Secondary Deuterium Kinetic Isotope Effects in Irreversible Additions of Hydride and Carbon Nucleophiles to Aldehydes: A Spectrum of Transition States from Complete Bond Formation to Single Electron Transfer

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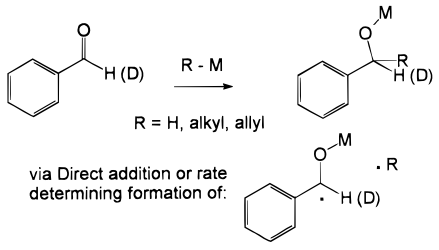
Abstract: The competitive kinetics of hydride and organometallic additions to benzaldehyde-H and -D were determined at −78 °C using $LiAlH_4$, $LiBEt_3H$, $NaBH_4$, $LiBH_4$, $LiAl(O\text{-}tert\text{-}butoxy)_3H$, $NaB(OMe)_3H$, $NaB(OAc)_3H$ (at 20° C). methyl, phenyl, and allyl Grignard, and methyl-, phenyl-, *n*-butyl-, *tert*-butyl-, and allyllithium. The additions of hydride were found to have an inverse secondary deuterium kinetic isotope effects in all cases, but the magnitude of the effect varied inversely with the apparent reactivity of the hydride. In the additions of methyl Grignard reagent and of methyllithium and phenyllithium, inverse secondary deuterium isotope effects were observed; little if any isotope effect was observed with phenyl Grignard or *n*-butyl- and *tert*-butyllithium. With allyl Grignard and allyllithium, a normal secondary deuterium kinetic isotope effect was observed. The results indicate that rate-determining single-electron transfer occurs with allyl reagents, but direct nucleophilic reaction occurs with all of the other reagents, with the extent of bond formation dependent on the reactivity of the reagent. In the addition of methyllithium to cyclohexanecarboxaldehyde, a less inverse secondary deuterium kinetic isotope effect was observed than that observed in the addition of methyllithium to benzaldehyde, and allyllithium addition to cyclohexanecarboxaldehyde had a kinetic isotope effect near unity. The data with organometallic additions, which are not incompatible with observations of carbonyl carbon isotope effects, suggest that electrochemically determined redox potentials which indicate endoergonic electron transfer with energies less than ca. 13 kcal/mol allow electron-transfer mechanisms to compete well with direct polar additions to aldehydes, provided that the reagent is highly stabilized, like allyl species. Methyl- and phenyllithium and methyl and phenyl Grignard reagents are estimated to undergo electron transfer with endoergonicities greater than 30 kcal/mol with benzaldehyde, so these react by direct polar additions. A working hypothesis is that butyllithium reagents undergo polar additions, despite redox potentials which indicate less than 13 kcal/mol endoergonic electron transfer, because of the great exoergonicity associated with the two-electron addition, which is responsible for a low barrier for polar reactions.

Irreversible addition of hydride and carbon nucleophiles to the carbonyl group is of major importance in organic chemistry.[1] The mechanism of this process is therefore of concern, particularly in connection with questions of face selectivity.[2] Two extreme mechanisms can be envisioned: a direct attack of the base with its two electrons on the carbocation-like carbonyl carbon (polar mechanism) or a single-electron transfer (SET) from the base to generate a carbonyl radical anion−base radical cation pair which collapses to the tetrahedral adduct (Scheme 1).[3]

In the latter event, rapid radical−radical anion combination compared with back-electron transfer requires rate-determining SET, but reversible SET followed by slow combination is indistinguishable from the direct (two-electron, polar) attack unless some spectroscopic or trapping technique provides evidence for SET prior to the rate-determining step. Within this mechanistic range is a related concern as to the extent of complexation of the carbonyl oxygen *in the transition state* with whatever Lewis acid is present in the system.

Scheme 1



While there have been concerns that SET pathways were involved in lithium aluminum hydride reductions of ketones based on suggestive but irreproducible experiments involving alkyl halide reductions,[4] large carbon-14 kinetic isotope effects

(1) *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vols. 1 and 2.

(2) Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; John Wiley & Sons: New York, 1994; pp 875−888. Coxon, J. M.; Houk, K. N.; Luibrand, R. T. *J. Org. Chem.* **1995**, *60*, 418 (for calculations with AlH3). Wu, Y.-D.; Houk, K. N.; Paddon-Row, M. N. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1019 (for caculations with LiH).

(3) For a review with a penetrating analysis, see: Walling, C. *J. Am. Chem. Soc.* **1988**, *110*, 6846.

(4) For a summary, see: Ashby, E. C.; Welder, C. O. *Tetrahedron Lett.* **1995**, 7171.

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in all but DIBAL reductions indicate rate-determining C−H bond formation.[5] However, additions of primary and tertiary Grignard reagents to aromatic ketones[6] at room temperature appear to favor the SET pathway, as judged by the formation of 5-hexenyl radical cyclization products, although these could be side reactions unrelated to the addition reaction. Further, a carbonyl carbon isotope effect of unity in the addition of allyl Grignard reagent to benzophenone has been cited as evidence for rate-determining SET, and substantial carbonyl carbon isotope effects for additions of alkyl and phenyl Grignard reagents have been interpreted in terms of preequilibrium SET followed by rate-determining C−C bond formation.[7] In the additions of methyllithium (and lithium dimethylcuprate), allyllithium, and phenyllithium to benzophenone, the carbonyl carbon-14 kinetic isotope effect is near unity, and all of these have been interpreted in terms of rate-determining SET.[8]

Carbonyl carbon isotope effects in additions of carbon nucleophiles to aldehydes have not been studied, except for addition of phenyllithium to benzaldehyde, where the effect is unity, which was interpreted in terms of rate-determining SET,[8b] and addition of lithium pinacolate to benzaldehyde, where the ^{13}C effect is 1.019, which suggests rate-determining C−C bond formation.[9] Secondary deuterium kinetic isotope effects (SDKIEs) at the carbonyl carbon of aldehydes can also distinguish between rate-determining polar (two-electron) attack and rate-determining SET. The polar (two-electron) addition involves a transition state with one more bond, which usually results in an increase in bending frequencies at the reacting carbon, which results in a greater lowering of the zero point energy upon deuterium substitution than occurs in the aldehyde starting material. This leads to an inverse SDKIE at the carbonyl carbon.[10] A relevant example involves the observation of a very large inverse SKDIE in the addition of a silyl ketene acetal to benzaldehyde, which seems to indicate "late" C−C bond formation.[11] However, rate-determining formation of a ketyl radical anion, which necessarily has looser bonds than starting aldehyde, should result in a normal SDKIE at the carbonyl carbon.[12] Finally, rate-determining Lewis acid complexation might be expected to result in an SDKIE of less than unity since the low-frequency aldehydic C−H stretch is converted to a C−H stretch in a carbocation.[13a] However, prior protonation or lithiation of a carbonyl oxygen is a less likely process, given the low basicity of aldehydes and the rapidity of hydride and organometallic additions. Even in acid-catalyzed additions of oxygen nucleophiles to aldehydes, general acid catalysis is observed; further, the secondary deuterium kinetic isotope effect at the carbonyl carbon is large and inverse, which indicates that protonation occurs only after or during nucleophilic attack and not before.[13b]

A further utility of the SDKIE is its ability to reflect the extent of bond formation at the site bearing deuterium, provided that its value can be compared with the isotope effect expected for complete bond formation. This latter value may be the equilibrium isotope effect for the overall process, a value interpolated from tables of deuterium fractionation factors between various types of carbon,[14] or a value calculated from molecular orbital theory using calculated Harmonic frequencies and the Biegeleisen equation, assuming complete bond formation.[15]

Another important example of the use of SDKIEs is Hill's determination of $k^H/k^D = 1/1.13$ for the sodium borohydride reduction of benzaldehyde carbonyl H/D in isopropyl alcohol solvent.[16a] The inverse SDKIE is consistent with a polar addition, and comparison of this KIE to what would be expected for complete bond formation (∼1/1.28) suggests that hydride transfer is roughly 50% complete in the transition state. Thus, Hill argued for a later transition state in this reaction, which is consistent with other observations.[16b] Since the determination of SDKIEs using aldehydes provides information on processes closely analogous to those utilized in many synthetic precedures, we report here the SDKIEs for a number of hydride reagents, Grignard and lithium reagent additions to benzaldehyde, and allyl- and methyllithium additions to cyclohexanecarboxyaldehyde.

