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Isotope Effects and the Mechanism of Chlorotrimethylsilane-Mediated Addition of Cuprates to Enones

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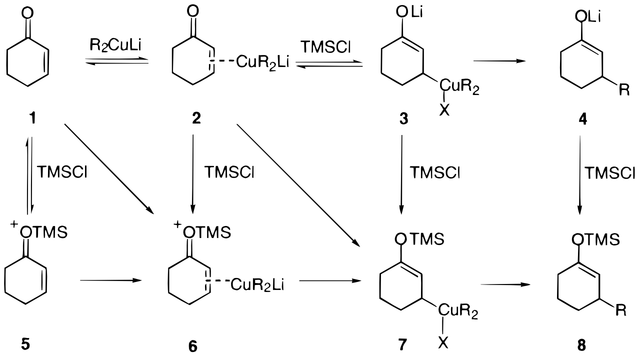
Abstract: Kinetic isotope effects were determined for the chlorotrimethylsilane-mediated reactions of cyclohexenone with lithium dibutylcuprate in tetrahydrofuran and with lithium butyl(*tert*-butylethynyl)cuprate in ether. For the reaction in tetrahydrofuran, the observation of a significant carbonyl oxygen isotope effect ($^{16}k/^{17}k = 1.018-1.019$) and small olefinic carbon isotope effects ($^{12}k/^{13}k = 1.003-1.008$) is consistent with rate-limiting silylation of an intermediate π-complex. Theoretically predicted isotope effects for model reactions support this conclusion. Rate-limiting silylation is also supported by relative reactivity studies of chlorotrimethylsilane versus chlorodimethylphenylsilane. The absence of a significant butyl-group carbon isotope effect on product formation indicates that the cuprate butyl groups are nonequivalent in the intermediate leading to the product-determining step. In diethyl ether the isotope effects revert to values similar to those found previously in reactions of cyclohexenone with lithium dibutylcuprate in the absence of chlorotrimethylsilane, consistent with no change in the overall mechanism in this solvent. A mechanistic hypothesis for the differing effects of TMSCl with changes in solvent and substrate is presented.

Introduction

Organocuprate conjugate addition reactions are an important tool in synthetic organic chemistry.[3] The success of these reactions and the stereochemistry of the products are often dependent on the detailed reaction conditions, including choice of solvent and the presence of additives. Due to a hazy mechanistic understanding of cuprate conjugate addition reactions in general, the nature of the effects of solvents and additives is not well understood.

Scheme 1



The important but mechanistically perplexing effect of additives is exemplified by cuprate conjugate additions in the presence of chlorotrimethylsilane (TMSCl). TMSCl has a remarkable effect on the rate and stereochemical outcome of many cuprate reactions and can allow reactions to proceed which would otherwise fail.[2−5] However, several conflicting theories have arisen as to the origin of these effects (Scheme 1). Corey and Boaz suggested that TMSCl accelerates the conjugate addition of cuprates to α,β-enones by the silylation of a d,π^*-complex to produce the silyl enol ether of a "Cu^{III}" β-adduct (e.g., **2** → **7**).[3] Kuwajima has contended that TMSCl acts as a Lewis acid to activate the enone by complexation with the enone oxygen (**1** → **5**).[6,7] Lipshutz has presented NMR evidence that the chloride of TMSCl acts as a Lewis *base* in an association with a lithium cation of cuprate dimers, and this is proposed to result in a "push−pull" effect on the conjugate addition (e.g., **1** → **6**).[8] More recently, Snyder and Bertz have suggested that the chloride of TMSCl coordinates with copper to stabilize the

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(6) Horiguchi, Y.; Komatsu, M.; Kuwajima, I. *Tetrahedron Lett.* **1989**, *30*, 7087.

(7) This proposal has been criticized based on negligible Lewis acidity of TMSCl *itself*. See: Lipshutz, B. H.; Aue, D. H.; James, B. *Tetrahedron Lett.* **1996**, *37*, 8471. However, this does not exclude the discreet silylation of enones apparently depicted in ref 6.

(8) Lipshutz, B H.; Dimock, S. H.; James, B. *J. Am. Chem. Soc.* **1993**, *115*, 9283.

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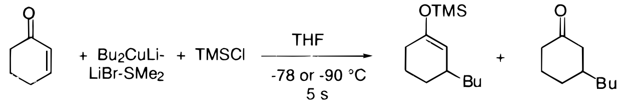
formation of the formal Cu^{III} intermediate (**7**, X = Cl-TMS)[9] (with a Cu^{I}-like electronic distribution).[10]

The problem in distinguishing these diverse proposals is that there is no direct evidence regarding the mechanistic effect of TMSCl. Thus, it has not been resolved whether the changes in rate and product stereochemistry arise from a fundamental change in the rate-limiting step as in the Corey and Kuwajima proposals or are the result of TMSCl coordination with either the cuprate reagent itself or intermediates along the reaction pathway. The difficulty has been compounded by large changes in the effect of TMSCl with solvent[5e,i] and by some uncertainty as to whether a silyl enol ether (e.g., **8**) or an enolate (e.g., **4**) is the initial product in these reactions (vide infra).

We have recently demonstrated the utility of kinetic isotope effects (KIEs) in the mechanistic study of cuprate conjugate additions.[11] The observation of significant ^{13}C KIEs for both the β carbon of the enone and the first carbon of the entering alkyl group was indicative of rate-limiting reductive elimination, and theoretically predicted KIEs for various mechanistic possibilities were found to support this interpretation. KIEs do not provide direct information as to overall reaction pathways or cuprate reagent structure, but they are uniquely illuminative as to the major bonding changes occurring in the rate-limiting step. We report here the results of a study of the ^{13}C and ^{17}O KIEs for the TMSCl-mediated addition of organocuprates to cyclohexenone in both THF and ether. The results provide a clear indication of how TMSCl changes the cuprate conjugate addition mechanism in these cases and how the effect of TMSCl changes with solvent.

