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The Mechanism of Aluminum-Catalyzed Meerwein–Schmidt–Ponndorf–Verley Reduction of Carbonyls to Alcohols

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Abstract: The mechanistic details of the Meerwein–Schmidt–Ponndorf–Verley (MSPV) reduction of ketones to the corresponding alcohols were investigated both experimentally and computationally. Density functional theory (DFT) was used to assess the energetics of several proposed pathways (direct hydrogen transfer, hydridic, and radical). Our results demonstrate that a direct hydrogen transfer mechanism involving a concerted six-membered ring transition state is the most favorable pathway for all calculated systems starting from a small model system and concluding with the experimentally investigated BINOLate/Al/PrOH/MePhC=O system. Experimental values for the activation parameters of acetophenone reduction using the BINOLate/Al/PrOH system ($\Delta G^\ddagger = 21.8$ kcal/mol, $\Delta H^\ddagger = 18.5$ kcal/mol, $\Delta S^\ddagger = -11.7$ au) were determined on the basis of kinetic investigation of the reaction and are in good agreement with the computational findings for this system. Calculated and experimental kinetic isotope effects support the concerted mechanism.

Introduction

The Meerwein–Schmidt–Ponndorf–Verley (MSPV) reduction of carbonyl substrates to alcohols, first reported in the mid 1920s,^{1–3} is a highly chemoselective reaction that can be performed under mild conditions.⁴ It utilizes a secondary alcohol, most often 2-propanol (ⁱPrOH), as an inexpensive hydride source and is mediated by easily accessible and regenerable aluminum alkoxides. However, since the classical protocol for this reduction requires superstoichiometric amounts of Al(OⁱPr)₃ for satisfactory yields,⁴ it was largely supplanted in the late 1950s by methods utilizing boro- and aluminum hydrides.^{5,6}

Recently, we demonstrated that the catalytic behavior of the MSPV reduction is highly dependent upon the aggregation state of the aluminum complex. Using freshly prepared, largely nonaggregated aluminum alkoxides as catalysts, high yields of alcohol can be achieved under mild reaction conditions for various AlR₃/ⁱPrOH/ketone systems.⁷ Furthermore, a practical, enantioselective, and catalytic MSPV reduction was also demonstrated with ⁱPrOH as the achiral hydride source and using

AlMe₃ and enantiopure 2,2'-dihydroxy-1,1'-binaphthyl (BINOL) as the precatalyst and chiral ligand, respectively.⁸ Following literature precedents,^{9–11} we proposed that the mechanism of the MSPV reaction involves a direct and concerted hydride transfer. However, such a pathway was only speculative and has never been confirmed.¹¹ Herein we report a combined theoretical and experimental mechanistic investigation of the MSPV reduction and suggest a general operative mechanism for the aluminum-catalyzed MSPV reduction of ketones and aldehydes to alcohols on the basis of both the computational and the experimental findings.

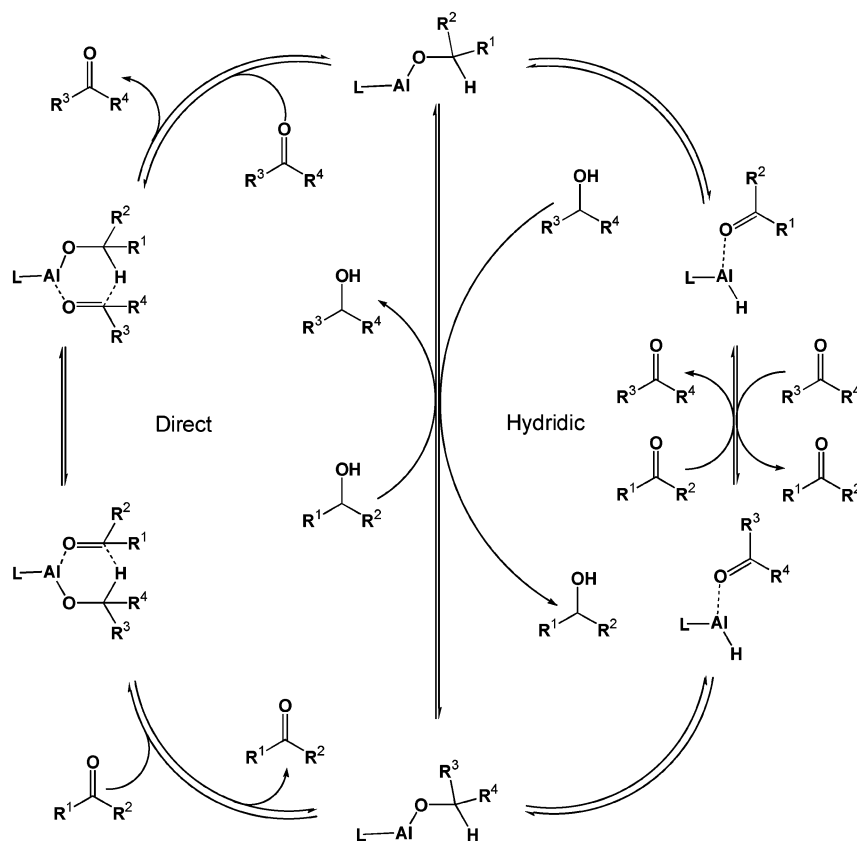
Both a stepwise “hydridic route” and a concerted “direct hydrogen transfer” process were proposed for the MSPV reduction (Scheme 1).¹¹ The “hydridic route” involves formation of a metal hydride derivative followed by hydride transfer from the metal to the substrate, a pathway that is often invoked for transition-metal and lanthanide catalysts.^{11–13} The “direct hydrogen transfer” implies a concerted hydrogen transfer where both the H-donor and the H-acceptor are held in close proximity by the catalyst. In the classical MSPV reduction, the aluminum

