic.

(19) Brown, H. C.; Park, W. S.; Cho, B. T. *J. Org. Chem.* **1986**, *51*, 1934−1936.

Scheme 3



mechanism proposed for the base-catalyzed hydrogenation of ketones, this work



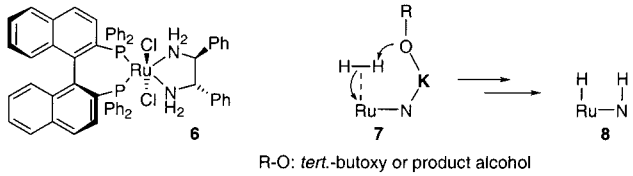
transition state of the Ru-catalyzed transfer hydrogenation by Noyori (ref. 5,7,23)

Deuteride transfer from D−D is unique as it contains a "double-primary isotope effect", not to mention differences in pK_a's and O−H versus O−D bond strengths in deuterated versus protic *tert*-butanol.[20] It may also be argued that the low rate observed under these conditions might indicate a rate-limiting transfer of H^+ versus D^+ to the product alcoholate. Instead, we assume that the assembling of highly ordered transition states such as the ones shown in Scheme 2 limits the rate of reaction. It is interesting to note that a *bent* arrangement of H_2 and an oxygen base was calculated by Radom et al. as the transition state of the hydrogenation of an imidazolidinium cation, mediated by a carboxylate base.[21] This calculation was intended to model a naturally occurring case of transition-metal-free hydrogenation, that is, the catalysis effected by the so-called metal-free hydrogenase found in methanogenic archaea.[22]

Please note that for the mechanism postulated in Scheme 2 (left), an analogy exists in the highly efficient and extremely enantioselective ruthenium-catalyzed transfer hydrogenation of ketones developed by Noyori et al.[5,7,23] Theoretical studies strongly support a six-membered transition state for this process, as shown in Scheme 3 (right). In the direction of ketone reduction, the NH-proton of the ligand bound to Ru interacts with the oxygen atom of the substrate, and a hydride is transferred by the Ru−H moiety to the carbonyl C-atom. Norton recently reported the first example of an ionic and enantioselective Ru-catalyzed hydrogenation of iminium cations.[24] In the latter process, a Ru-hydride species results from the fission of H_2 by the cationic CpRu(diphosphine)-catalyst and subsequent deprotonation. Again, hydride is transferred to the substrate from the Ru−H-intermediate, followed by protonation of the resulting amine (a stepwise additon of H^- and H^+ to the C=N-double bond).[24] The related Mo- or W-catalyzed hydrogenation of ketones reported by Bullock and Voges[25] follows a similar mechanism, but with the opposite order of the proton/hydride transfer.

Finally, the dependence of the hydrogenation rate on the nature of the alkali ion shall be discussed. The covalency of the metal oxygen bonds increases in the order Cs−Rb−K−Na−Li.[26] However, we believe that this is not the exclusive cause for the observed reactivity order. Again, a mechanistic analogy to the Ru-catalyzed asymmetric hydrogenation of ketones seems to exist. Formula **6** (Scheme 4) represents a ruthenium complex, developed by Noyori et al., that allows for the asymmetric hydrogenation of a variety of ketones with excellent yields and enantioselectivities (up to 99%).[5,7,8] Interestingly, the hydrogenation protocol involves the addition of