Results

Reactions in THF. In exploratory reactions, $Bu_2CuLi-LiBr-SMe_2$ (generated from *n*-butyllithium and $CuBr\cdot SMe_2$) in THF was added rapidly to 1.1 equiv of TMSCl and 1.25 equiv of cyclohexenone dissolved in THF. In reactions with initial temperatures of −78 and −90 °C quenched after 5 s by rapid mixing with aqueous NH_4Cl, there was approximately quantitative formation (by GC analysis, based on reaction of one butyl group) of 3-butyl-1-(trimethylsilyloxy)cyclohexene (**9**). A parallel reaction without TMSCl required ~30 min at −90 °C for complete reaction. In the presence of TMSCl at −78 °C the formation of 1−2% of 3-butylcyclohexanone (**10**) was observed and at −90 °C no 3-butylcyclohexanone (<1%) was observed. In no case could 1-butyl-2-cyclohexen-1-ol be detected (<3%). Control reactions employing <1 equiv of cyclohexenone did not return any detectable unreacted cyclohexenone. This indicates that there was no significant formation of an enolate of cyclohexenone, which would interfere with the isotope effect determination below. As a control reaction for the possibility that the reactions were occurring on mixing with the warmer aqueous quench, reactions quenched after 5 s by addition of a large excess of cold (−78 °C) methanol were also complete. (As a control on the quenching ability of methanol, no reaction occurred when the methanol was added first.) However, extensive hydrolysis of the silyl enol ether occurs in the methanol-quenched reactions (verified by the addition of purified **9** to the reaction mixture). In reactions in which the Bu_2CuLi was generated from CuI we were unable to cleanly stop the reaction at the utilization of one butyl group per Bu_2CuLi (with excess cyclohexenone present).[12] Because significant reaction of butylcopper could complicate the isotope effect analysis, we did not study the reactions of Bu_2CuLi generated from CuI in detail. The ^{13}C KIEs for this reaction were determined by a recently reported methodology for the combinatorial high-precision determination of small KIEs at natural abundance.[13] Reactions using natural abundance cyclohexenone on a 0.3 mol scale were taken to 87.6 ± 0.9, 86.2 ± 1.2, and 78.5 ± 1.3% conversion (based on unreacted cyclohexenone) by the rapid addition of $Bu_2CuLi-LiBr-SMe_2$ to vigorously stirred THF solutions of TMSCl/cyclohexenone (as in the exploratory reactions, except using TMSCl/$Bu_2CuLi-LiBr-SMe_2$/cyclohexenone in a 1:1:~1.1 ratio) at −85 °C. (See Method A in the Experimental Section.) The temperature of the reaction mixtures rapidly rose to ca. −65 °C, and the reactions were quenched after 5 min. The unreacted cyclohexenone was recovered by an extractive workup followed by column chromatography and analyzed by ^{13}C NMR[8] compared to a standard sample of original cyclohexenone from the same bottle. The changes in ^{13}C isotopic composition were calculated using C_6 as an "internal standard" assuming that its isotopic composition does not change during the reaction.[14] From the changes in ^{13}C isotopic composition the KIEs and errors were calculated using the previously reported method.[13]



9 **10**

-78 °C : 1-2%
-90 °C : <1%

The ^{17}O KIE was determined by a novel method[15] that is a variation on the above procedure. To both recovered and standard samples of cyclohexenone was added ~1 mole equiv of diethyl ether (taken from the same bottle for each sample). The ^{13}C NMR integrations of C_6 versus the methylene carbon of diethyl ether were then used to precisely determined the *relative* ratios of diethyl ether in the two samples. The relative integration of the ^{17}O peaks could then be used to calculate the change in ^{17}O isotopic composition in the recovered material versus the standard, which could be used to calculate the ^{17}O KIEs. This is the first determination of ^{17}O KIEs by NMR and this simple methodology should find general utility.

The ^{13}C KIEs for the incoming butyl group were determined by analysis of the product from reactions taken to low conversion. Reactions of natural-abundance $Bu_2CuLi-LiBr-SMe_2$ in THF and 1 equiv of TMSCl at −85 °C were taken to ~10% conversion by the addition of 0.1 equiv of cyclohexenone. (See Method B in the Experimental Section.) The quantitatively formed **9** was completely hydrolyzed using either aqueous NH_4Cl or TBAF, and the resulting **10** was isolated by an extractive workup followed by column chromatography. An NMR-standard sample of **10** was prepared by the addition of BuLi (from the same bottle as used to form the $Bu_2CuLi-LiBr-SMe_2$) to excess 3-ethoxy-2-cylohexen-1-one followed by hydrolysis (1N HCl) and hydrogenation (H_2/Pd/C). The two

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[10] Snyder, J. P. *J. Am. Chem. Soc.* **1995**, *117*, 11025.

[11] Frantz, D. E.; Singleton, D. A.; Snyder, J. P. *J. Am. Chem. Soc.* **1997**, *119*, 3383. A recent paper has concluded that the rate-limiting step is formation of the Cu(III) intermediate (see: Canisius, J.; Gerold, A.; Krause, N. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 1644); however, this appears inconsistent with the observed isotope effects.

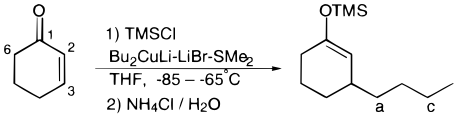
[12] Butylcopper is known to add to cyclohexenone at −78 °C in the presense of TMSCl. See ref 5b.

[13] Singleton, D. A.; Thomas, A. A. *J. Am. Chem. Soc.* **1995**, *117*, 9357.

[14] The KIEs determined here are *relative*, being determined based on relative integrations versus C_6 of cyclohexenone and C_c of butylcyclohexanone. (See ref 13.) These carbons were chosen as internal standards because their ^{13}C peaks were most cleanly separated from other peaks in the ^{13}C NMR and potential impurities. Small deviations from KIEs of 1.000 for these carbons will not affect the conclusions.

[15] This method was developed by S. R. Merrigan in this laboratory.

Table 1. ^{13}C and ^{17}O KIEs ($^{12}k/^{13}k$ or $^{16}k/^{17}k$) for the Addition of $Bu_2CuLi-LiBr-SMe_2$ to Cyclohexenone/TMSCl in THF (−85 to −65 °C)



KIEs based on starting material[a−c]	experiment 1	2	3
C_1	1.005(2)	1.001(2)	1.000(2)
C_2	1.003(2)	1.007(1)	1.006(2)
C_3	1.007(2)	1.004(2)	1.008(2)
O	e	1.018(6)	1.019(7)

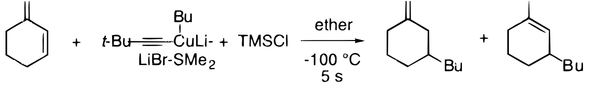
KIEs determined from *product*[b−d]	experiment 4	5	6
C_a	0.996(6)	0.999(4)	1.002(5)

[a] Experiments 1−3 are reactions carried to 87.6(9), 86.2(1.2), and 78.5(1.3)% completion, respectively, to determine the KIEs for cyclohexenone. [b] The numbers in parentheses are standard deviations in the last digit. [c] See ref 14. [d] Experiments 4−6 are reactions carried to ≈10% completion to determine the KIEs for the incoming butyl group. [e] Not determined.

samples of **10** were compared by ^{13}C NMR, and the ^{13}C KIEs were calculated directly from the change in integrations relative to C_c as internal standard.[14] The precision of KIEs determined in this manner (±0.3−0.6%) is limited by the reproducibility of ^{13}C NMR integrations but is sufficient for the purpose at hand.

The ^{13}C and ^{17}O KIEs observed in THF are summarized in Table 1. The most notable observations are (1) a substantial ^{17}O KIE, (2) very small but significant normal ^{13}C KIEs at both the α and β carbons of the enones, and (3) the complete absence of a ^{13}C KIE for the first carbon of the butyl group.