Results

The KIEs for various additions were determined by reaction of a mixture of benzaldehyde-H and -D with a deficiency (approximately 0.1 equiv) of reagent in (mostly) ethereal solvents at −78 °C. The resulting alcohol products were converted to the methyl ethers by reaction with dimethyl sulfate in hexane containing triethylamine or by reaction with sodium hydride followed by treatment with methyl iodide. The methyl ethers were then purified by preparative gas chromatography and analyzed by ^{1}H NMR In the case of the hydride addition product, benzyl methyl ether, the single deuterium shifts the methylene proton resonance 0.02 ppm upfield to allow integration of the singlet from diprotio material and the 1:1:1 triplet

(5) (a) Yamataka, H.; Hanafusa, T. *J. Org. Chem.* **1988**, *53*, 772. All reactions had a small positive ρ value, except for reaction with 9BBN, which had a negative ρ value. (b) Yamataka, H.; Hanafusa, T. *J. Am. Chem. Soc.* **1986**, *108*, 6643. (NaBH4 in IPA and LiBH4 in ether, 1.066 and 1.089, respectively; LAH in ether, 1.024.

(6) Ashby, E. C.; Bowers, J. R., Jr. *J. Am. Chem. Soc.* **1981**, *103*, 2242. See also: Ashby, E. C.; Chao, L.-C.; Neumann, H. M.; Laemmle, J. T. *Acc. Chem. Res.* **1974**, *7*, 272. Ashby, E. C. *Pure Appl. Chem.* **1980**, *52*, 545; *Acc. Chem. Res.* **1988**, *21*, 414. Holm, T. *Acta Chem. Scand.* **1983**, *B37*, 569.

(7) Yamataka, H.; Matsuyama, T.; Hanafusa, T. *J. Am. Chem. Soc.* **1989**, *111*, 4912.

(8) (a) Yamataka, H.; Fujimura, N.; Kawafuji, Y.; Hanafusa, T. *J. Am. Chem. Soc.* **1987**, *109*, 4305. (b) Yamataka, H.; Kawafuji, Y.; Nagareda, K.; Miyano, N.; Hanafusa, T. *J. Org. Chem.* **1989**, *54*, 4706.

(9) Yamataka, H.; Sasaki, D.; Kuwantani, Y.; Mishima, M.; Tsuno, Y. *Chem. Lett.* **1997**, 271; *J. Am. Chem. Soc.* **1997**, *119*, 9975.

(10) do Amaral, L.; Bull, H. G.; Cordes, E. H. *J. Am. Chem. Soc.* **1972**, *94*, 7579. do Amaral, L.; Bastos, M. P.; Bull, H. G.; Cordes, E. H. *J. Am. Chem. Soc.* **1973**, *95*, 7369. Archila, J.; Bull, H. G.; Lagenaur, C. *J. Org. Chem.* **1971**, *36*, 1345. Pires, J. R.; Stachissini, A. S.; do Amaral, L. *J. Phys. Org. Chem.* **1994**, *7*, 192. Rossi, M. H.; Stachissini, A. S.; do Amaral, L. *J. Org. Chem.* **1990**, *55*, 1300.

(11) (a) Myers, A. G.; Widdowson, K. L.; Kukkola, P. J. *J. Am. Chem. Soc.* **1992**, *114*, 2765. (b) Others (Abu-Hasanayn, F.; Streitwieser, A. *J. Org. Chem.* **1998**, *63*, 2954) found a large inverse equilibrium SDIE in the addition of a lithium enolate to benzaldehyde.

(12) For experimental observations with the benzene radical cation, see: Stevenson, G. R.; Espe, M. P.; Reiter, R. C. *J. Am. Chem. Soc.* **1986**, *108*, 532. The ^{13}C isotope effects in this work are controversial, but the deuterium effects are reproduced by theory: Hrovat, D. A.; Hammonds, J. H.; Stevenson, C. D.; Borden, W. T. *J. Am. Chem. Soc.* **1997**, *119*, 9523. Thus, to the extent that an olefinic sp^2 carbon becomes a radical-like carbon in the radical anion, the frequencies at that carbon should be lower, see also: Pacansky, J.; Koch, W.; Miller, M. D. *J. Am. Chem. Soc.* **1991**, *113*, 317.

(13) (a) The calculated value for the equilibrium: acetaldehyde-H + conjugate acid-D ⇌ acetaldehyde-D + conjugate acid-H is 0.83 at 25 °C at the MP2/6-31G** level with no scaling of frequencies. (b) Jencks, W. P. *Acc. Chem. Res.* **1976**, *9*, 425−32. Funderburk, L. H.; Aldwin, L.; Jencks, W. P. *J. Am. Chem. Soc.* **1978**, *100*, 5444−59. Hill, E. A.; Milosevich, S. A. *Tetrahedron Lett.* **1976**, 4553−54. The possibility that both protonation and nucleophilic attack are reversible with the rate-determining step involving general base catalysis in the removal of a proton, which would also give rise to general acid catalysis, is not involved.

(14) Shiner, V. J., Jr.; Neumann, T. E. *Z. Naturforsch.* **1989**, *44a*, 337. For earlier work on fractionation factors, see: Hartshorn, S. R.; Shiner, V. J., Jr. *J. Am. Chem. Soc.* **1972**, *91*, 9002.

(15) For a systematic theoretical study of small-molecule deuterium fractionation factors, see: Harris, N. J. *J. Phys. Chem.* **1995**, *99*, 14689.

(16) (a) Hill, E. A.; Milosevich, S. A. *Tetrahedron Lett.* **1976**, 3013. (b) For an excellent review, see: Wigfield, D. C. *Tetrahedron* **1979**, *35*, 449.

Table 1. KIEs for Irreversible Additions to PhCHO/PhCDO

reagent[a]	solvent	temp (°C)	KIE[b]	KIE (25 °C)[c]	EIE (25 °C)[d]	*i* (25 °C)
$LiAlH_4$	THF	−78	0.975 (±0.01)	0.984	0.85	0.12
$LiBEt_3H$	THF	−78	0.965 (±0.01)	0.977	0.85	0.14
$NaB(OMe)_3H$	EtOH	−78	0.91	0.94	0.78	0.25
$NaBH_4$	EtOH	−78	0.82	0.88	0.78	0.51
$LiBH_4$	THF	−78	0.885 (±0.01)	0.92	0.85	0.51
$LiAl(OtBu)_3H$	Et_2O/THF	−78	0.88	0.92	0.85	0.51
$NaB(OAc)_3H$	HOAc	20	0.75	0.75	0.78	1.16
CH_3MgBr (0.1 M)	Et_2O	−78	0.95	0.97	0.78	0.13
CH_3MgBr (0.01 M)	Et_2O	−78	0.87	0.90	0.78	0.44
CH_3MgBr (0.01 M)	Et_2O	25		0.93	0.78	0.31
phenylMgBr (0.1 M)	Et_2O	−78	1.00	1.00	0.78	0
allylMgBr (0.1 M)	Et_2O	−78	1.04	1.03	0.78	SET
allylMgBr (0.01 M)	Et_2O	−78	1.04	1.03	0.78	SET
allyllithium	Et_2O	−78	1.095	1.06	0.78	SET
CH_3Li (0.1 M)	Et_2O	−78	0.87	0.90	0.78	0.44
CH_3Li (0.01 M)	Et_2O	−78	0.88	0.91	0.78	0.40
CH_3Li−0.5 equiv of MeOH	Et_2O	−78	0.89	0.92	0.78	0.37
Phenyl-Li (0.1 M)	Et_2O	−78	0.95	0.97	0.78	0.13
n-butyllithium	Et_2O[e]	−78	0.99	1.0	0.78	0
tert-butyllithum	pentane	−78	0.99	1.0	0.78	0