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Scheme 1. Possible Mechanistic Pathways for the Al-Catalyzed MSPV Reduction of Ketones and Aldehydes^a

^a Left: The concerted hydride-transfer pathway. Right: The hydridic pathway.

center is believed to be tetracoordinated during the hydride transfer from one of the isopropoxide ligands to the coordinated ketone substrate. A cyclic transition state has been conjectured for the concerted MSPV reduction.¹¹ A radical mechanism was also proposed.¹⁴

Results

MSPV Mechanism Elucidation by DFT. To examine the feasibility of the aforementioned mechanistic pathways, Density functional theory (DFT) calculations were performed at the mPW1k¹⁵/SDB-cc-pVDZ//mPW1k/SDD level of theory using the Gaussian 98 program package.¹⁶ Various levels of model systems were considered, including our experimental catalyst⁸ as the final, most comprehensive model.

We first considered the concerted and the hydridic mechanisms. The di-oxo-butadiene (DOB) ligand was used together with MeOH and H₂C=O as an initial model for the experimental BINOLate/Al/ⁱPrOH/ketone system.⁸ Both hydridic and direct mechanisms (Scheme 1) were checked for different ligands and

different substrates, including the actual experimental one (Figures 1 and 2).

The hydridic route starts with β -H elimination from the alkoxy ligand of a putative tricoordinated (L₂)Al(OCHR¹R²) complex (L₂ = DOB, BiPhO, BINOLate; R = H, Me) (Figure 1). Dissociation of the resulting coordinated ketone (or aldehyde) leads to formation of a high-energy tricoordinate (L₂)Al-H species. Coordination of another ketone substrate and insertion of the carbonyl carbon atom into the Al-H bond generate the corresponding alkoxy ligand, which could then be protonated into the corresponding alcohol, completing the catalytic cycle (Scheme 1). We did not find evidence for the associative coordination of the ketone to the tetracoordinate (L₂)Al(H)-(R¹R²C=O) complex prior to the insertion reaction. Searches for pentacoordinate aluminum compounds always resulted in the elimination of one ligand, leading to tetracoordinated species. It was previously suggested that pentacoordinated aluminum species are not active, but rather that tetracoordinated complexes are the reactive intermediates in hydride transfer reactions involving ketones and aldehydes.¹⁷ Formation of agostic C-H species prior to the β -H elimination was not found; the β -H elimination route proceeds directly from the (L₂)Al(OCHR¹R²) intermediate.

The direct mechanism, on the other hand, was found to begin with a low-energy tetracoordinated (L₂)Al(OCHR¹R²)(R³R⁴C=O) complex rather than a relatively high-energy tricoordinated one as in the hydridic case (Figure 1). In the direct mechanism, the aluminum center brings together the coordinated ketone and

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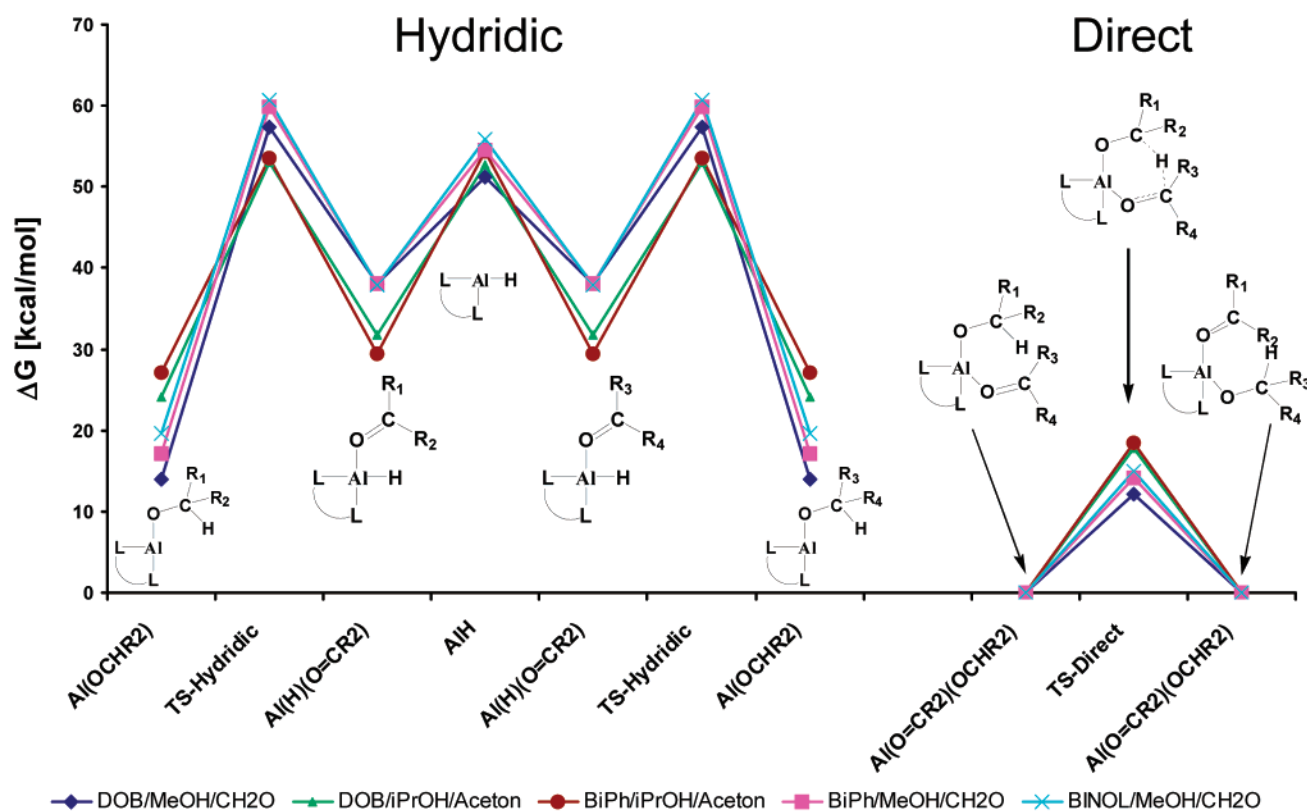


Figure 1. Energetic comparisons of the hydridic vs direct hydrogen transfer mechanism for the DOB/MeOH/H₂C=O, DOB/*i*PrOH/Me₂C=O, BiPhO/MeOH/H₂C=O, BiPhO/*i*PrOH/Me₂C=O, and BINOLate/MeOH/H₂C=O systems.