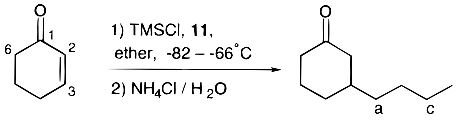
Reactions in Ether. We were unable to cleanly stop the reactions of $Bu_2CuLi-LiBr-SMe_2$/TMSCl with cyclohexenone at the utilization of one butyl group with excess cyclohexenone present. For this reason the reactions in ether employed the mixed cuprate **11** (prepared from the sequential reaction of $CuBr{\cdot}SMe_2$ with lithium *tert*-butylacetylide then *n*-BuLi) in which the *tert*-butylethynyl group is a “non-transferable ligand”. Reactions of **11** with 1−1.1 equiv of TMSCl and 1.25 equiv of cyclohexenone quenched after 5 s at −100 °C were >90% complete, and afforded 3-butylcyclohexanone nearly quantitatively with 1−3% 3-butyl-1-(trimethylsilyloxy)cyclohexene as the only detectable cyclohexenone-derived byproduct. A parallel reaction without TMSCl was also >90% complete in 5 s. In contrast, the reaction of **11** with cyclohexenone/TMSCl in THF at −78 °C afforded a 98:2 ratio of **9**:**10**. This suggests that the divergent results with $Bu_2CuLi-LiBr-SMe_2$ in THF and **11** in ether are due to the change in solvent and not due to the change in cuprate structure.



11 **10** **9** 1-3%

To determine the KIEs for the reactions of **11** in ether, reactions of cyclohexenone on a 0.3 mol scale were taken to 80.6 ± 1.4 and 84.9 ± 0.8% completion by the rapid addition of **11** to vigorously stirred solutions of cyclohexenone and TMSCl (using TMSCl/**11**/cyclohexenone in a 1:1:1.1−1.2 ratio) at −82 °C. The temperature of the reaction mixtures rapidly rose to ca. −66 °C, and the reactions were quenched after 10 min. The unreacted cyclohexenone was recovered and analyzed by ^{13}C and ^{17}O NMR as described for the THF reactions. The ^{13}C KIEs for the incoming butyl group were determined from reactions of cyclohexenone with **11** and 1 equiv of TMSCl taken to ∼10% conversion by using limiting cyclohexenone, and the product **10** was analyzed as before.

Table 2. ^{13}C and ^{17}O KIEs ($^{12}k/^{13}k$ or $^{16}k/^{17}k$) for the Addition of **11** to Cyclohexenone/TMSCl in Ether (−82 to −66 °C)



KIEs based on starting material[a−c]	experiment 7	8
C_1	1.002(4)	1.003(3)
C_2	1.001(4)	1.005(4)
C_3	1.014(6)	1.018(4)
O	*e*	1.003(10)

KIEs determined from *product*[b−d]	experiment 9	10
C_a	1.009(4)	1.010(3)

[a] Experiments 7−8 are reactions carried to 80.6(5) and 84.9(7)% completion, respectively, to determine the KIEs for cyclohexenone.[b] The numbers in parentheses are standard deviations in the last digit. [c] See ref 14. [d] Experiments 9−10 are reactions carried to ≈10% completion to determine the KIEs for the incoming butyl group. [e] Not determined.

The ^{13}C and ^{17}O KIEs observed in ether are summarized in Table 2. Most notable of the observations are significant ^{13}C KIEs at both the β carbon of the enone and first carbon of the butyl group and the absence of a significant ^{17}O KIE.

Theoretical Calculations and Predicted Isotope Effects. To aid in the interpretation of the experimental isotope effects, the model reactions in Figure 1 were examined in Becke3LYP density-functional theory calculations employing Ahlrichs’ “SVP” all-electron basis set for copper[16] and a 6-31G* basis set for the lighter elements.[17] Structure **14** has been previously reported.[18] Equilibrium or kinetic isotope effects were calculated by the method of Bigeleisen and Mayer[19] using the program QUIVER,[20] with frequencies scaled by 0.9614.[21] Tunneling corrections were applied to the kinetic isotope effects using a one-dimensional infinite parabolic barrier model.[22] The accuracy of these isotope effect calculations for simpler reactions has been strongly supported by recent studies.[23] The predicted isotope effects are summarized in Figure 1, and the calculated structures and energies are summarized in the Supporting Information.

On the basis of the predicted equilibrium isotope effects for formation of the π complex in Figure 1c,d, we considered in

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(16) Schäfer, A.; Horn, H.; Ahlrichs, R. *J. Chem. Phys.* **1992**, *97*, 2571.

(17) For a discussion of theoretical methodology for organocuprate structures, see: Nakamura, E.; Mori, S.; Nakamura, M.; Morokuma, K. *J. Am. Chem. Soc.* **1997**, *119*, 4887.

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(21) Scott, A. P.; Radom, L. *J. Phys. Chem.* **1996**, *100*, 16502.

(22) Bell, R. P. *The Tunnel Effect in Chemistry*; Chapman & Hall: London, 1980; pp 60−63.

(23) Beno, B. R.; Houk, K. N.; Singleton, D. A. *J. Am. Chem. Soc.* **1996**, *118*, 9984. Singleton, D. A.; Merrigan, S. R.; Liu, J.; Houk, K. N. *J. Am. Chem. Soc.* **1997**, *119*, 3385.

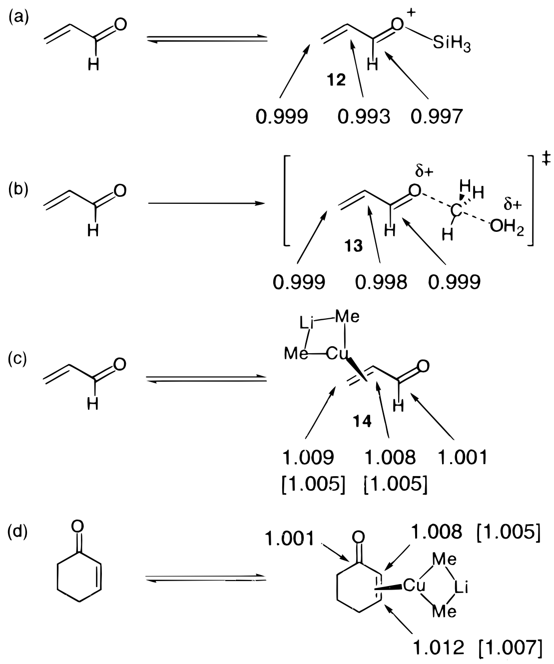


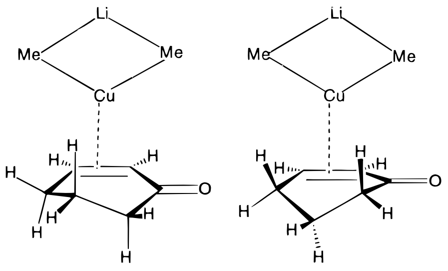
Figure 1. Theoretically predicted equilibrium or kinetic ^{13}C isotope effects ($k_{^{12}\mathrm{C}}/k_{^{13}\mathrm{C}}$) for model reactions at −78 °C. The prediction in part d is based on the most stable chair form **15**. Numbers in brackets in parts c and d are predicted values for the observed KIEs for rate-limiting silylation of the π complexes, based on a simulation of eq 1 (see text).