[a] Commercially available reagents were used where available. [b] Average deviation is ±0.03 except as noted. [c] KIE values measured at −78 °C were corrected to 25 °C assuming the KIEs depend only on ΔH. [d] Theoretical EIE values from RCHO + RCD(R′)OM = RCDO + RCH(R′)−OM, where R′ = H or alkyl and M = H or Li (or Mg) from MP2/6-311+G** on acrolein-1-*d*, allyl alcoholate derivatives, acrolein, and allyl-1-*d*-alcoholate derivatives; thus, complete C−C bond formation is the standard here (see text). This value applies only to polar, two-electron mechanisms. [e] Butyllithium in pentane was added to an ether solution of the aldehyde.

Table 2. KIEs for Irreversible Additions to Cyclohexanecarboxaldehyde H/D

reagent[a]	solvent	temp (°C)	KIE[b]	KIE (25 °C)[c]	EIE (25 °C)[d]	*i* (25 °C)
MeLi	Et_2O	−78	0.92 (±0.03)	0.95	0.78	0.20
allyl-Li	Et_2O	−78	0.98 (±0.03)	0.99	0.78	0.05

[a] Commercially available reagents were used where possible. [b] Average deviation is ±0.03. [c] See footnote *c*, Table 1. [d] See footnote *d*, Table 1.

of the monodeuterio material. Capillary GC on an optically active nickel compound was also utilized since the deuterium compound has a shorter retention time than the protio compound. The composition of the mixture of aldehyde H and D was determined by reaction with an excess of reagent and analysis of the product methyl ether by the same technique as used for the competition experiments in an effort to reduce systematic errors. Under these circumstances, k^H/k^D = H/D product(reagent limiting)/H/D product(aldehyde limiting). The results from various hydride, Grignard, and lithium reagent additions to benzaldehyde-D are given in Table 1.

In the case of methyl and allyl Grignard reagents, the concentrations of the reactants were varied over a factor of 10, leading to diminished inverse isotope effects at higher concentrations only in the case of methyl Grignard. In the case of methyl Grignard, the reaction was also performed at room temperature at the highest dilution studied at low temperatures, and this led to a KIE that is less inverse than the KIE from low temperatures extrapolated to room temperature. In the case of methyllithium additions, inverse SDKIEs were also observed, but their magnitudes did not depend on concentration. Further, prior reaction of methyllithium with 0.5 equiv of methanol did not dramatically affect the SDKIE for addition of methyllithium to benzaldehyde. The SDKIE determinations with allylmagnesium bromide and allyllithium additions to a mixture of benzaldehyde and benzaldehyde-*d* were conducted at 0.1 M concentrations in diethyl ether solvent, and allyl Grignard determination was also conducted at 0.01 M, all at −78 °C. All allyl reagent additions revealed a normal SDKIE.

Since the SDKIEs with benzaldehyde varied over a wide range, a limited SET of experiments with methyl- and allyllithium reaction with cyclohexanecarboxaldehyde-*d* were conducted, recognizing that rate-determining SET mechanisms are less accessible with aliphatic aldehydes due to their higher reduction potentials. These data are given in Table 2.

To provide a standard for comparison of the KIEs, the equilibrium constant for the equilibration (the deuterium fractionation factor, eq 1) of acrolein-1-*d* and allyl alcoholate

$$CH_2{=}CHCHO + CH_2{=}CHCHDO{-}M \rightleftharpoons CH_2{=}CHCDO + CH_2{=}CHCH_2O{-}M \quad (1)$$

$$M = H^+, Li^+, \text{nothing}$$

with acrolein-1-H and allyl-1-*d* alcoholate in the gas phase was determined from the harmonic frequencies obtained from MP2/6-311+G** calculations.[15] The counterion of allyl alcoholate was either H^+, Li^+, or nothing. The values for these equilibria are 1/1.28, 1/1.17, and 1.11, respectively, at 25 °C. While these values provide appropriate comparisons for the hydride addition, they were corrected downward by 11% for additions of carbon nucleophiles, recognizing that replacement of hydrogen by carbon results in increased stabilization of deuterium relative to hydrogen on the carbonyl carbon when the substitution occurs.[14] It was further assumed that this fractionation factor equilibrium (FF) with magnesium counterion is the same as that for the lithium counterion to provide a standard for the Grignard additions.

To make the comparisons, the kinetic isotope effects were extrapolated to room temperature, assuming that there are no entropic contributions so that the exponent, *i*, of the linear free energy relationship, SDKIE = FF^i, between the SDKIE and the FF data could be obtained. Such a relationship assumes that there are no factors affecting the transition state that are not reflected in the relative stabilities of H- and D-substituted reactants and products.

While all of the SDKIEs reported in the tables were the result of analysis of the product alcohol as its methyl ether, attempts were made to examine the hydrogen/deuterium fractionation in the starting benzaldehyde in the reactions with methyl Grignard and methyllithium as well as with allyl-, *n*-butyl-, and *tert*-butyllithium.[17] Generally, the SDKIEs determined in this manner at short reaction times were consistent with those determined from the product alcohol (converted to its methyl ether). However, at greater extents of conversion, the SDKIEs determined from benzaldehyde with *n*-butyl- and allyllithium became larger than unity and proportional to the extent of conversion. Further small amounts of benzyl alcohol were formed in each reaction (typically 1% of the product). The use of a deficiency of reagent and long reaction times (overnight) before quenching led to substantial amounts of benzyl alcohol. These results suggest incursion of a large, normal primary hydrogen isotope effect due to hydride transfer which dramatically fractionates starting material, particularly at long reaction times.