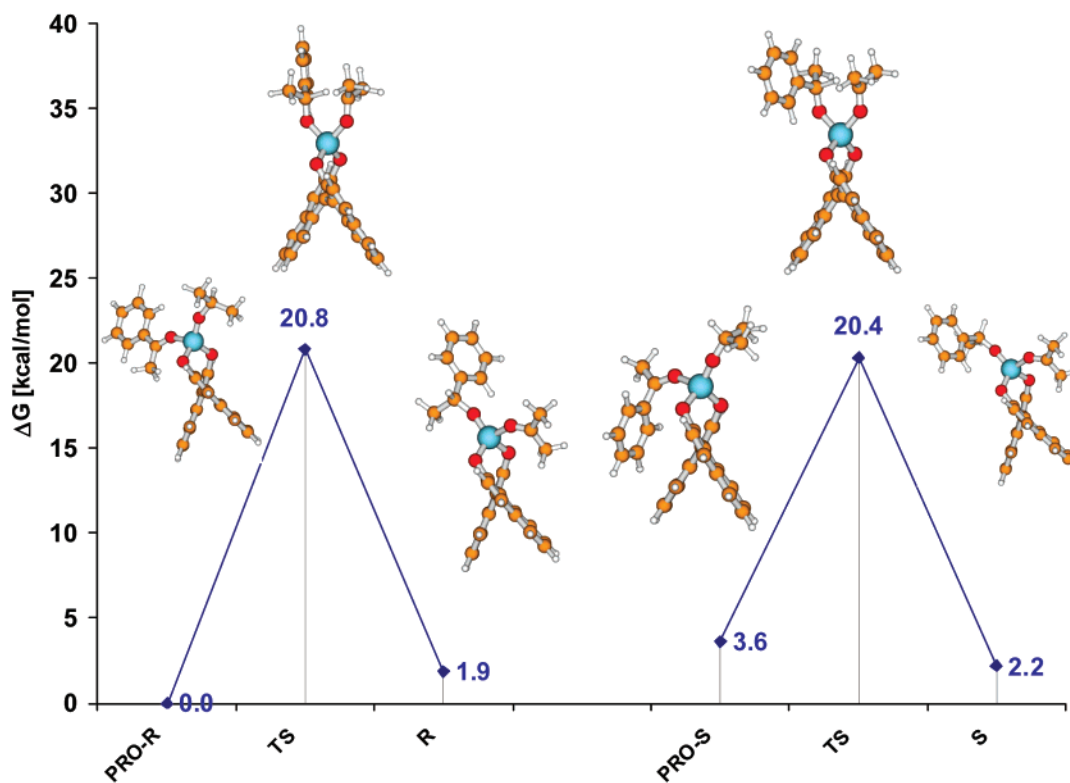


Figure 2. Relative free-energy calculation of the intermediates in the direct hydrogen transfer pathway for the experimental BINOLate/Al/*i*PrOH/MePh-C=O system (blue = Al, red = O, gold = C, white = H).

alkoxy ligands prior to the hydrogen transfer. A six-membered cyclic transition state, in which the alkoxy hydrogen lies between the coordinated ketone carbon and the alkoxide carbon, was

found for the hydrogen transfer process (Figure 1), which then leads to the corresponding product (L₂)Al(R¹R²C=O)(OCHR³R⁴). This process is much lower in energy than the hydridic route

Table 1. Relative Free Energies in Kilocalories per Mole of the Various Intermediates and Transition States of the Hydridic and Direct Mechanisms^a

	(L ₂)Al(H)	(L ₂)Al(H)(Y)	TS-hydridic	(L ₂)Al(X)	TS-direct	(L ₂)Al(X)(Y)
L ₂ = DOB X = OMe Y = H ₂ C=O	51.2	38.0	57.4	13.9	12.1	0.0
L ₂ = DOB X = O ⁱ Pr Y = Me ₂ C=O	52.7	31.8	53.0	24.2	17.8	0.0
L ₂ = BiPhO X = OMe Y = H ₂ C=O	54.6	38.1	59.9	17.1	14.1	0.0
L ₂ = BiPhO X = O ⁱ Pr Y = Me ₂ CO	54.4	29.5	53.6	27.2	18.4	0.0
L ₂ = BINOLate X = OMe Y = H ₂ C=O	55.9	37.9	60.7	19.7	15.0	0.0
L ₂ = S-BINOLate X = O ⁱ Pr (OCHPhMe) Y = MePhC=O (Me ₂ C=O)	51.1	32.5 (25.1)	49.8 (61.7)	22.2 (35.4)	20.8 (R) 20.4 (S)	0.0 (R); 3.6 (S) (1.9) (R); (2.2) (S)

^a L₂ = DOB, BiPhO, BINOLate; X = OMe, OⁱPr, OCHPhMe; Y = H₂C=O, Me₂C=O, MePhC=O.

energy profile, to the extent that the energies of the most stable intermediates in the hydridic route lie above the direct route transition state (Figure 1).