detail the observed *kinetic* isotope effect to be expected if the mechanism involved rate-limiting silylation of the π complex as in eq 1 . The overall KIE for rate-limiting silylation of a π

$$\mathbf{1} + \mathrm{R_2CuLi} \overset{K}{\rightleftharpoons} \mathbf{2} \xrightarrow[\substack{\text{TMSCl} \\ \text{rate-limiting step}}]{k} \mathbf{6} \text{ or } \mathbf{7} \qquad (1)$$

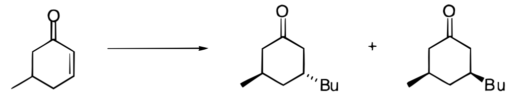
complex would be a complex function of the equilibrium isotope effect for formation of the π complex, the kinetic isotope effect for the silylation step, and the relative amounts of π complex and free enone present in the reaction mixture. The latter should change as the reaction proceeds, further convoluting a calculation of the KIE observed in recovered starting material from reactions taken to high conversion. To allow for these complications, the reaction of eq 1 was simulated in an Excel spreadsheet (see the Supporting Information). Isotope effects ($^{12}k/^{13}k$) in the silylation step of 1.000 were assumed for the α and β enone carbons. In the limiting case where free enone is absent, the observed α and β enone KIEs would then be 1.000. In the opposite limiting case of minimal π-complex formation, the observed KIEs would equal the equilibrium isotope effects for formation of the π complex. Using the actual experimental concentrations and a K of 110,[24] the observed KIEs would be slightly over half of the equilibrium isotope effects (Figure 1c,d).

For the complex of cyclohexenone with $\mathrm{Me_2CuLi}$, the two chair forms **15** and **16** were found. Of these, **15** was predicted to be more stable than **16** by 1.4 kcal/mol (including ZPE). (Structures **15** and **16** are geometrically based on the calculated structures; see the Supporting Information for the detailed geometries. Structures **14**, **15**, and **16** are simplistic models for the complex dimeric solvent-coordinated species actually in solution.)



15 **16**

Effect of TMSCl on Stereochemistry. The stereochemistry of cuprate additions to 5-methyl-2-cyclohexenone (**17**) was studied under the conditions of the isotope effect studies and also in the absence of TMSCl. After treatment of the crude product mixtures with $\mathrm{Bu_4NF}$ (when using TMSCl), the ratio of *trans*- and *cis*-5-methyl-3-butylcyclohexanones (**18** and **19**) was analyzed by integration of the ^{13}C signals for the C_2 and C_6 carbons (with delays $>5T_1$). For additions of $\mathrm{Bu_2CuLi{-}LiBr{-}SMe_2}$ in THF the ratio of trans and cis products in the absence of TMSCl was 99:1 (in rough agreement with previous observations[25]) but the selectivity decreased to 90:10 with TMSCl. For the addition of **11** in ether the cis isomer could not be detected (>150:1) in either the presence or absence of TMSCl.



17 **18** **19**

$\mathrm{Bu_2CuLi\text{-}LiBr\text{-}SMe_2}$ / THF / no TMSCl - 99:1
$\mathrm{Bu_2CuLi\text{-}LiBr\text{-}SMe_2}$ / THF / TMSCl - 90:10
11 / ether / no TMSCl - >150:1
11 / ether / TMSCl - >150:1

Discussion

We analyze here our results within the mechanistic framework of possibilities shown in Scheme 1. The commonly proposed general reaction scheme involving an initial π complex followed by a formal Cu(III) intermediate appears consistent with experimental observations.[3,26] However, there are many unestablished details within this framework, particularly with regard to the cuprate cluster structure, and other more complex mechanisms cannot be excluded. A specific alternative mechanism worth noting is the 1,2-addition of a Cu−R bond across the C=C bond of enones to afford α-cuprio ketones.[27] This mechanism was first proposed in the 1970s and a variation of it has recently been revived based on theoretical calculations on the addition of the cluster $\mathrm{(Me_2CuLi)_2}$ to acrolein.[18] This mechanism does not account for the observed KIEs[11,28] nor does it provide an explanation for the effect of TMSCl on cuprate-mediated cis−trans isomerization of enones (vide infra). Considering the critical influence of solvent on the course of these

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(24) Krauss, S. R.; Smith, S. G. *J. Am. Chem. Soc.* **1981**, *103*, 141−148. The observed equilibrium in this paper probably reflects a combination of π complex formation and lithium coordination to the enone oxygen. See: Vellekoop, A. S.; Smith, R. A. J. *J. Am. Chem. Soc.* **1994**, *116*, 2902.

(25) House, H. O.; Fischer, W. F., Jr. *J. Org. Chem.* **1968**, *33*, 949.

(26) (a) Hallnemo, G.; Olsson, T.; Ullenius, C. *J. Organomet. Chem.* **1985**, *282*, 133. (b) Lipshutz, B. H.; Dimock, S. H.; James, B. *J. Am. Chem. Soc.* **1993**, *115*, 9283. (c) Bertz, S. H.; Smith, R. A. J. *J. Am. Chem. Soc.* **1989**, *111*, 8276. (d) Alexakis, A.; Sedrani, R.; Mangeney, P. *Tetrahedron Lett.* **1990**, *31,* 345. (e) Krause, N.; Wagner, R.; Gerold, A. *J. Am. Chem. Soc.* **1994**, *116,* 381. (f) Vellekoop, A. S.; Smith, R. A. J. *J. Am. Chem. Soc.* **1994**, *116,* 2902.

(27) (a) Berlan, J.; Battioni, J.; Koosha, K. *J. Organomet. Chem.* **1978**, *152*, 359−365. (b) Berlan, J.; Battioni, J.; Koosha, K. *Bull. Soc. Chim. Fr.* **1979**, 183−190.

(28) Allowance for the equilibrium presence of the enone π complex as done here may decrease the discrepancy between experimental and calculated isotope effects in these reactions. See: Mori, S.; Nakamura, E. *Chem. Eur. J.* **1999**, *5*, 1534−1543.

reactions,[29] further calculations involving solvated reactants may resolve these problems.

A major point of confusion in TMSCl-mediated reactions has been the identity of the initial product. Many workers have used workup conditions which would hydrolyze silyl enol ethers such as **9**, and most others have not attempted to distinguish between direct formation of a silyl enol ether and silylation of an initially formed enolate. Nonetheless, it has often been assumed that silyl enol ethers or related intermediates are the initial products in these reactions. It was therefore surprising when it was reported that the reaction of $Bu_2CuLi{\cdot}LiI$ with cyclohexenone in THF in the presence of 6 equiv of TMSCl afforded **10** as the major product (after quenching of a presumed initial enolate) with only 27% of silyl enol ether **9** found at the shortest reaction time.[9] Recent workers have found that TMSI-mediated reactions of $Bu_2CuLi{\cdot}LiI$ with cyclohexenone afford predominately **9**,[30] and a footnote in that paper reports a private communication from one of the previous workers stating that the use of only 1−2 equiv of TMSCl affords “mainly TMS enol ether”. Apparently the use of 6 equiv of TMSCl and aqueous quenching resulted in the hydrolysis of some of the initially formed **9**. In our experiments using only 1 equiv of TMSCl and cuprate derived from $CuBr{\cdot}SMe_2$, the silyl enol ether **9** is virtually the exclusive product present at very short reaction times in THF.