Finally, to determine the magnitude of the SDKIE at aldehydic carbon expected in rate-determining formation of an organolithium complex, MP2/6-31G** calculations of harmonic frequencies were performed on acrolein-H and -D as well as on the carbonyl oxygen complex with methyllithium. After geometry optimization to a structure with the oxygen, the lithium, and the methyl nearly collinear, the lithium is syn to the aldehydic H (or D). The equilibrium constant calculated for eq 2 at 25 °C is 0.94 with unscaled frequencies (0.95 with appropriately scaled ones).

$$CH_2CHCHO + CH_2CHCHDO{-}Li{-}CH_3 \rightleftharpoons CH_2CHCDO + CH_2CHCH_2O{-}Li{-}CH_3 \quad (2)$$

Discussion

Hydride Reductions. With the hydride reagents studied, all of which are anionic, the SDKIEs are inverse, suggesting rate-determining C−H bond formation. Further, the extent of hydride transfer as measured by the *i* values varies from small (0.12 ± 0.05) with lithium aluminum hydride to apparently more than complete (1.16 ± 0.2) with sodium triacetoxyborohydride. In the latter case, the excessively large *i* value is still within experimental error of 1.0. While there may be some concern about the maximum expected SDKIE in all cases, it is unlikely that there are large discrepancies unless cation bonding to the oxygen anion is less than complete. If this were the case, then the extent of bonding would be greater than that suggested by the *i* values of Table 1. This is because deuterium lowers the zero point energy of the aldehyde to a greater extent than it lowers the zero point energy of an unsolvated alkoxide ion product. This is probably the result of low frequencies associated with groups attached to carbon bearing the oxyanion due to negative ion hyperconjugation.[18]

It is interesting to note that the extent of hydride transfer to benzaldehyde suggested by the SDKIEs (the *i* values) at −78 °C are not very different than the extent of hydride transfer to benzophenone near room temperature as deduced from carbon-14 effects for the same reagent (lithium aluminum hydride, sodium and lithium borohydride).[5] Thus, there may be a coincidence of mechanisms for the two substrates. In the case of lithium aluminum hydride reductions, the nature of the reagent is of some concern, but the SDKIE determinations reported here provide little information about this. The SDKIEs reflect only the extent of change in bonding at the carbonyl carbon. Nonetheless, it should be noted that lithium aluminum hydride is ionized at low concentrations in tetrahydrofuran but forms solvent-separated ion pairs above 0.001 M.[19a] Furthermore, lithium cation is essential for the reaction, since lithium cation sequestering agents inhibit the reaction.[19b] In addition, lithium aluminum hydride reductions in tetrahydrofuran occur with first-order kinetics,[19c] but in diethyl ether solvent, the reduction is second order in lithium aluminum hydride.[19d] Nonetheless, the primary deuterium kinetic isotope effect for LAH/LAD reductions is similar in both solvents, suggesting similar transition-state structure in the vicinity of the carbonyl group.

Still another concern in the hydride reductions is the changing nature of the reagent being studied during the reaction. The SDKIE determinations require a deficiency of reagent, which therefore means that all of the reagent is consumed, and, in the case of lithium aluminum hydride and tetrahydridoboron reagents, it must change in response to changes in the ligands due to replacement of hydride by alkoxides, which may also result in changes in aggregation. The SDKIE determinations of Tables 1 and 2, therefore, represent an average over all the changes in the reagent during the reaction. One clear case of this is the sodium borohydride reduction. The SDKIE determined for sodium trimethoxyborohydride, the reagent present in the last 25% of the borohydride reduction in methanol, is less inverse than that observed for the overall reaction. This suggests that the SDKIE from reaction of tetrahydridoboron anion itself must be more inverse than that observed for the overall reduction. Nonetheless, in the discussions below, the focus will be on the average nature of the reagent, as revealed by the SDKIE.

The results with hydride reagents reveal dramatic changes in transition-state structure. The very reactive hydrides, namely lithium aluminum hydride, lithium triethylborohydride, and sodium trimethoxyborohydride, give SDKIEs which approach unity, but the least reactive, namely sodium triacetoxyborohydride, reacts with a very large inverse SDKIE that is comparable to the equilibrium fractionation factor for the reaction. There are also examples of hydride reagents whose inverse SDKIEs are intermediate in value, namely sodium and lithium borohydride and lithium aluminum tri-*tert*-butoxy hydride. Further, as indicated above, it is likely that the *i* value for reaction of borohydride ion is larger than the average *i* value for all reducing agents in the sodium borohydride reaction, so even here the transition state appears to be "late" with respect to reactants and products. This is surprising, considering the exothermicity of the reaction; however, it has been previously suggested in work that is not contradicted by the current results that the exothermicity in the borohydride reduction results from carbonyl oxygen−boron bond formation after rate-determining generation of the tetrahedral addition product.[20] In hydroxylic media, this is not unreasonable, since protonation of the alkoxide in the tetrahedral species (or perhaps before its formation in acetic

(17) See, for example: Delmonte, A. J.; Haller, J.; Houk, K. N.; Sharpless, K. B.; Singleton, D. A.; Strassner, T.; Thomas, A. A. *J. Am. Chem. Soc.* **1997**, *119*, 9907.

(18) DeFrees, D. J.; Bartmess, J. E.; Kim, J. K.; McIver, R. T., Jr.; Hehre, W. J. *J. Am. Chem. Soc.* **1977**, *99*, 6451. These authors showed that the equilibration of methanol and trideuteriomethoxide with trideuteriomethanol and methoxide favored the latter pair by 0.5 kcal/mol at room temperature in an ICR cell.

(19) (a) Hogen-Esch, T. E.; Smid, J. *J. Am. Chem. Soc.* **1966**, *88*, 318. Ashby, E. C.; Dobbs, F. R.; Hopkins, H. P., Jr. *J. Am. Chem. Soc.* **1973**, *95*, 2823. (b) Pierre, J. L.; Handel, M.; Perrand, R. J. *Tetrahedron* **1975**, *31*, 2795. (c) Eliel, E. L.; Senda, Y. *Tetrahedron* **1970**, *26*, 2411. Ashby, E. C.; Boone, J. R. *J. Am. Chem. Soc.* **1976**, *98*, 5524. (d) Wiegers, K. E.; Smith, S. G. *J. Am. Chem. Soc.* **1977**, *99*, 1480.

(20) Adams, C.; Gold, V.; Reuben, D. *J. Chem. Soc., Perkin Trans. 2* **1977**, 1472.

acid) can easily occur. Whether the same is true, i.e., extent of metalation of the oxygen, of the reductions in ethereal solvents is of concern. However, the SDKIE and the *i* value for lithium aluminum tri-*tert*-butoxy hydride are consistent with substantial interaction of the carbonyl oxygen with lithium cation, or the SDKIE would be much less inverse, as suggested from the calculation of fractionation factor above with no counterion for the oxygen.

Additions of Carbon Nucleophiles. Methyl Grignard Reagents and Methyllithium. Additions of methyl Grignard were conducted at different concentrations and different temperatures. The SDKIE at low concentrations (0.01 M) was more inverse than the SDKIE at a 10-fold higher concentration at −78 °C. The data indicate that the reaction does not involve rate-determining SET. Further, with the assumption that the fractionation factor for the alkoxide with a magnesium counterion is the same as that with the lithium counterion calculated above, the extent of CC bond formation in the transition state for methyl Grignard addition to benzaldehyde is roughly 30% in the more dilute reactions. At higher concentrations of Grignard reagent, it is reasonable that a higher concentration of dimeric species is present, but why this results in a less inverse SDKIE is unclear. It may be significant that the SDKIE for reaction of methyl Grignard in dilute solution at room temperature is roughly intermediate between that extrapolated from the −78 °C experiments at both 0.1 and 0.01 M, but more careful determinations are necessary to make distinctions.

Consistent with the current results are the carbonyl carbon KIEs in additions of methyl and phenyl Grignard reagents to benzophenone, which are substantial.[7] These have been interpreted in terms of a polar mechanism or one involving preequilibrium SET with rate-determining C−C bond formation. It is also important to note that Holm found inverse secondary deuterium kinetic isotope effects (SDKIEs) at the α carbon of methyl and ethyl Grignard in their additions to benzophenone, and these were interpreted in terms of a polar mechanism.[21] Interestingly, earlier Holm found that the logarithms of the relative rates of addition of many Grignard reagents to benzophenone (with benzophenone in excess) correlated with the ease of oxidation of the reagent, and these reactions were interpreted in terms of an SET mechanism.[22]

The reactions of methyllithium with benzaldehyde and with cyclohexanecarboxyaldehyde in diethyl ether at −78 °C reported in Tables 1 and 2, respectively, reveal inverse SDKIEs, indicative of rate-determining C−C bond formation in each case, with perhaps less bond formation with the aliphatic aldehyde. These results are consistent with a polar reaction that has an earlier transition state with the less stabilized aldehyde than with benzaldehyde. By contrast, the addition of methyllithium to benzophenone in diethyl ether at 0.0 °C occurs with no carbonyl carbon-14 KIE, which was interpreted in terms of rate-determining SET.[8a] Finally, it was important to find that the SDKIE determined for a methyllithium reagent which had reacted partially with methanol was nearly the same as that for methyllithium itself. This reveals that the reagent, though changing during the reaction, has similar reactivity in its various forms.