Several points should be noted regarding the different model systems investigated. For the DOB/Al/MeOH/H₂C=O model system, the rate-determining step for the hydridic mechanism was found to be the β-H elimination with a barrier of 44 kcal/mol, while the barrier for the direct mechanism is only 12 kcal/mol (Figure 1, Table 1). Replacing the MeOH and H₂C=O substrates with ⁱPrOH and Me₂C=O, respectively, reduced the barrier to 29 kcal/mol for the hydridic route, compared to 18 kcal/mol for the direct mechanism. The reduction in the barrier height is mostly a result of decreased stability of the starting tricoordinated intermediate (L₂)Al(OⁱPr) prior to the β-H elimination step, and to a lesser extent due to a decrease in the energy of the β-H elimination transition-state geometry. It should be noted that, although the barriers of the hydridic and the direct mechanisms are more comparable in this case, the tetracoordinated intermediate of the direct mechanism is much lower in energy (by 24 kcal/mol) than the tricoordinated (DOB)Al(OⁱPr) from which the hydridic route takes place, making the hydridic route more energetically demanding than the concerted path and thus less likely to take place.

The above data suggest that increasing the steric bulk of the substrates reduces the barrier for the hydridic route. Therefore, steric influence on the mechanism was further probed by increasing the bulk on the ligand. The bidentate DOB ligand was replaced with the more bulky biphenolate (BiPhO), which is also closer in structure to the BINOLate ligand experimental system.⁸ The BiPhO results are qualitatively similar to those obtained for the DOB ligand system (Figure 1, Table 1). The increased steric hindrance of the BiPhO ligand did not affect the energetics of the reaction significantly with respect to the DOB ligand system, as did the change in the hydride source/substrate from MeOH/CH₂=O to ⁱPrOH/Me₂C=O. Thus, in the BiPhO ligand system, as in the DOB one, there is a decrease in the free-energy barrier for the β-H elimination step with respect to the direct hydrogen transfer barrier when changing the hydride

source/substrate from MeOH/CH₂=O to ⁱPrOH/Me₂C=O (Figure 1, Table 1). Increasing the bulk even further by replacing BiPhO with S-BINOLate did not significantly affect the results for the MeOH/H₂C=O (Figure 1, Table 1) or for the ⁱPrOH/MePhC=O system (Figure 2, Table 1). In contrast to the calculated MeOH/CH₂=O and ⁱPrOH/Me₂C=O identity reactions, the ⁱPrOH/MePhC=O couple has different reactants—ⁱPrOH, MePhC=O—and products—Me₂C=O, Me(Ph)HC(OH) (Figure 2). In addition, since the (S-BINOLate)Al(OⁱPr) catalyst is chiral (because of the chirality of the S-BINOLate ligand), there are different tendency for the Al-catalyst to form the (S)- and the (R)-1-phenylethanol (MePhCH*OH) isomers (that in the reported experiment were shown to result in 30% enantiomeric excess (ee) of the S isomer⁸).¹⁸ In the ⁱPrOH/MePhC=O system, as observed in the other cases, the direct mechanism is energetically well below the hydridic one (Table 1). Thus, the preference for a direct mechanism over the hydridic one was found for all investigated systems, irrespective of the ligand environment, the substrate, and the hydride source. This preference could be explained by comparing not only the barriers for the two mechanisms but also the stability of the intermediates. In the direct mechanism the intermediates are tetracoordinate complexes stabilized by a strong Al—O bond (BDE_{Al—O} = 120 kcal/mol),¹⁹ while in the hydridic mechanism the intermediates are either less stable tricoordinate complexes or tetracoordinate ones involving a much weaker Al—H bond (BDE_{Al—H} = 65 kcal/mol).¹⁹ Thus, in all investigated systems, the hydridic mechanism reaction profile is energetically “hotter” than that for the direct mechanism. It should be noted that, in most cases of transition-metal systems, the opposite is true, and the hydridic mechanism is preferred.^{11–13}

We also considered a radical mechanism. For the alkali-metal-catalyzed MSPV reduction of benzophenone, a radical reaction that proceeds via single-electron transfer was proposed

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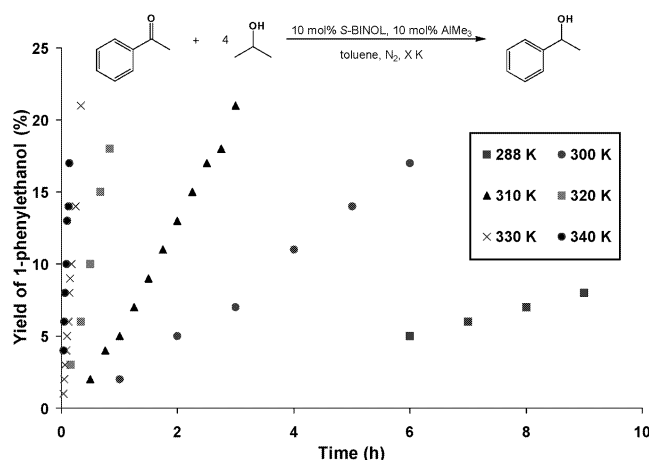


Figure 3. Kinetic plots for the reduction of MePhC=O to Me(Ph)HC(OH) at various temperatures.