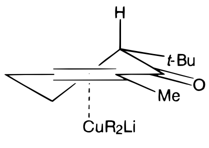
However, the observation of silyl enol ether at short reaction times does not in itself conclusively establish whether silylation is an integral part of the reaction mechanism or occurs “after the fact”, i.e., after the rate-limiting step by silylation of an enolate. In this regard the ^{17}O KIEs observed in these reactions are telling. The substantial ^{17}O KIE observed in THF is indicative of the carbonyl oxygen undergoing a major bonding change in the rate-limiting step. The ^{17}O KIE in THF is much larger than would be expected from a 1,4-addition to the enone: very small ^{18}O KIEs are observed in carbonyl addition reactions.[31] In contrast, the ^{17}O KIE in ether, where there is no significant formation of silylated product (consistent with previous observations[9]), is within experimental error of unity. Taken together, these results strongly implicate rate-limiting silylation of the carbonyl oxygen in THF.

The involvement of silylation in the rate-limiting step in THF places significant constraints on the mechanism. If TMSCl were simply acting as a Lewis acid as proposed by Kuwajima, then the coordination of TMSCl with cyclohexenone to form **5** would have to be rate limiting and (surprisingly!) irreversible under the reaction conditions. The cyclohexenone ^{13}C isotope effects would reflect this silylation step, and would be expected to be approximately unity at the olefinic carbons. The small but significant positive deviation from unity of the ^{13}C KIEs at both the α and β carbons argues against this mechanism. This conclusion is supported by the theoretically predicted isotope effects for model reactions. The equilibrium ^{13}C KIEs for the formation of **12** were calculated as a rough model for the *secondary* KIEs expected if silylation of the starting enone is rate limiting, since the carbons are not being transferred in this step.[32] The predicted equilibrium isotope effects for the formation of **12**, as well as the predicted kinetic isotope effects for methylation of acrolein, are all slightly inverse (Figure 1a,b). This supports the qualitative argument that rate-limiting silylation of the starting enone cannot account for the observed KIEs.

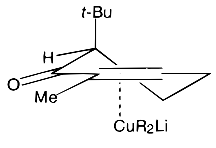
An important basis for the Corey proposal of silylation of a d,π^*-complex was the observation that acyclic enones underwent cis−trans isomerization in the absence of TMSCl but not in the presence of TMSCl in THF.[3] It was proposed that the cis−trans isomerization without TMSCl is the result of reversible formation of a “Cu^{III}” β-adduct before the rate-limiting step, and this proposition has recently been strongly supported in KIE studies.[11] The lack of isomerization with TMSCl would then be consistent with a switch to an earlier rate-limiting step, but does not by itself distinguish between rate-limiting silylation of a π complex, rate-limiting formation of the Cu β-adduct with rapid silylation, or rate-limiting formation of the π complex. The last of these has often been assumed in stereochemical arguments[6,5g] (misleadingly! vide infra), but the latter two possibilities are both excluded here by the requirement for a rate-limiting silylation step.

The remaining possibility of rate-limiting silylation of a π complex is supported by the theoretically predicted isotope effects. From Figure 1c,d, small normal kinetic ^{13}C isotope effects are predicted at both the α and β enone carbons. These predictions involve ad hoc assumptions regarding the kinetic isotope effects for the silylation step and the equilibrium constant for formation of the π complex, as well as a simplistic modeling of a likely more complex enone−π complex structure. Nonetheless the striking agreement between the predicted and experimental KIEs demonstrates that the observed α and β enone ^{13}C KIEs are consistent with rate-limiting silylation of a π complex.

Rate-limiting silylation of the π complex also provides an explanation for the enigmatic stereochemical results of Kuwajima which had led to the proposal of an initial Lewis acid complex.[6] The key observation was that while the cis π complex **20** was expected to be most stable in additions to 6-*tert*-butyl-2-methylcyclohexenone, the trans product was predominant in the presence of TMSCl. However, the stereoelectronically enforced approach of TMSCl in the plane of the carbonyl group (toward the lone pairs of the carbonyl oxygen) would be highly sterically hindered, blocking the formation of the cis product. The trans product can be formed by the less disadvantageous silylation of conformation **21** that places the *tert*-butyl group in a pseudoaxial position.[33]



20



21

The stereochemistry of the TMSCl-mediated addition of $Bu_2CuLi{-}LiBr{-}SMe_2$ to 5-methylcyclohexenone in THF may also be rationalized by rate-limiting silylation of a π complex. Based on the theoretical predictions for **15** and **16**, the trans π complex **22** would be expected to be preferred over the cis

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(29) (a) Kingsbury, C. L.; Smith, R. A. J. *J. Org. Chem.* **1997**, *62*, 7637. (b) Kingsbury, C. L.; Smith, R. A. J. *J. Org. Chem.* **1997**, *62*, 4629.

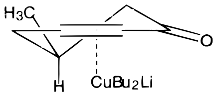
(30) Eriksson, M.; Johansson, A.; Nilsson, M.; Olsson, T. *J. Am. Chem. Soc.* **1996**, *118*, 10904. See especially footnote 20. In addition, a recent paper by one of the original authors in ref 9 also states that with the use of a large excess of TMSCl, hydrolysis of the initially formed silyl enol ether occurs upon workup. See: Bertz, S. H.; Chopra, A.; Eriksson, M.; Ogle, C. A.; Seagle, P. *Chem. Eur. J.* **1999**, *5*, 2680.

(31) Marlier, J. F. *J. Am. Chem. Soc.* **1993**, *115*, 5953. O’Leary, M. H.; Marlier, J. F. *J. Am. Chem. Soc.* **1979**, *101*, 3300.

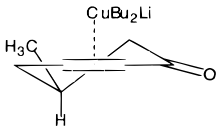
(32) (a) It is commonly assumed that equilibrium secondary hydrogen isotope effects are an upper bound for the kinetic isotope effect, though exceptions have been noted. See: Glad, S. S.; Jensen, F. *J. Org. Chem.* **1997**, *62*, 253. (b) Modeling of the secondary KIEs using equilibrium isotope effects is bolstered by the expectation that the endothermic silylation step should have a late transition state.

(33) Molecular mechanics calculations (MM2) predict that having the *tert*-butyl group axial in 6-*tert*-butylcyclohexenone is disfavored by only 0.8 kcal/mol.

complex **23**, but not overwhelmingly. If **22** and **23** are assumed to be equally reactive in the rate-limiting silylation, the trans:cis product ratio should reflect the energy difference between **22** and **23**. The $\Delta\Delta G^{\ddagger}$ of 0.9 kcal/mol for formation of **18** and **19** (based on a 91:9 ratio at -78 °C) is in very reasonable agreement with the predicted difference of 1.4 kcal/mol for **15** and **16**. It should be noted that the observation of rate-limiting silylation of the π complex does not exclude an important role for TMSCl$-$lithium coordination as proposed by Lipshutz or the stabilization of the formal Cu^{III} intermediate by a TMSCl$-$copper coordination proposed by Snyder and Bertz. The latter, however, would occur after the rate-limiting step and could not be responsible for the rate and stereoselectivity effects of TMSCl in THF.