Scheme 4



R-O: *tert.*-butoxy or product alcohol

ca. 10 equiv (relative to Ru-catalyst) of potassium *tert*-butanolate. A recent study by Chen and Hartmann revealed that both the alkoxide base *and* the proper choice of the alkali ion are crucial for efficient catalysis.[27] It was proposed that the hydrogen molecule is coordinated to the Ru-center and that the heterolysis of the H_2 molecule occurs in the ternary complex **7**, again via a six-membered transition state (Scheme 4, right). As the final result, H_2 is split into a protic NH and a hydridic Ru−H (**8**). The transfer of the H-atoms to the substrate ketone finally occurs as depicted in Scheme 3 (right). Chen thus pointed out the crucial role of the potassium ion as the Lewis acid that properly positions the alkoxide base for the heterolysis of the H_2-molecule. Furthermore, an explanation was offered why, in the case of the Noyori catalyst **6**, potassium is the most active alkali ion (K > Na ≈ Rb > Li).[27] This order of reactivity follows neither the covalency of the bases nor the Lewis acidities of the alkali ions. Instead, a molecular modeling study revealed that the deprotonated amide nitrogen atom, together with two aryl substituents, forms a preorganized binding pocket for the alkali cation.[27] The complexation of alkali ions to aromatic π-systems is well documented in the literature.[28−31] In this particular case, the size of the binding site is optimal for potassium. How about the transition-metal-free hydrogenation discussed here? Clearly, also benzhydrolate can "chelate" alkali ions by interaction with the negatively charged oxygen atom and additional π-complexation. Several studies have shown that in coordinating solvents (as opposed to, e.g., the gas phase), π-complexation of benzene residues is stronger with K^+ than it is with Na^+.[28−31] As shown in Figure 1, the aromatic ketones **1** and **3** are hydrogenated more rapidly than purely aliphatic ones (**4**, **5**). In the latter cases, the product alcohols and thus the catalytically active alkoxide bases do not carry aromatic residues. Their lower rates of hydrogenation may be considered as additional support for π-complexing of the potassium ions. However, lower steric accessibility of the carbonyl C-atoms in the cases of **4** and **5** or the electron-withdrawing effect of the phenyl residues in ketones **1** and **3** may account for their lower reactivity as well.

Conclusions

We have shown that a series of nonenolizable ketones can be hydrogenated in the presence of substoichiometric amounts of base, and in the absence of a transition-metal catalyst. Low but significant asymmetric induction was observed when a prochiral ketone was hydrogenated in the presence of a chiral base. Kinetic studies revealed that the base-catalyzed hydroge-

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nation is first order in ketone, hydrogen, and base, in agreement with the assumption of a six-membered cyclic transition state involving the H_2-molecule and an aggregate of the catalytic base, alkali cation, and ketone. There seem to be analogies to the ruthenium catalysts developed by Noyori which transfer hydrogen to ketones by a two-stage mechanism. First, the heterolysis of the H_2-molecule is effected by binding to the Ru-center and subsequent attack of a Brønsted base. The resulting ensemble of hydridic Ru−H and protic N−H reduces the substrate ketone. In the absence of a hydrogen-binding and hydride-accepting transition-metal center, the main problem of a purely base-catalyzed hydrogenation of ketones seems to lie in the proper preorientation of the substrate ketone and the catalytically active base. Apparently, the fission of the H_2-molecule is not rate-limiting. Instead, poor population of the "reactive" conformation of the substrate-base assembly most likely accounts for the relatively low efficiency of the process at its current stage. Further work in our laboratory aims at improving the preorganization of substrate and base.

Experimental Section

Solvents and Chemicals. *tert*-Butanol, *tert*-butanol-*d*, and diglyme were purchased from Aldrich, purified by repeated distillation from sodium, and stored under argon. Commercially available benzophenone (**1**) was purified by repeated recrystallization from ethanol and drying in vacuo. Pivalophenone (**3**), di-*tert*-butyl ketone (**4**), and 2,2,5,5-tetramethylcyclopentanone (**5**) were prepared according to published procedures.[32] The corresponding alcohols were obtained from the ketones by LAH- and LAH-d_4-reduction, respectively. Lithium and sodium *tert*-butanolate were purchased from Fluka, potassium *tert*-butanolate from Riedel-de Haen. These alkali *tert*-butanolates were purified by sublimation at 180 °C, ca. 1 Torr, prior to use. Rubidium and cesium *tert*-butanolate were prepared by dissolving the alkali metals (Aldrich) in abs. *tert*-butanol. Pressurized deuterium (2.7) was supplied by Messer-Griesheim.