Table 2. Rate of Acetophenone Reduction via the BINOLate System at Various Temperatures

temperature (K)	observed rate constant $k \times 10^4$ (s ⁻¹)	fit parameter R^2
288	2.4 ± 0.1	0.98
300	7.6 ± 0.2	0.98
310	18.2 ± 0.4	0.98
320	59.9 ± 0.6	0.99
330	162.0 ± 3.2	0.98
340	338.0 ± 3.4	0.99

to take place.²⁰ It was suggested that such a radical transition state could potentially be involved in an aluminum-catalyzed MSPV reaction.¹⁴ We are aware of one experimental study of the MSPV reduction that demonstrated that the use of radical scavenger reagents did not affect the reduction rate, invalidating the radical mechanism.²¹ To further investigate the suggestion for a radical mechanism, we searched for a biradical (triplet) transition state for the DOB/Al/MeOH/CH₂=O system. The energy found for this biradical transition state was about 20 kcal/mol higher than the one for the closed-shell singlet transition state of the direct mechanism. Such a large singlet–triplet gap²² rules out the possibility of a single electron-transfer reaction in the aluminum system.

Kinetic Study. To gain additional insight into the mechanism of the reaction and to verify the reliability of the computational findings, we performed kinetic experiments on the S-BINOLate/Al/ⁱPrOH/MePhC=O system, which was previously shown⁸ to be active in the MSPV reduction, and was investigated here computationally for the (*R*)- and (*S*)-Me(Ph)HC(OH) enantiomers. The rate of MePhC=O reduction was determined under pseudo-first-order conditions (with a 4-fold excess of ⁱPrOH relative to MePhC=O) on the basis of the yield of Me(Ph)HC(OH) (*R* + *S*) in time (Figure 3). The rates of the reaction were calculated at various temperatures within a range of 52 K (Figure 3, Table 2) and the activation parameters (ΔH^\ddagger , ΔS^\ddagger ,

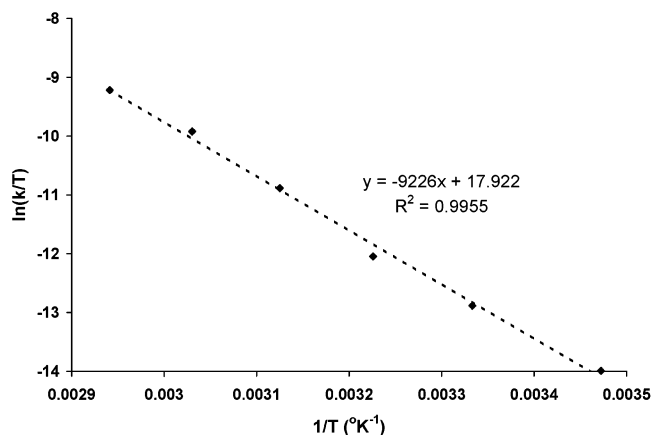


Figure 4. Eyring plot for reduction of MePhC=O to Me(Ph)HC(OH) in toluene ($T = 288\text{--}340\text{ K}$).

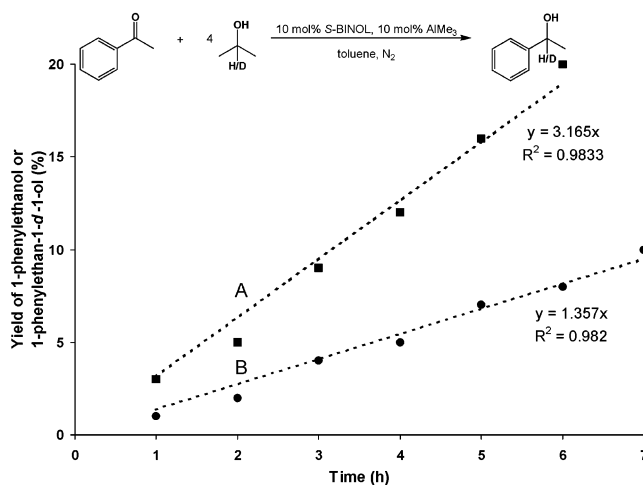


Figure 5. Kinetics of the reduction of MePhC=O with Me₂C(H)OH (A) and Me₂C(D)OH (B).

and ΔG^\ddagger) for the reduction of MePhC=O to Me(Ph)HC(OH) were determined from the corresponding Eyring plot (Figure 4).

The activation parameters obtained for the overall reduction of MePhC=O to Me(Ph)HC(OH) based on the Eyring plot are the following: $\Delta H^\ddagger = 18.5$ kcal/mol, $\Delta S^\ddagger = -11.7$ au and $\Delta G^\ddagger = 21.9$ kcal/mol. These values can reasonably be attributed to the rate-determining step of the reaction. The negative entropy of activation indicates an organized transition state, as suggested by the six-membered nonpolar transition state for the direct mechanism. To verify that the hydride transfer is the rate-determining step of the reaction, ²H-kinetic isotope effect (KIE) experiments were performed for the BINOLate/Al/ⁱPrOH/MePhC=O system. The rates of MePhC=O reduction using either Me₂CH(OH) or Me₂CD(OH) were measured independently under the same conditions (Figure 5); the reaction using Me₂CH(OH) was found to be approximately twice as fast as that using Me₂CD(OH), the k_H/k_D value being 2.33. This substantial k_H/k_D value, indicative of a primary isotope effect, suggests that the C–H bond is being broken and formed in the rate-determining step of the reaction, i.e., the hydride transfer is the rate-determining step of the reaction rather than ligand association and dissociation or protonation of the alkoxy ligand. This also indicates that the activation parameters correspond to the hydride transfer step. The experimentally obtained activation

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parameters values are in good agreement with the computationally results for the *direct* mechanism of the (*S*)-BINOLate/ $\text{Al}/\text{PrOH}/\text{MePhC=O}$ system ($\Delta G^\ddagger \approx 20.5$ kcal/mol, $\Delta H^\ddagger \approx 17.1$ kcal/mol, and $\Delta S^\ddagger \approx -11.4$ eu).²³ Furthermore, the calculated free energy of activation found for the rate-determining step of the *hydridic* mechanism (β -H elimination) is significantly higher ($\Delta G^\ddagger = 27.6$ kcal/mol) than that of its experimental counterpart. Thus, the experimentally obtained activation parameters combined with the KIE evidence for the hydride transfer to be the rate-determining step of the reaction provide additional support for the suggestion that the *direct* mechanism rather than the *hydridic* one is operating. It should be noted that hydride transfer is generally considered to be the rate-determining step of the MSPV reduction process.^{24–26} The experimentally found $k_{\text{H}}/k_{\text{D}}$ value is similar to the one found for the Cannizzaro reaction (1.8–1.9),²⁷ which is known to follow a direct mechanism for hydride transfer in a manner very similar to what is suggested for aluminum MSPV reduction.