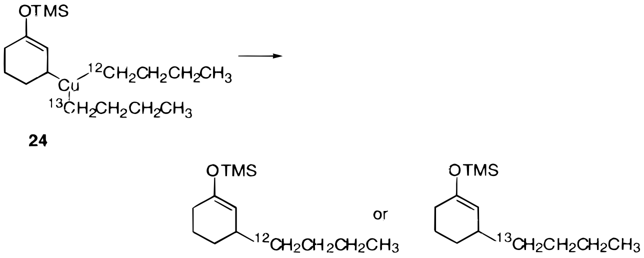


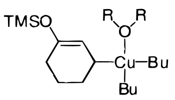
22



23

An intriguing feature of the isotope effects observed in THF is the complete absence of a ^{13}C KIE for the first carbon of the butyl group. Obviously, the butyl group is not being transferred in the rate-determining step, but a subtle yet important inference may be made about the *product-determining* step. If the intermediate before reductive elimination were, for example, **24**, in which the two butyl groups are equivalent (except for isotopic substitution), then the intramolecular competition between these butyl groups would result in an isotope effect on which product is formed. It can be deduced that **24** is not the penultimate intermediate! In more general terms it can be concluded that in the intermediate preceding product formation the butyl groups are neither equivalent nor do they rapidly interconvert relative to the rate of product formation. This observation may be taken as being consistent with the proposal of Snyder that a formal Cu^{III} intermediate would require stabilization by solvation in a square-planar complex,[10] with the proviso that the butyl groups are diastereotopic (i.e. cis) as in **25**. A more complex cuprate cluster in which the butyl groups are nonequivalent could also account for this result.





25

It is well-known that TMSCl has less effect on additions to enones in ether than in THF,[5e,i] but it was important to establish the mechanistic basis for this difference. The KIE results in ether are very different from those in THF. The KIEs for the reaction of **11** with cyclohexenone in the presence of TMSCl (1.014$-$1.018 at the β enone carbon, 1.009$-$1.010 at the first carbon of the butyl group) are very similar to those observed previously in the reaction of $Bu_2CuLi-LiBr-SMe_2$ with cyclohexenone without TMSCl (1.020$-$1.0026 at the β enone carbon, 1.011$-$1.016 at the first carbon of the butyl group).[11] There is thus no indication that TMSCl changes the rate-limiting step in ether, and the results are consistent with rate-limiting reductive elimination. This conclusion is supported by Corey's observation that TMSCl did not inhibit cis$-$trans isomerization of an acyclic enone in ether,[5f] in contrast to observations in THF. (Notably, the use of trimethylsilyl triflate in ether instead of TMSCl did inhibit cis$-$trans isomerization.) Unlike the THF reaction, TMSCl did not affect the stereochemistry of addition of **11** to 5-methylcyclohexenone. There is no clear indication that TMSCl affects the additions of **11** to enones in ether at all.

However, TMSCl does have a large impact on *some* cuprate conjugate additions in ether, particularly those involving additions to α,β-unsaturated esters, amides, and nitriles.[2b,5g] It is notable that these are relatively unreactive substrates for uncatalyzed cuprate conjugate additions. The large changes observed in the reactivity of unsaturated amides[2b] and the stereochemistry of additions to unsaturated esters[5g] would indicate that TMSCl is not merely improving yields by trapping enolates but is mediating a mechanistic change akin to its effect on addition to cyclohexenone in THF.

A consistent mechanistic hypothesis for the differing effects of TMSCl with changes in solvent and substrate starts with the observation that the coordination of lithium to the carbonyl oxygen is a critical factor in cuprate conjugate additions without additives. No reaction occurs in the presence of excess 12-crown-4.[34] In ether the lithium coordination is sufficient for the reaction to proceed rapidly with cyclohexenone, and the TMSCl-accelerated process cannot compete. (However, as mentioned above, the more powerful electrophile trimethylsilyl triflate can.) In the more basic THF the lithium coordination is attenuated[28] and acceleration by irreversible silylation of an enone$-$cuprate π complex dominates. The irreversible nature of the silylation brings about the change in the rate-limiting step from carbon$-$carbon bond formation in the absence of TMSCl. (It is important to remember that the cuprate reagent itself has changed in going from ether to THF, but we would emphasize the effect of lithium coordination.) With unsaturated esters and amides the lithium$-$carbonyl coordination is not sufficient, even in ether, to activate the conjugate addition (though more powerful Lewis acids can[35]) and the TMSCl-mediated process takes over.

Conclusions

The central cause of the effect of TMSCl on the addition of Bu_2CuLi to cyclohexenone in THF is a change in the rate-limiting step. The KIEs observed are qualitatively consistent with Corey's proposal that TMSCl traps an intermediate π complex, with the important specification that silylation is the rate-limiting step. This interpretation is supported by theoretically predicted isotope effects and is consistent with a variety of observations. The results have no bearing on the "push$-$pull" proposal of Lipshutz (e.g., **1** → **6**) but do not support any importance for TMSCl coordination of the initial enone or TMSCl coordination of a formal Cu^{III} intermediate. There is still considerable uncertainty as to the cuprate cluster structure at every stage of the reaction pathway, but a consistent qualitative mechanistic picture is emerging.

The outcome of the black box of organocuprate reactions can depend on cuprate structure, substrate, solvent, additives, and

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(34) Ouannes, C.; Dressaire, G.; Langlois, Y. *Tetrahedron Lett.* **1977**, *10*, 815.

(35) Yamamoto, Y.; Yamamoto, S.; Yatagai, H.; Ishiyama, Y.; Maruyama, K. *J. Org. Chem.* **1982**, *47*, 119.

the detailed reaction conditions, and the mechanistic understanding of these effects should greatly aid progress in the area. We anticipate that kinetic isotope effects will continue to be an effective tool toward that end.

Experimental Section

All reactions were carried out in dried glassware and freshly purified solvent under a positive pressure of nitrogen using standard airless techniques. Chlorotrimethylsilane was distilled from tributylamine immediately before use.

Reactions in THF. Method A. To a mixture of 55.50 g (0.27 mol) of $CuBr{\cdot}SMe_2$ and 1.5 L of THF at −78 °C was added dropwise (maintaining a temperature below −70 °C) 211 mL (0.54 mol) of a freshly titrated 2.56 M solution of *n*-butyllithium in hexanes, and the mixture was stirred for 30 min. This mixture was then added, in less than 10 s via a glass-tubing connection, to a vigorously mechanically stirred separate flask containing 28.84 g (0.30 mol) of 2-cyclohexenone, 2.0 L of THF, 29.33 g (0.27 mol) of chlorotrimethylsilane, and 5.11 g of dodecane (internal standard) at −85 °C. The temperature of the resulting mixture rapidly increased to −65 °C. After 5 min the reaction was quenched by the rapid addition of 1 L of saturated aqueous NH_4Cl. The percent conversion based on GC analysis of an aliquot was 87.6 ± 0.9%. The reaction mixture was allowed to come to room temperature and was extracted in 1-L portions with three 500-mL portions of diethyl ether (adding sufficient water initially to make all salts dissolve). The ether extracts were combined, washed with saturated NH_4Cl, brine, and water, dried ($MgSO_4$), and concentrated under vacuum. The residue was then chromatographed on a 4 cm × 30 cm silica gel column using 10% ethyl acetate/petroleum ether (30−60 °C) as eluent to afford 0.98 g of 2-cyclohexenone in 99% purity by GC.