Allyllithium and Allyl Grignard SET Reactions. The additions of allyllithium and allyl Grignard reagent to benzaldehyde at −78 °C are remarkable in that they have SDKIEs which are greater than unity. Further, unlike the methyl Grignard addition, the SDKIE in the addition of allyl Grignard is independent of concentration. These results indicate that these reactions occur by rate-determining SET. It is interesting that there is only a small difference (0.16 V) in the oxidation potentials of allyl Grignard and allyllithium determined by Holm[22] and Breslow,[23] respectively, once corrected for the reference electrode, but neither determination could be conducted under conditions of reversible electron transfer, and the oxidation of the lithium reagents was conducted in THF, so an exact comparison cannot be obtained. However, it is important to note that the ease of oxidation of the allyl reagents is ca. 0.5−0.9 V greater than those of methyl Grignard and methyllithium determined in the same way. Therefore, single-electron transfer is more favorable with the allyl reagents than with the methyl reagents. Finally, if electron transfer were rate-determining with allyllithium reacting with benzaldehyde, then this pathway should be less favored with a nonconjugated aldehyde since the reduction potentials of these are more negative by at least 0.3 V.[24] Indeed, this appears to be the case from the data of Table 2, where the SDKIE is near unity.

Phenyl- and Butyllithium Additions. It is interesting that phenyl-, *n*-butyl- and *tert*-butyllithium additions to benzaldehyde have SDKIEs near unity. Whether this reflects the extreme reactivity of these reagents leading to an early transition state or a competition between rate-determining SET and polar addition is unclear, but we would suggest that these reactions are very exothermic polar additions with very early transition states, especially in the case of the phenyl reagents, which are not easy to oxidize by one electron, in contrast to the butyllithium reagents (see below).

Redox Potentials and Electron Transfer and Comparison to Polar Additions. Efforts to assess the involvement of single-electron transfer in organometallic additions to carbonyl compounds often focus on redox potentials of the reagents.[25] Arnett's study of the reduction potentials of benzaldehydes and benzophenone and the reversible oxidation potential of lithium pinacolate indicates that rate-determining electron transfer is unfavorable by ca. 40 kcal/mol.[25] Though this would appear to rule out rate-determining SET, Arnett was cautious in not dismissing the possibility, given the differences in the media between the actual reaction and the electrochemical determinations. However, in the case of addition of lithium pinacolate to benzaldehyde, carbonyl carbon KIEs are substantial,[9] and unpublished results in our laboratory indicate an inverse SDKIE (0.94 at −78 °C). Both of these results suggest rate-determining C−C bond formation. It is important to note that the reduction potentials of benzaldehyde and benzophenone are similar and equal to roughly −1.8 V relative to SCE,[24] so the evidence for SET mechanisms in additions to benzophenone is not simply a function of the ease of reduction of it relative to benzaldehyde.

The apparent oxidation potential of methyl Grignard in diethyl ether under irreversible conditions is −0.25 V relative to a standard hydrogen electrode.[22] By comparison, the oxidation potential of methyllithium in THF under irreversible conditions is −0.75 V relative to SCE.[23] Since the difference in the reference electrodes is 0.242 V, methyl Grignard is more

(21) Holm, T. *Acta Chem. Scand.* **1994**, *48*, 362.

(22) Holm, T. *Acta Chem. Scand.* **1983**, *B37*, 569. E_o(relative to SHE): allylMgBr = −1.16 V; MeMgBr = −0.25 V, in diethyl ether at 25 °C. For phenylMgBr, E_o = 0. Eberson, L. *Acta Chem. Scand.* **1984**, *B38*, 439.

(23) Jaun, B.; Schwanz, J.; Breslow, R. *J. Am. Chem. Soc.* **1980**, *102*, 5741. Approximate E_o (relative to SCE; E_o relative to SHE, 0.242 V): allylLi = −1.24 V; BuLi = −1.41 V; MeLi = −0.72 V; PhLi = −0.34 V, all in THF at −60 °C, except allyl at −25 °C.

(24) Evans, D. H. Carbonyl Compounds. In *Encyclopedia of Electrochemistry of the Elements*, Vol XII; Bard, A. J., Lund, H., Eds.; Marcel Dekker: New York, 1978; pp 1−259.

(25) Palmer, C. A.; Ogle, C. A.; Arnett, E. M. *J. Am. Chem. Soc.* **1992**, *114*, 5619. This paper provides an excellent review of the efforts to distinguish between rate-determining C−C bond formation and SET.

difficult to oxidize than methyllithium by ca. 0.25 V. However, the values suggest that the free energy for electron transfer to benzaldehyde from these methyl reagents is 30−35 kcal/mol, which appears to be very large relative to the low barriers that exist in these reactions. The apparent SET reaction of methyllithium with benzophenone relative to the polar reaction of methyl Grignard as suggested from carbonyl carbon KIEs might arise because of the 5 kcal/mol greater ease of oxidation of methyllithium and the steric difficulty encountered in polar additions to benzophenone relative to benzaldehyde. On the other hand, the free energy change involved in the electron transfer from the allyl reagents to benzaldehyde is roughly +13 kcal/mol based on electrochemical measurements, which suffer from irreversibility in the oxidation of the organometallic and counterion and solvent effects in the reduction of benzaldehyde.[25] Nonetheless, this relatively low endoergonicity is sufficient to allow the SET mechanisms to dominate over the polar addition pathway, even with benzaldehyde. The fact that allyl Grignard reacts much faster than expected on the basis of its oxidation potential relative to other Grignard reagents is also suggestive of a different mechanism, and this would appear to be the SET pathway and not the cyclic mechanism. The latter mechanism was proposed[26] to occur with allyl Grignard to distinguish it from the other Grignard reagents which, at the time, were assumed to proceed via SET but now should be recognized as polar, two-electron additions.

The use of redox potentials to characterize the nature of the addition reactions is reinforced by the current observations, even to the point of rationalizing the SDKIE results of the additions to cyclohexanecarboxaldehyde. Since the reduction potential of aliphatic aldehydes is roughly 5 kcal/mol higher than that of benzaldehyde,[24] the SET mechanism is less dominant. The only remaining concern given the data of Table 1 is the observation of SDKIEs of unity in additions of *n*-butyl- and *tert*-butyllithium to benzaldehyde, despite the apparent fact that the ease of oxidation of these reagents is higher than that of allyllithium.[23] We would suggest that these reagents can also add via a two-electron polar mechanism in an exceedingly exothermic fashion so as to effectively compete with the SET pathway. The exothermicity of the polar, two-electron pathway suggests an early transition state leading to an SDKIE of near unity, which is consistent with the observations. Evidence for the great exothermicity derives from Arnett's determination of the heat of reaction of various lithium reagents with *tert*-butyl alcohol (−50 kcal/mol for reaction of *n*-butyllithium in 9:1 hexane/ether).[27] Simple bond dissociation considerations would suggest that additions of lithium reagents to aldehydes and ketones would be even more exothermic. For example, the summation of reaction 4 ($\Delta H = -5.4$ kcal/mol[28]) and reaction 3, which is the reaction of methyllithium with *tert*-butyl alcohol to give lithium *tert*-butoxide and methane with a heat of reaction of −41.6 kcal/mol, provides the exothermicity of the addition of methyllithium to acetone (reaction 5), which is −47 kcal/mol.