DFT Study of Kinetic Isotope Effects. ^2H -KIEs were calculated at 298.15 K for the BINOLate/ $\text{Al}/\text{Me}_2\text{CD}(\text{OH})/\text{MePhC=O}$ system using the unscaled theoretical vibrational frequencies obtained by the method of Bigeleisen and Mayer.^{28–30} The accuracy for predicting $k_{\text{H}}/k_{\text{D}}$ values for hydrogen transfer reactions by these calculations is limited by transition-state theory approximation,³¹ 1D semiclassical tunneling corrections, and the rigid rotor harmonic oscillator approximation for vibrational frequencies. Nevertheless, the motivation for performing these calculations was to qualitatively differentiate between concerted and stepwise mechanisms and to correlate them with experimentally determined values. The rate constant $k(T)$ was calculated using the expression $k(T) = (\kappa k_{\text{B}}T/h) \exp(-\Delta G^\ddagger/RT)$ where ΔG^\ddagger is the calculated free energy of activation, κ is a transmission coefficient (unity in the absence of tunneling), k_{B} is the Boltzmann's constant, T is temperature, h is Planck's constant, and R is the gas constant. Tunneling corrections to κ were estimated using the one-dimensional infinite parabolic barrier model according to Wigner³² and Truhlar³³ and was found to be minor (Wigner and Truhlar H/D transmission ratios of 1.03 and 1.04, respectively). DFT $k_{\text{H}}/k_{\text{D}}$ values were calculated on the basis of the computationally suggested rate-determining steps of the stepwise (β -H elimination) and the concerted (hydride transfer) mechanisms and found to be approximately 6.5 and 3.0, respectively. The calculated value for the concerted mechanism ($k_{\text{H}}/k_{\text{D}} = 3.0$) is more easily reconciled with the value obtained experimentally ($k_{\text{H}}/k_{\text{D}} = 2.3$). As a more rigorous treatment of tunneling would increase both computed isotopic ratios away from experiment, the isotopic ratios appear to corroborate our assertion that the concerted

mechanism rather than the hydridic one takes place in the reported system.

Discussion

As early as 1945, Woodward et al.¹⁰ proposed that the MSPV reduction mechanism proceeds through a six-membered ring concerted transition state. We are aware of only one case of mechanistic investigation of the MSPV reaction in which an evidence for a direct mechanism was found from deuterium tracer experiments.³⁴ The deuterium experiments demonstrated that the alcoholic hydrogen did not bind to the carbonyl carbon. On the basis of this evidence, it was proposed that the hydrogen is transferred directly from the alkoxy ligand to the carbonyl carbon, supporting the direct mechanism. However, this evidence is not sufficient to disprove the hydridic mechanism. That $\text{Al}(\text{OR})_2\text{H}$, an important intermediate in the hydridic mechanism, is an isolable³⁵ and stable species^{36,37} and has been employed in the reduction of ketones and aldehydes³⁸ also suggests that we should not discount the hydridic mechanism so readily at the beginning of our investigation.

Our theoretical investigation of the MSPV reaction mechanism strongly supports the *direct* mechanism and invalidates the *hydridic* one on the basis of several model systems, including an actual experimental one (BINOLate/ $\text{Al}/\text{PrOH}/\text{MePhC=O}$). These systems show a great energetic preference of the direct mechanism over the hydridic one, while a radical mechanism can likewise be ruled out on energetic grounds. The direct mechanism was computationally shown to proceed through a chelated, six-membered ring transition state for the hydride transfer process in which the hydride is symmetrically located between two carbons (Figure 6). The six-membered ring transition state has a rigid planar ring shape rather than a cyclohexane-type one (twisted), most probably in order to minimize the C–H–C distances that are cleaved and formed during the transition state. In all model systems where the hydride transfer process is degenerate ($\text{MeOH}/\text{H}_2\text{C=O}$ and $^i\text{PrOH}/\text{Me}_2\text{C=O}$ cases), the transition-state structure is symmetrical and the transferred hydrogen is situated equidistantly to both carbons (C–H bond distance of 1.33–1.34 Å for all symmetrical systems) (Figure 6). However, in the case for the realistic, nondegenerate BINOLate/ $\text{Al}/\text{PrOH}/\text{MePhC=O}$ system (both *pro-R* and *pro-S*), the transferred hydride is closer to the acetophenone carbon than to the ^iPrO carbon. A concerted six-membered ring transition state was suggested to be involved in hydride transfer reactions mediated by some transition-metal-based catalysts as well.¹¹

Asymmetric MSPV reductions employing chiral ligand around the aluminum center were shown to give only low to moderate enantiomeric excess of alcohol products.^{8,39} It was suggested that the low enantiomeric excess values are due to

(23) The computed activation parameters correspond to the difference between the lowest-energy intermediate (*pro-R*, $\Delta G^\ddagger = 0.0$ kcal/mol, Table 1) and the average between the two energies of the transition states leading to *S* and *R* isomers ($\Delta G^\ddagger = 20.4$ and 20.8 kcal/mol, respectively, Table 1). Taking into account a ratio of 2:1 of *S* isomer to *R* (based on 30% ee of the *S* isomer), the same is done for ΔH^\ddagger . ΔS^\ddagger is calculated based on $\Delta G = \Delta H - T\Delta S$ for $T = 298.15$ K.