Two reactions carried out by analogous procedures proceeded to 86.2 ± 1.2% and 78.5 ± 1.3% conversion.

Method B. In a typical procedure, 156 mL (0.40 mol) of a 2.56 M solution of *n*-butyllithium in hexanes was added dropwise (maintaining a temperature below −70 °C) to a mixture of 41.1 g (0.20 mol) of $CuBr{\cdot}SMe_2$ and 1.5 L of THF at −78 °C, and the mixture was stirred for 30 min. At this point, the reaction was cooled to −85 °C and 21.73 g of chlorotrimethylsilane was added. The mixture was stirred for 1 min and 1.92 g (20 mmol) of 2-cyclohexenone in 50 mL of THF was added dropwise over 30 min. 2-Cyclohexenone could not be detected by GC analysis of an aliquot taken after 10 min. The reaction was then quenched by the addition of 1 L of saturated aqueous NH_4Cl, and the solution was allowed to warm to room temperature and then stirred until all of the 3-butyl-1-(trimethylsilyloxy)cyclohexene was hydrolyzed to 3-butylcyclohexanone. An extractive workup as in Method A yielded a residue that was chromatographed on a 4 cm × 30 cm silica gel column using 7% ethyl acetate/petroleum ether as eluent to afford 1.7 g of 3-butylcyclohexanone (>99% purity by GC).

Reactions in Ether. Method A. A mixture of 200 mL of ether, 76 mL (0.20 mol) of a 2.62 M solution of *n*-butyllithium in hexanes, and 17.25 g (0.21 mol) of *tert*-butylacetylene (added last, dropwise) was stirred at −78 °C for 30 min and 0 °C for 30 min. The resulting solution was then transferred to a mixture of 41.12 g (0.20 mol) of $CuBr{\cdot}SMe_2$ and 1.2 L of Et_2O at 0 °C and stirred until all of the $CuBr{\cdot}SMe_2$ dissolved. At this point the solution was cooled to −78 °C and 72.2 mL (0.19 mol) of a 2.62 M solution of *n*-butyllithium in hexanes was added dropwise, and the resulting light brown solution of **11** was stirred at −78 °C for 1 h. The solution of **11** was then added, in less than 10 s via a glass-tubing connection, to a vigorously mechanically stirred separate flask containing 23.07 g (0.24 mol) of 2-cyclohexenone, 2.0 L of Et_2O, 21.73 g (0.20 mol) of chlorotrimethylsilane, and 6.13 g of dodecane (internal standard) at −82 °C. The temperature of the resulting mixture rapidly increased to −66 °C. After 10 min the reaction was quenched by the rapid addition of 1 L of saturated aqueous NH_4Cl. The percent conversion based on GC analysis of an aliquot was 80.6 ± 1.4%. An extractive workup and chromatography as in Method A of the THF reactions, using 90:10 v/v saturated NH_4Cl:NH_4OH in place of the saturated NH_4Cl in the extractions, afforded 1.54 g of recovered cyclohexenone in 99% purity by GC analysis.

Table 3. Average Integrations for Cyclohexenone[a,b]

experiment	C_1	C_2	C_3
THF			
1	991.6(2.1)	1096.1(2.9)	1103.5(2.7)
standard	980.9(2.6)	1089.7(3.5)	1087.6(4.4)
R/R_0	1.011(0.003)	1.006(0.004)	1.015(0.005)
2	990.2(2.8)	1095.9(1.9)	1104.6(3.7)
standard	987.4(2.0)	1081.5(2.1)	1095.8(3.5)
R/R_0	1.003(0.003)	1.013(0.003)	1.008(0.005)
3	985.3(1.9)	1096.0(2.4)	1098.4(2.4)
standard	985.2(1.7)	1085.4(1.7)	1085.1(1.2)
R/R_0	1.000(0.003)	1.010(0.003)	1.012(0.003)
ether			
7	980.2(4.2)	1097.3(5.6)	1127.1(8.7)
standard	977.3(4.2)	1095.8(3.2)	1101.8(4.6)
R/R_0	1.003(0.006)	1.001(0.006)	1.023(0.009)
8	954.0(3.0)	1085.1(5.4)	1107.9(3.9)
standard	948.8(4.7)	1073.9(5.5)	1072.2(5.7)
R/R_0	1.005(0.006)	1.010(0.007)	1.033(0.007)

[a] See Tables 1 and 2 for the numbering scheme for experiments and carbons. [b] Integrations are relative to C_6 which was set at 1000. The integrations are averaged from five spectra for each sample. Standard deviations are shown in parentheses.

A second reaction performed by an analogous procedure proceeded to 84.9 ± 0.7% conversion.

Method B. In a typical procedure, 21.73 g (0.20 mol) of chlorotrimethylsilane was added to a solution of **11** at −78 °C prepared as described in Method A. After the mixture was stirred for 5 min, 1.92 g (20 mmol) of 2-cyclohexenone in 50 mL of ether was added dropwise. 2-Cyclohexenone could not be detected by GC analysis of an aliquot taken after 10 min, and the reaction was quenched by the addition of 1 L of saturated aqueous NH_4Cl. An extractive workup as in Method A yielded a residue that was chromatographed on a 4 cm × 30 cm silica gel column using 7% ethyl acetate/petroleum ether as eluent to afford 3-butylcyclohexanone (>99% purity by GC).

NMR Standard 3-Butylcyclohexanone. To a mixture of 60 mL of ether and 4.91 g (35 mmol) of 3-ethoxy-2-cyclohexen-1-one at 0 °C was added dropwise 30 mmol of *n*-butyllithium in hexanes (taken from the same bottle used to generate the cuprate in each case). After being stirred for 30 min at 0 °C, the reaction mixture was quenched with excess 1 N HCl, extracted with three 20-mL portions of ether, dried ($MgSO_4$), and concentrated under vacuum. The residue was dissolved in 100 mL of absolute ethanol and hydrogenated using 0.1 g of 5% Pd/C in a Parr apparatus at 42 psi of H_2. Filtration and concentration of the reaction mixture followed by silica gel chromatography using 7% ethyl acetate/petroleum ether as eluent afforded 3-butylcyclohexanone (>99% purity by GC).