$$\mathrm{MeLi} + (\mathrm{CH_3})_3\mathrm{-OH} \rightarrow \mathrm{Me-H} + (\mathrm{CH_3})_3\mathrm{-OLi} + 41.6\ \mathrm{kcal/mol} \quad (3)$$

$$\mathrm{Me-H} + (\mathrm{CH_3})_2\mathrm{C{=}O} \rightarrow (\mathrm{CH_3})_3\mathrm{-OH} + 5.4\ \mathrm{kcal/mol} \quad (4)$$

$$\mathrm{MeLi} + (\mathrm{CH_3})_2\mathrm{C{=}O} \rightarrow (\mathrm{CH_3})_3\mathrm{-OLi} + 47.0\ \mathrm{kcal/mol} \quad (5)$$

Since the heat of protonation of phenyllithium is the same as that of methyllithium, one might expect the exothermicity for the addition of phenyllithium to carbonyl compounds to be similar to that for addition of methyllithium. However, substitution of methyllithium by other butyllithium reagents should provide even more exothermic addition reactions. On the other hand, allyllithium is stabilized relative to simple aliphatic lithium reagents due to electron delocalization, so it should not provide as exothermic a reaction in either proton removal or a two-electron, polar addition. Allyllithium is, of course, not stabilized with respect to loss of an electron since a delocalized allyl radical is the result, which is not the case with loss of an electron from *n*-butyl- or *tert*-butyllithium.

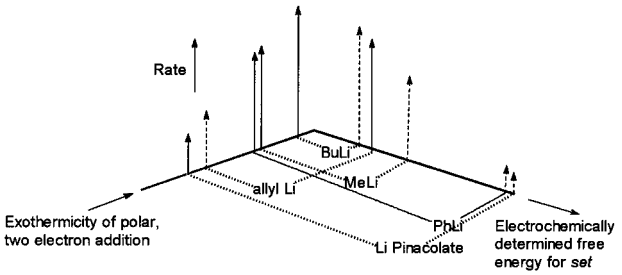

Figure 1. Semiquantitative relationship between the rates of two-electron (polar) and SET additions of lithium reagents to benzaldehyde based on the energetics of each reaction. Solid vertical arrows represent the favorable pathway.

The analysis above is, however, not quantitatively correct in the case of lithium pinacolate addition to benzaldehyde in THF solvent at 25 °C, where Arnett measured the reaction enthalpy to be −16 kcal/mol,[27] a value roughly 15 kcal/mol more exothermic than might be suggested by the analysis using reactions similar to 3−5. Differential solvent effects may be important here. However, the relative exothermicities for addition, as suggested by the heat of reaction of the lithium reagents with *tert*-butyl alcohol, are probably not out of line.

An important, perhaps obvious, conclusion from these results is that the combination of an easily oxidized organometallic reagent that is not highly basic and a good electron acceptor that is also sterically hindered provides the best opportunity for rate-determining SET pathway to compete with a two-electron, polar addition. It is also reasonable that less easily oxidized reagents are unlikely to undergo single-electron transfer prior to the rate-determining step. An example of the latter case is the lithium aldolate addition to benzaldehyde, where the electrochemically determined endoergonicity is roughly 45 kcal/mol.[25] Here the exoergonicity in the polar, two-electron addition is only −16 kcal/mol,[27] yet this pathway dominates, as judged by isotope effects, because of the very unfavorable SET reaction. Other examples having the SET pathway with very unfavorable energetics are the additions of phenyllithium and phenyl Grignard to benzaldehyde. Finally, in the additions to carbonyl compounds where the electron-transfer pathway is less endoergonic than roughly 13 kcal/mol, a highly exoergonic two-electron, polar addition can compete effectively with the SET pathway. Figure 1 is an attempt to provide a semiquantitative relationship between the two reaction pathways and the energetics of each pathway in the reaction of lithium reagents with benzaldehyde. It is necessarily incomplete because steric effects should retard the polar addition relative to the SET pathway, so highly hindered organometallic reagents, e.g., tertiary Grignard reagents, reacting with hindered carbonyl compounds, e.g.,

(26) Holm, T. *J. Am. Chem. Soc.* **1993**, *115*, 916.

(27) Arnett, E. M.; Moe, K. *J. Am. Chem. Soc.* **1991**, *113*, 7068. See also: Arnett, E. M.; Palmer, C. A. *J. Am. Chem. Soc.* **1990**, *112*, 7354.

(28) From Benson's Group Additivity Tables: Benson, S. W. *Thermochemical Kinetics*, 2nd ed.; John Wiley & Sons: New York, 1976; pp 272−275.

benzophenone, may prefer the SET pathway over the polar one, as has been suggested by Ashby.

Extent of C−C Bond Formation in Lithium Reagent Additions−Comparison to Calculations. The *i* values represent one approach to the question of the extent of bond formation to the carbonyl carbon. As described above, the *i* value is equal to the fraction of the kinetic isotope effect to the expected equilibrium isotope effect in free energy terms. It therefore assumes, as indicated above, that there are no factors affecting the $3N - 7$ vibrations of the transition state that cannot be interpolated between reactant and product state. Some caveats were described. In particular, concern was expressed for the extent of cation binding to the developing negative charge on the carbonyl oxygen. However, there is another approach to assessing transition-state structure which has been used effectively in recent years, namely the calculation of kinetic isotope effects from ab initio calculations of reactant and transition state structures.[11b,16] If the experimental KIEs can be reproduced by the calculations, then the structures giving rise to the differences in frequencies are assumed to be the correct ones. In the case of addition of the lithium enolate of *p*-(phenylsulfonyl)isobutyrophenone to benzaldehyde-*d*, a large inverse SDEIE (0.74) was determined at room temperature.[11b] HF/6-31++g** calculations of the ground state and transition state for gas-phase addition of lithium enolate to formaldehyde provided an SDKIE of 0.84, even though the C−C bond being formed was long, namely 2.221 Å. Since the calculated EIE was 0.82, the transition-state structure would suggest a much smaller inverse KIE by the reasoning proposed above. Just why the calculated KIE is not a bad match to the experimental EIE despite a transition-state structure that would descredit the relationship between KIEs and EIE proposed above is unclear. We note, however, that like all gas-phase ion−molecule reactions, the transition state is more stable than reactants, −12.2 kcal/mol in this case, so solvents play an important role and may be responsible for the discrepancies. We shall continue to employ the linear free energy relationship, $KIE = EIE^i$, as well as pursue calculations to establish a meaningful relationship between calculations on such transition states and the LFER.

Finally, we note that the calculated equilibrium deuterium isotope effect for formation of the methyllithium−acrolein complex prior to the transition state is 0.95 using scaled harmonic frequencies. This value might be interpreted to indicate that the origin of the inverse SDKIEs in the current study is rate-determining complex formation. However, the very small SDKIEs in the additions of butyllithium to benzaldehyde suggest that complex formation is not rate-determining in these cases and perhaps in no other organolithium addition. This is not to argue that Lewis acid−carbonyl complexes[29] could not be formed in the rate-determining step of additions catalyzed by strong Lewis acids such as boron trifluoride.