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(37) Although Al–H can, in theory, react with alcohol to give aluminum alkoxide and hydrogen gas, this reaction becomes more sluggish as the degree of alkoxide substitution around the Al center increases. For example, the reaction of $\text{LiAl}(\text{OR})_2\text{H}_2$ with alcohol to give $\text{LiAl}(\text{OR})_3\text{H}$ is quite sluggish and requires significant input of heat (Boireau, G.; Deberly, A.; Toneva, R. *Synlett* **1993**, 585–587). That between $\text{LiAl}(\text{OR})_3\text{H}$ and alcohol is even more difficult. It was also shown that $\text{Al}(\text{OR})_2\text{H}$ reagents can be isolated (see ref 35).

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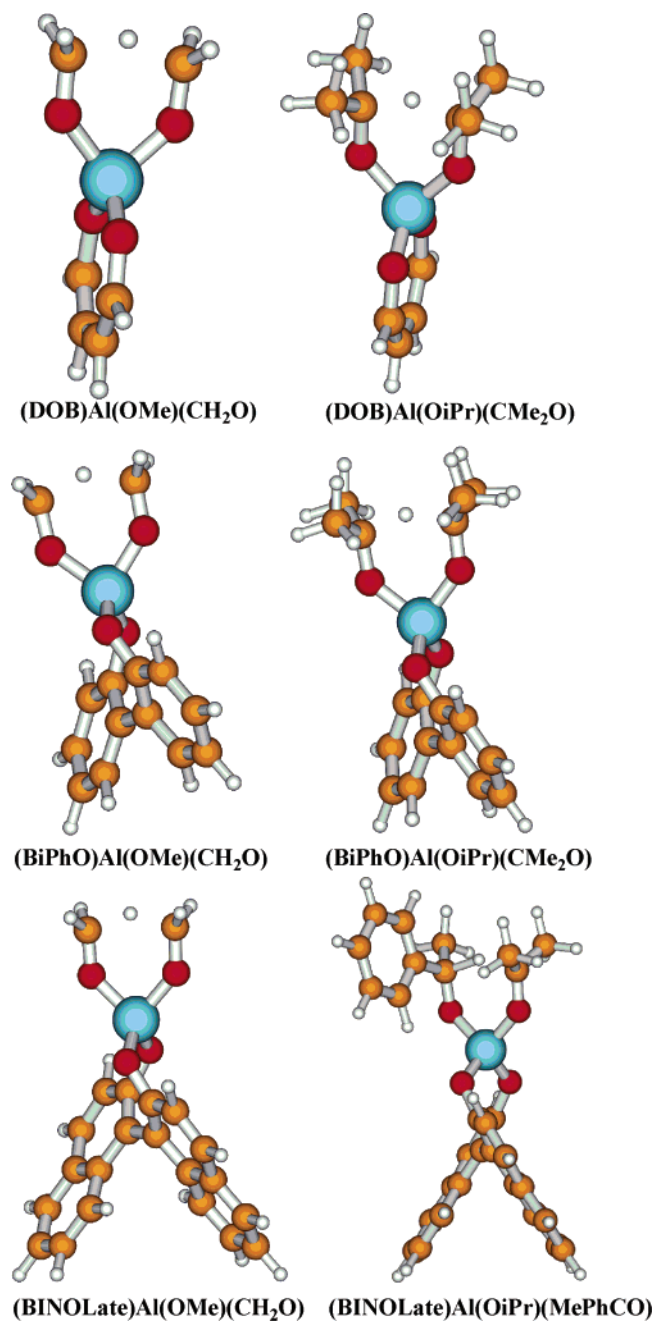


Figure 6. Direct hydride transfer transition-state structures for all systems investigated (blue = Al, red = O, gold = C, white = H).

the small energy difference of the flexible six-membered monocyclic transition states in which the controlling factor of the enantiofacial selectivity of the carbonyl group is the bulkiness of the substituents on the ketone ligand and the alcohol hydride source. It can be seen in Figures 2 and 6 that both BINOLate/Al/ⁱPrOH/MePhC=O transition states leading to the (*R*)- and the (*S*)-Me(Ph)HC(OH) products have very similar structures, and as a result they have comparable energies. It seems that the ring flexibility is less relevant since in the transition state the ring is rather planar and not twisted. We believe that the lack of high ee is a result of insufficient steric constraints on a certain facial coordination. To obtain higher values of ee, the energy differences between the two diastereomeric transition states must be higher than the calculated values ($\Delta\Delta G^\ddagger = 0.5$ kcal/mol). The estimated computational error

resulting from the presently used DFT method might be on the same order of magnitude as the absolute energy difference corresponding to 30% ee ($\Delta\Delta G^\ddagger \approx 0.4$ kcal/mol). As a result of dispersion-like interactions and solvation effects that are not taken into consideration here, the computational results should be regarded with caution and for only qualitative purposes.

Experimental Section

Computational Methods. All calculations were carried out using the Gaussian 98 program, revision A.11,¹⁶ running on a Linux PC Farm at the Faculty of Chemistry, Weizmann Institute of Science. The mPW1k (modified Perdew–Wang 1-parameter for kinetics) exchange–correlation functional of Truhlar and co-workers¹⁵ was employed in conjunction with the SDD and SDB-cc-pVDZ basis sets (see below). The mPW1k functional was very recently shown⁴⁰ to yield more reliable reaction barrier heights than other exchange–correlation functionals.