Additions to 5-Methyl-2-cyclohexenone (17). The reactions of **17**[36] were carried out by adding 220 mg (2.0 mmol) of **17** dropwise to either 2.0 mmol of $Bu_2CuLi{-}LiBr{-}SMe_2$ (prepared as described above) in 20 mL of THF or 2.0 mmol of **11** (prepared as described above) in 20 mL of ether, with or without 272 mg (2.5 mmol) of TMSCl (added 1 min before the **17**). All of the reactions were stirred for 30 min at −78 °C and quenched by the addition of 10 mL of saturated NH_4Cl (reactions in THF) or 10 mL of 90:10 v/v saturated NH_4Cl:NH_4OH (reactions in ether). After an extractive workup and treatment of the product mixtures with Bu_4NF (when using TMSCl), the crude product was analyzed by ^1H and ^{13}C NMR.

NMR Measurements. NMR samples were generally prepared using 1.00 g of material in a 10 mm NMR tube with a sample height of 5.0 cm, and in all cases recovered and standard material samples were prepared identically. A T_1 determination by the inversion−recovery method was carried out for each NMR sample, and the T_1 for each carbon remained constant within experimental error from sample to sample.

The ^{13}C spectra were obtained at 100.577 MHz on a Varian XL400 broadband NMR spectrometer, with inverse gated decoupling, calibrated

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(36) Blanchard, J. P.; Goering, H. L. *J. Am. Chem. Soc.* **1951**, *73*, 5863.

Table 4. Average Integrations for 3-Butylcyclohexanone[a,b]

experiment	C_a in sample	C_a in standard
THF		
4	1067.9(5.9)	1063.6(3.1)
5	1064.5(3.1)	1063.6(3.1)
6	1034.6(4.6)	1036.2(1.8)
ether		
9	1026.3(3.3)	1035.5(1.7)
10	1025.0(2.6)	1035.5(1.7)

[a] See Tables 1 and 2 for numbering the scheme for experiments and carbons. [b] Integrations are relative to C_c which was set at 1000. The integrations are averaged from five spectra for each sample. Standard deviations are shown in parentheses.

Table 5. Average Integrations for Spectra of Cyclohexenone/Ether Mixtures

experiment	C_6 in ^{13}C NMR	C═O in ^{17}O NMR
THF		
2	229.9(0.2)	572.0(2.1)
standard	454.9(0.4)	1092.6(11.4)
3	233.6(1.0)	479.4(2.8)
standard	220.1(1.2)	438.7(2.4)
ether		
8	390.7(7.0)	915.9(3.4)
standard	470.1(1.4)	1095.0(1.4)

45° pulses, 120-s delays between pulses, and at a controlled temperature of 30 °C. To obtain sufficient digital resolution (5 points/$\nu_{1/2}$ is minimal), a 220032 point FID was zero-filled to 512K points before Fourier transformation. Integrations were determined numerically using a ±3.0 Hz region for each peak. A zeroth-order baseline correction was generally applied, but in no case was a first-order (tilt) correction applied.

The ^{17}O spectra were taken on samples of cyclohexenone containing ∼1 mole equiv of diethyl ether at 54.219 MHz using calibrated 90° pulses. An acquisition time of 0.050 s was used and 4032 points were collected. A linear prediction based on the first 256 points of the FID was used to back-calculate the first two points to avoid a roll in the baseline. Integral regions of ca. ±5 times the peak width at half-height were used, using identical regions for corresponding peaks from the standard and the reisolated samples. ^{13}C spectra were obtained for these samples, as before except at ambient temperature, immediately before or after the ^{17}O spectra.

Results from All Reactions. The integrations for the relevant peaks in cyclohexenone or 3-butylcyclohexanone were set relative to integrations of 1000 for C_6 of cyclohexenone or 1000 for C_c of 3-butylcyclohexanone, and the averaged results from five spectra for each sample are shown in Tables 3 and 4. The relative changes in isotope composition (R/R_0) at each position in cyclohexenone were calculated as the ratio of average integrations in Table 3 relative to the standard. The standard deviations ($\Delta R/R_0$) were calculated from eq 2. In these

$$\Delta R/R_0 = R/R_0 \times \left(\left(\frac{\Delta\text{IntSample}}{\text{IntSample}}\right)^2 + \left(\frac{\Delta\text{IntStandard}}{\text{IntStandard}}\right)^2\right)^{1/2} \quad (2)$$

equations IntSample is the average integration for each carbon in the sample, IntStandard is the average integration for each carbon in the standard, and ΔIntSample and ΔIntStandard are the standard deviations in the integrations for the sample and standard, respectively.

The KIEs for cyclohexenone were then calculated from eq 3, with the standard deviations calculated from eqs 4, 5, and 6.[13]

$$\text{KIE}_{\text{calcd}} = \frac{\ln(1 - F)}{\ln[(1 - F)R/R_0]} \quad (3)$$

$$\Delta\text{KIE}_F = \frac{\partial\text{KIE}}{\partial F}\Delta F = \frac{-\ln(R/R_0)}{(1 - F)\ln^2[(1 - F)R/R_0]}\Delta F \quad (4)$$

$$\Delta\text{KIE}_R = \frac{\partial\text{KIE}}{\partial(R/R_0)}\Delta(R/R_0) = \frac{-\ln(1 - F)}{(R/R_0)\ln^2[(1 - F)R/R_0]}\Delta(R/R_0) \quad (5)$$

$$\Delta\text{KIE} = \text{KIE}^*(\Delta\text{KIE}_R/\text{KIE})^2 + (\Delta\text{KIE}_F/\text{KIE})^2)^{1/2} \quad (6)$$

The KIEs in Tables 1 and 2 for experiments 4−6, 9, and 10 were calculated from the data in Table 4, without correction for percent conversion, using eq 7, and the standard deviations (Δ*K*IE) were calculated using eq 8.

$$\text{KIE} = \frac{\Delta\text{IntStandard}}{\text{IntSample}} \quad (7)$$

$$\Delta\text{KIE} = \text{KIE} \times \left(\left(\frac{\Delta\text{IntSample}}{\text{IntSample}}\right)^2 + \left(\frac{\Delta\text{IntStandard}}{\text{IntStandard}}\right)^2\right)^{1/2} \quad (8)$$

^{17}O KIE Results. For the cyclohexenone/ether mixtures, the integration of cyclohexenone C_6 in the ^{13}C spectra and the carbonyl oxygen in the ^{17}O spectra were set relative to integrations of 1000 for the methylene carbon of ether and 1000 for the ether oxygen, respectively. The averaged results from four ^{13}C spectra and five ^{17}O spectra are shown in Table 5. The R/R_0 for the cyclohexenone carbonyl oxygen was then calculated from eq 9, and $\Delta R/R_0$ was calculated in a standard fashion from the square root of the sum of the squares of the standard deviations in the integrations used to calculate R/R_0. The R/R_0's for experiments 2, 3, and 8 were 1.036(0.011), 1.030(0.011), and 1.006(0.019), respectively. From these values, the KIEs in Tables 1 and 2 were calculated using eqs 3−6.

$$R/\text{R}_0 = \frac{\text{CStandard}}{\text{CSample}} \times \frac{\text{OSample}}{\text{OStandard}} \quad (9)$$

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Supporting Information Available: Energies and full geometries of all calculated structures and equations for spreadsheet simulation of eq 1 (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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