Experimental Section

General. ^{1}H NMR spectra were obtained on Bruker AM-500 (500 MHz), Varian VXR 400 (400 MHz), or Varian XL-300 (300 MHz) spectrometers. Chemical shifts are reported in δ units relative to TMS in chloroform-*d* solution, where chloroform-H is the reference which is assumed to be at δ 7.26 ppm. Column chromatography were performed on Merck silica gel (100−200 mesh), and thin-layer chromatography was performed on Merck silica gel (0.25 mm) precoated glass sheets. IR spectra were obtained on a Perkin-Elmer 298 or on a Mattson Instruments Galaxy 4020 Fourier transform spectrophotometer. Preparative GC was performed using a Varian 4700 gas chromatograph with thermal conductivity detection and either a DB-5 (6 ft × $^1/_4$ in.) column or a Carbowax (12 ft × $^1/_4$ in.) column. A Varian 3700 gas chromatograph with flame ionization detection was used for analytical gas chromatography. The capillary columns used were DB-5 (50 m × 0.25 mm), Supelcowax-10 (60 m × 0.35 mm), SPB-5 (100 m × 0.25 mm) in series with SP-2330 (60 m × 0.25 mm), and nickel bis(3-heptafluorobutyryl-(1*R*)-camphorate/OV-1 (25 m × 0.25 mm), a Schurig column. The latter two columns were used for isotopic separations. Integration of relative peak heights was accomplished with either a Varian 4240 or a Hewlett-Packard 3390A integrator. Dry tetrahydrofuran and diethyl ether were obtained by distillation under N_2 from sodium benzophenone ketyl. All glassware for addition reactions was flame-dried under vacuum with an N_2 purge. Precise temperature measurements were performed with a Newport series 2600 digital thermocouple indicator with a type E thermocouple.

Benzaldehyde-*d* (Adapted from Ref 30). A mixture of anhydrous diethyl ether (1.5 dmol[3]), 379.2 g (2 mol) of anhydrous stannous chloride, and 628.0 g (8 mol) of acetyl chloride was added to a 5-L three-neck flask equipped with a stirrer, a dropping funner, and a mercury bubbler. The flask was cooled to −10 °C, and 150.2 g (7.5 mol) of deuterium oxide was added in small portions such that the temperature did not rise above 10 °C. To the homogeneous solution was added 103.1 g (1 m) of benzonitrile, and stirring was continued for 12 h at room temperature. The precipitated crystalline stannic chloride complex was filtered away from the solution, washed with ether, and dried in the dark. Hydrolysis of the complex to benzaldehyde-D was accomplished upon addition to hot water. Extraction of the benzaldehyde-D from the aqueous solution by diethyl ether followed by drying the ethereal solution over anhydrous magnesium sulfate, removal of the solvent at reduced pressure, and distillation at reduced pressure, provided quantitative yield of benzaldehyde-D with 98.0% deuterium at the aldehydic carbon.

General Procedures for Methyl Ether Formation from Benzylic Alcohols: Procedure A. A dispersion of sodium hydride in mineral oil was washed thoroughly with pentane, and the residue was dried and weighed (0.133 g, 5.5 mmol) into a flask with with methyl iodide (0.68 g, 4.8 mmol) with 5 mL of dry THF. The dried alcohol derived from aldehyde and reagent addition (typically 0.35 mmol) was added to the mixture and allowed to stir at room temperature for 8 h. Then, 3 mL of a 1 M aqueous sodium hydroxide solution was added dropwise. The aqueous layer was extracted with ether (3 × 3 mL), and the combined organic layers were dried over anhydrous sodium sulfate and then filtered and concentrated by rotory evaporation. The solution was either analyzed directly on capillary or subjected to purification by preparative GC and analyzed by capillary GC.

Procedure B. A solution of benzyl alcohol (0.5 g, 4 mmol) in hexane (2 mL) was stirred with dimethyl sulfate (0.7 g, 5.5 mmol) and triethylamine (0.020 g) over sodium hydroxide pellets (0.5 g, 12.5 mmol) for 8 h. The solution was then heated at reflux for 3 h, cooled, and diluted with water (1 mL). After the mixture was stirred for 30 min, the organic layer was removed, and the aqueous layer was extracted with benzene (1 mL). The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, and concentrated to give a yellow oil. The product was eluted through a short column of silica gel with light petroleum ether/diethyl ether (5:1). Preparative GC on carbowax 20M was performed prior to analysis by ^{1}H NMR.

^{1}H NMR (methyl benzyl ether): δ 3.38 (s, 3H), 4.46 (s, 2H), 7.3 (m, 5H). For α-D-methyl benzyl ether, all resonances are in nearly the same positions, except for that at δ 4.46, which appears at δ 4.44 (three lines, $J = 1.6$ Hz, 1H).

General Procedure for Determination of Kinetic Isotope Effects from Lithium Aluminum Hydride, Lithium Triethylborohydride, and Lithium Borohydride Reductions by GC. For the lithium aluminum hydride, lithium triethylborohydride, and lithium borohydride reductions in tetrahydrofuran, a typical experiment was conducted in a 50-mL three-neck flask which had been oven-dried and fitted with a thermometer, magnetic stirrer, nitrogen inlet, and septum. The flask was charged with 25 mL of dry THF and 2 mL of a 1:1 mixture of

(29) Denmark, S. E.; Almstead, N. G. *J. Am. Chem. Soc.* **1993**, *115*, 3133 and references therein.

(30) Turner, L. *J. Chem. Soc.* **1956**, 1686.

benzaldehyde-H and benzaldehyde-D. After the flask was cooled to −78 °C, 1 mL of a 1.0 M solution of lithium triethylborohydride as added via syringe at such a rate as to maintain the temperature. After addition, the reaction mixture was poured slowly into 50 mL of a 5% aqueous sodium bicarbonate solution. Then, 30 mL of diethyl ether was added, the organic layer was separated, and the aqueous layer was extracted with 20 mL of diethyl ether. The combined organic layers were washed with water, concentrated aqueous sodium bisulfate, water, and saturated brine and then dried over anhydrous sodium sulfate. After chromatography on silica gel, eluting with 10% ethyl acetate in hexane, 73 mg of benzyl alcohol was obtained and converted to the methyl ether by procedure A. Capillary gas chromography on the nickel bis-(3-heptafluorobutyryl-(1*R*)-camphorate/OV-1 column at 23 psi and 75 °C resulted in a separation of the D and H compounds by ca. 40 s peak-to-peak at 19 min. The separation was within 10% of the baseline relative to the smallest peak.

The procedure was repeated with excess lithium triethylborohydride to obtain the ratio of H and D in the starting mixture. All analyses were performed in triplicate.

General Procedure for Determination of Kinetic Isotope Effects from Lithium Tri-*tert*-butoxy Hydride, Sodium Borohydride, Sodium Trimethoxy Borohydride, and Sodium Triacetoxyborohydride Reductions by ^{1}H NMR. For the lithium tri-*tert*-butoxy hydride reduction in tetrahydrofuran, the sodium borohydride reduction in ethanol, the sodium trimethoxy borohydride reduction in methanol, and the sodium triacetoxyborohydride reduction in acetic acid, after the reaction was quenched with water and the excess benzaldehyde removed by washing the ether or ether−THF layer with aqueous sodium bisulfite, followed by conversion of the resulting alcohol to the methyl ether by procedure B above, ^{1}H NMR was used to determine the isotope ratios. The methylene singlet of $PhCH_2OCH_3$ was separated by 8.5 Hz from the methine triplet of $PhCHDOCH_3$ at 400 MHz, and the methoxy group of the deuterated and nondeuterated compounds were separated by 1.5 Hz, while each had a line width of 0.4 Hz. Thus, the ratio of the methylene singlet of protio material to the methoxy singlet of the deuterated material was used to determine the kinetic isotope effects.