The SDD basis set is the union of the Huzinaga–Dunning double- ζ basis set for lighter elements with the Stuttgart–Dresden basis set relativistic effective core potential (RECP) combination⁴¹ for the transition metals. The SDB-cc-pVDZ basis set combines the Dunning cc-pVDZ basis set⁴² for the main group elements with the Stuttgart–Dresden basis set RECP combination for the transition metals, with an f-type polarization exponent taken as the geometric average of the two f-exponents given in the Appendix to ref 40.

The energetics for our final reaction profile were validated by single-point energy calculations, using the mPW1k/SDD reference geometries, at the higher level of theory mPW1k/SDB-cc-pVDZ.

General Procedure and Materials. Toluene was dried over alumina and Q5 via the Dow-Grubbs solvent system⁴³ installed by Glass Contours. 2-Propanol was distilled over Mg(O^{*i*}Pr)₂. Acetophenone was distilled over CaH₂. All solvents and reagents were distilled under nitrogen and saturated with nitrogen prior to use. (*S*)-2,2'-Dihydroxy-1,1'-binaphthyl was purchased from the Sumkin Chemical Company and used as received. All other reagents were purchased from the Aldrich Chemical Co. and used without further purification, unless otherwise noted.

Gas chromatographic (GC) analyses of reaction mixtures were carried out on a Hewlett-Packard 5890A instrument equipped with a FID detector interfaced to an HP3396A integrator. The column used was a 30-m HP-5 capillary column with a 0.32-mm inner diameter and a 0.25- μ m film thickness. Flow rate (He) = 1.8 mL/min. GC yields were determined through integration of the product peak against 1,2,4,5-tetramethylbenzene (internal standard) using pre-established response factors. 1-Phenylethan-1-*d*-1-ol⁴⁴ was independently synthesized to confirm GC retention time. All reactions were carried out under a dry nitrogen atmosphere.

General Reaction Conditions for the Reductions of Acetophenone Used in the Eyring Plot. To an 8-mL vial was added a magnetic stirring bar and (*S*)-2,2'-dihydroxy-1,1'-binaphthyl (28.6 mg, 0.1 mmol). Toluene (3 mL) was added followed by AlMe₃ (9.6 μ L, 0.1 mmol), and the vial was capped with a Teflon-lined silicone septa. The reaction mixture was stirred for 0.5 h at room temperature, after which 2-propanol (306 μ L, 4.0 mmol) was added and the reaction was subjected to the specific reaction temperature (10, 22, 32, 42, 52, or 62 °C). After 0.5 h, acetophenone (115 μ L, 1.0 mmol) in toluene (1 mL) was added to the reaction via syringe, and the reaction was stirred at the specific temperature. The reaction was sampled regularly; an aliquot (100 μ L) of the reaction was passed through a plug of

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aluminum oxide (activated, neutral, Brockmann activity 1, ~150 mesh), rinsed with methanol (15 mL), and analyzed by GC. Product yields were determined by GC (GC method: start temp = 80 °C, initial time = 4 min, ramp = 5 °C/min, final temp = 90 °C, final time = 1 min; retention times: 1-phenylethanol, 4.804 min; acetophenone, 4.959 min).

Reaction Conditions for the Determination of the k_H/k_D Value in the Reduction of Acetophenone. An 8-mL vial equipped with a magnetic stirring bar was charged with (*S*)-2,2'-dihydroxy-1,1'-binaphthyl (28.6 mg, 0.1 mmol) and dissolved in toluene (4 mL). AlMe_3 (9.6 μL , 0.1 mmol) was added, and the vial was capped with a Teflon-lined silicone septa. The reaction was stirred for 0.5 h at room temperature, after which either 2-propanol (306 μL , 4.0 mmol) or 2-propan-2-*d*-ol (311 μL , 4.0 mmol) was added and the reaction was stirred for another 0.5 h. Acetophenone (115 μL , 1.0 mmol) was then added, and the reaction was stirred at room temperature. The reaction was sampled regularly; an aliquot (100 μL) of the reaction was passed through a plug of aluminum oxide (activated, neutral, Brockmann activity 1, ~150 mesh), rinsed with methanol (15 mL), and analyzed by GC (see above).

Conclusion

In conclusion, we describe here, for the first time, a detailed computational investigation of the mechanism for the aluminum-catalyzed MSPV reduction of ketones and aldehydes. Our results demonstrate that a direct hydrogen transfer mechanism involving a concerted six-membered ring transition state is the most favorable pathway in all calculated models, including the

experimental BINOLate/Al/HO^{*i*}Pr/MePhC=O system.⁸ Experimentally determined values of the activation energy and k_H/k_D data suggest that the hydride transfer is the rate-determining step of the aluminum-catalyzed MSPV reaction and support the aforementioned computational findings. That a concerted mechanism is more likely to take place in the aluminum-catalyzed MSPV reduction is in stark contrast to transition-metal-based carbonyl reduction catalysts where β -hydride reduction pathways have been shown to be predominant.¹¹

Acknowledgment. We gratefully acknowledge financial support from the NSF and the DOE through a grant administered by the Northwestern University Institute for Environmental Catalysis. J.M.L.M. is a member of the Lise Meitner Minerva Center for Computational Quantum Chemistry and acknowledges support by the Minerva Foundation and by the Helen and Martin Kimmel Center for Molecular Design. S.T.N. additionally acknowledges support from Union Carbide, the Beckmann Foundation, the Packard Foundation, and the A. P. Sloan Foundation. C.R.G. is an NSERC PGS-D2 International Pre-doctoral Fellow.

Supporting Information Available: XYZ coordinates of the calculated structures. This material is available free of charge via the Internet at <http://pubs.acs.org>.

JA047613M