Base-Catalyzed Hydrogenations of Ketones in *tert*-Butanol, Kinetic Measurements. All reactions were run in a 300 mL Parr Instruments Ltd. Series 4560 autoclave, equipped with a temperature control unit, a glass liner, and a sampling tube. Typically, the autoclave was charged under argon (glovebox) with 40 mmol of the ketone and 8.0 mmol (20 mol %) of the alkali *tert*-butoxide in 100 mL of *tert*-butanol. For reactions catalyzed by alkali benzhydrolates, 1 equiv (relative to the base) of benzhydrol (**2**) was added, too. The autoclave was evacuated/flushed with hydrogen (or deuterium) twice and pressurized to an extent that the desired final pressure was reached upon heating. For the kinetic analyses, samples of ca. 200 μL were withdrawn by means of the sampling tube. These samples were quenched immediately by addition to a mixture of 1 mL of methanol, 100 μL of concentrated hydrochloric acid, and 2 mL of dichloromethane. After filtration through a plug of neutral alumina, the dichloromethane phases were analyzed by GLC on a 25 m HP-5 column. Calibration curves were recorded for all components for quantitative analysis. For each substrate, the hydrogenation experiments were worked up preparatively, and the products (and starting ketone in case of nonquantitative conversion) were isolated by column chromatography (silica gel, eluting with dichloromethane). In all cases, the mass balances were ≥95%.

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As a control experiment, deuterated benzhydrol (Ph_2CD-OH) was subjected to the above reaction conditions. After 48 h at 210 °C and 135 bar H_2, 91% of benzhydrol was reisolated. ^{1}H NMR analysis indicated that the deuterium label was almost completely replaced by hydrogen. When 2,2,4,4-tetramethyl-3-propanol-3-*d* was treated analogously for 72 h, reisolation (87%) and ^{1}H NMR analysis revealed that ≥98% of the deuterium label was still present.

Attempted Base-Catalyzed Hydrogenation of Benzophenone (1), Diglyme as Solvent. Benzophenone (**1**, 364 mg, 2.00 mmol) and potassium *tert*-butanolate (45−673 mg, 20−300 mol %) were dissolved in 5 mL of abs. diglyme. The solution was transferred into the autoclave, pressurized at ca. 20 °C with 54 bar H_2 or Ar, respectively, and heated to 130 °C. After 5 h, the mixture was poured into water, acidified with HCl, and extracted with ether. After being dried over anhydrous Na_2SO_4, the solvent was removed, and the residue was analyzed by GLC.

Monitoring of the H/D-Exchange between Gas Phase and Solution. The autoclave was charged with a solution of 0.90 g (8.00 mmol) of potassium *tert*-butanolate in 100 mL of abs. *tert*-butanol. After repeated evacuation and flushing with deuterium, the autoclave was heated to 210 °C, and the deuterium pressure was adjusted to 135 bar. Samples were withdrawn by means of the sampling tube and transferred directly into an NMR tube, equipped with an inner capillary containing $CDCl_3$ as reference and lock solvent. The deuterium content of the *tert*-butanol solvent was determined by ^{1}H NMR integration of the *tert*-butyl resonance and the OH-signal. The composition of the gas phase (H_2, HD, D_2) was analyzed as follows: When the NMR analysis of the solution indicated that equilibrium was reached (ca. 2 h), a sample of the gas phase was withdrawn and analyzed by GC, using a 1.1 m × 2 mm column packed with Fe(III)-doped alumina at liquid nitrogen temperature and heat capacity detection. Calibration with H_2, HD, D_2-mixtures of known composition allowed for the quantitative analysis: H_2:HD:D_2 = 1.0:2.1:3.04 (±0.05).

Hydrogenation of Pivalophenone (3) in the Presence of a Chiral Base. Potassium *R*-1-phenylethanolate was prepared from commercially available *R*-1-phenylethanol and potassium hydride. This material (64 mg, 0.40 mmol) was suspended in 324 mg (2.00 mmol) of pivalophenone (**3**). The mixture was transferred into the autoclave. After two cycles of evacuation−flushing with argon, the autoclave was pressurized to 83 bar H_2 at 25 °C and heated to 140 °C for 12 h. The reaction mixture was worked up as described above and analyzed by GLC. The enantiomeric excess of the 2,2-dimethyl-1-phenyl-propan-1-ol formed was analyzed on a WCOT-FS CP-Chiralsil-Dex column (25 m). The configuration of the major enantiomer was found to be *R* by co-injection with a sample of enantiomerically enriched *R*-2,2-dimethyl-1-phenyl-propan-1-ol, prepared according to ref 19.

When the reaction was run with potassium *R*-1-phenylethanolate of 85% ee, the 1-phenylethanol recovered after acidification of the reaction mixture had an ee of 83%. When enantiomerically enriched 2,2-dimethyl-1-phenyl-propan-1-ol (58% ee) was subjected to the reaction conditions, the recovered alcohol had an ee of 55%.

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