In a separate determination of the isotope effect in the sodium borohydride reduction in methanol at −78 °C using CG on the nickel complex capillary column, $k^H/k^D = 0.792$ was obtained, which compares favorably with the value determined from the reaction in ethanol by ^{1}H NMR, namely 0.82.

Procedure for Determination of Kinetic Isotope Effects from Addition of Methyl, Phenyl, and Allyl Grignard to Benzaldehyde. In a typical procedure, the Grignard reagent in ether was added to a mixture of benzaldehyde and benzaldehyde-*d*, which was dissolved in ether and cooled to −78 °C under a nitrogen atmosphere. To determine the ratio of H and D benzaldehyde, excess Grignard reagent was used. To determine the kinetic competition for reaction with H and D benzaldehyde, 0.1 equiv of Grignard reagent was used. In each case, the reaction was quenched with water, and in the case of use of a deficiency of Grignard reagent, the excess benzaldehyde was removed by washing the ether layer with aqueous sodium bisulfite. In all cases when the resulting alcohol was converted to the methyl ether by procedure A above, ^{1}H NMR was used to determine the isotope ratios by comparing the integration of the methine and the methoxy hydrogen signals.

General Procedure for Determination of Kinetic Isotope Effects from Methyllithium, Allyllithium, Phenyllithium, *n*-Butyllithium, and *tert*-Butyllithium Additions to Benzaldehyde and Methyl- and Allyllithium to Cyclohexanecarboxaldehyde by ^{1}H NMR. Additions of methyllithium in ether, allyllithium in ether,[31] phenyllithium in ether, *n*-butyllithium in ether, and *tert*-butyllithium in pentane to the aldehyde-H/D were conducted by adding 10 mol % (or higher if H/D fractionation in benzaldehyde was to be examined) of the reagent to the aldehyde at −78 °C at the concentrations indicated in Tables 1 and 2. Within 10 min of addition, each reaction was quenched with acetic acid, and then the organic layer was washed with aqueous bicarbonate followed by aqueous sodium bisulfite to remove the excess aldehyde. After evaporation of the solvent, the alcohol was converted to the methyl ether by procedure A above. ^{1}H NMR was used to determine the isotope ratios by comparing the integration of the methine and methoxy proton signals after purification of the methyl ether by preparative GC on a Carbowax column. Long delay times (20 s) were used between pulses to prevent saturation. In cases where the kinetic isotope effect for loss of benzaldehyde was determined, the average weighted ratio of the aldehydic proton to the ortho, meta, and para protons, which are separated to baseline at 400 MHz, was used for analysis.

^{1}H NMR (methyl methylphenylcarbinyl ether): δ 1.45 (d, J = 6.4 Hz, 3H), 3.22 (s, 3H), 4.29 (q, J = 6.4 Hz, 1H), 7.3 (m, 5H).

^{1}H NMR (methyl diphenylcarbinyl ether): δ 3.38 (s, 3H), 5.24 (s, 1H), 7.3 (bm, 10H).

^{1}H NMR (methyl butylphenylcarbinyl ether): δ 0.87 (t, J = 7.2 Hz, 3H), 1.3 (m, 4H), 1.62 (m, 1H), 1.80 (m, 1H), 3.20 (s, 3H), 4.07 (dd, J = 6.8, 6.0, 1H), 7.3 (m, 5H).

^{1}H NMR (methyl *tert*-butylphenylcarbinyl ether): δ 0.88 (s, 9H), 3.18 (s, 3H), 3.77 (s 1H), 7.3 (m, 5H).

^{1}H NMR (methyl allyl phenylcarbinyl ether): δ 2.49 (AB multiplet, 2H), 3.22 (s, 3H), 4.11 (dd, J = 7.5, 6.0 Hz, 1H), 5.0 (br d, J = 10.2, 5.04 (br d, J = 17.0 Hz, 1H), 5.76 (ddt, J = 17.0, 10.2, 7.0, 1H), 7.3 (m, 5H).

^{1}H NMR (methyl methylcyclohexylcarbinyl ether): δ 1.0 (d superimposed on multiplet, 5H), 1.2 (m, 3H), 1.39 (m, 1H), 1.62 (m, 3H), 1.74 (m, 3H), 3.02 (quint, J = 6.1 Hz, 1H), 3.30 (s, 3H).

^{1}H NMR (methyl allylcyclohexylcarbinyl ether): δ 1.1 (m, 5H), 1.45 (m, 1H), 1.7 (m, 3H), 2.28 (symm m, 2H), 2.94 (quart, J = 5.5 Hz, 1H), 3.33 (s, 3H), 5.04 (d, J = 10.0 Hz, 1H), 5.08 (d, J = 19.0 Hz, 1H), 5.85 (symm m, 1H).

Determination of Kinetic Isotope Effects in the Recovered Benzaldehyde. Reactions of benzaldehyde-H/D with methyllithium were conducted as described above except that more than 0.1 equiv of methyllithium was used. The NMR integration of the reaction mixture after workup was used to determine the extent of reaction as well as the deuterium content of the recovered benzaldehyde by integration of the aldehyde and ortho hydrogens to allow calculation[17] of the SDKIE. At 17.2% conversion at −78 °C, the KIE was 0.90; at 69.8% conversion the SDKIE was 1.04. In the addition of *n*-butyllithium at 17.6% conversion the SDKIE was 0.99; at 66.8% conversion the SDKIE was 1.18. With *tert*-butyllithium addition at 5.6% conversion, the SDKIE was 1.22, and at 69.3% conversion the SDKIE was 1.17. With allyllithium addition, the SDKIE at 35.1% conversion was 1.12, and at 64.8% conversion the SDKIE was 1.24. With phenyllithium addition at 30.0% conversion, the SDKIE was 1.10.

Ab Initio Computations. Acrolein and its Hydride Addition Product. Computations of the equilibrium isotope effect values were performed using the Gaussian[32] program at the MP2/6-311+G** level. *s-trans*-Acrolein-H(D) was used to model benzaldehyde, and propenoxide was used to model benzyl oxide. Energy second derivatives for C_s *cisoid* propenoxide, C_s methanol, C_{3v} methoxide, C_{3v} lithium methoxide, and C_{3v} sodium methoxide were computed at the minimum energy geometries. The force constants were used to compute the harmonic frequencies for protio and deuterio isotopomers. The frequencies were scaled[33] by a factor of 0.983 before being used to compute the reduced isotopic partition function ratio[34] for each molecule. The reduced isotopic partition function ratios for propenol and the sodium and lithium propenoxide salts were estimated from $(s_2/s_1)f_{ROM} = [(s_2/s_1)f_{RO^-}][s_2/s_1)f_{CH_3OM}/(s_2/s_1)f_{CH_3O^-}]$, where $(s_2/s_1)f_{RO^-}$ denotes the reduced isotopic partition function ratio for propenoxide anion, $(s_2/s_1)f_{CH_3O^-}$ denotes that for methoxide, and $(s_2/s_1)f_{CH_3OM}$ denotes that for methanol, lithium methoxide, or sodium methoxide. The value of $(s_2/s_1)f_{CH_3OH}$ for methanol differs depending on whether the deuterium substitution

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is anti or gauche to the O−H bond. The value of $(s_2/s_1)f_{propenol}$ was computed using the geometric mean of these two values.

Acrolein and Its Methyllithium Complex. Computations of the equilibrium isotope effect values were performed at the MP2/6-31G** level. The frequencies were used unscaled, although the calculated CH stretching frequencies were roughly 8% high. Correction would reduce the calculated value for the equilibrium in eq 2 to roughly 0.95.

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