C–H Functionalization

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On the Interpretation of Deuterium Kinetic Isotope Effects in C–H Bond Functionalizations by Transition-Metal Complexes**

*Eric M. Simmons and John F. Hartwig**

C–H functionalization · energy diagrams · isotope effects · kinetics · rate-determining step

A detailed understanding of the mechanism by which a chemical reaction proceeds enables one to control and improve a given synthetic process. Only by understanding the factors that govern the rate and selectivity of a transformation can the outcome of the reaction be precisely modulated through design of the catalyst, reagents, and conditions.[1] Historically, the field of physical organic chemistry was born from the desire to understand the intimate details of the reactions of organic molecules, and the principles that have emerged from this work have been vital to the development of synthetic organic chemistry.[1]

One of the most powerful and common techniques for studying reaction mechanisms is the measurement of kinetic isotope effects (KIEs).[1–3] Such experiments are taught in all physical organic chemistry courses and should be familiar to any organic chemist. When conducted appropriately, these experiments can provide important information about which bonds are broken or formed at different stages of a reaction, and, in some cases, about the properties of the transition state through which these bonds are cleaved.[4]

Over the past several decades, considerable effort has been devoted to the development of synthetic methods based on metal-mediated C–H bond functionalization.[5] Because such transformations, by definition, involve the cleavage of a C–H bond, the mechanistic details of these processes can potentially be revealed through the measurement of KIEs that result from differences in the rate for reaction at a C–H bond versus the analogous C–D bond.[6] In fact, such KIE experiments are especially well suited for mechanistic studies of C–H bond functionalization because C–H bonds do not generally undergo exchange in the absence of an external reagent or catalyst (in contrast to N–H and O–H bonds), and because carbon-bound deuterium labels can be introduced by a variety of synthetic methods. However, the interpretation of a KIE is not as simple as the measurement of a KIE. The choice of KIE measurement and interpretation of KIE data must be done carefully in order to avoid drawing mechanistic conclusions that are unsupported by the available data.

A number of recent publications describing synthetic methods involving C–H bond functionalization have included KIE experiments designed to probe the mechanism by which these transformations occur. Such experiments are now being undertaken routinely, and this trend should help to advance the field of C–H bond functionalization. However, many recent discussions of KIE data have concluded that C–H bond cleavage occurs during the "rate-determining step"[7] in cases when such a conclusion cannot be drawn from the experimental data.

In response to this growing trend, we provide in this essay a brief overview and analysis of three of the most common types of KIE experiments involving substrates containing deuterium. We subsequently illustrate the connection between each experiment and the expected KIE under a number of mechanistic scenarios that commonly occur in synthetic processes involving C–H bond functionalization. The purpose of this presentation is to diminish the number of future instances in which C–H bond cleavage is stated to be the rate-determining step (RDS)[7] of a reaction when the data do not support such a conclusion. It should be emphasized at the outset that no new information or concepts are presented in this essay. Rather, we provide only a reminder of the limitations of some of the most common KIE experiments and the relevance of an experiment to assessing whether the rate-determining step of a process involves C–H bond cleavage.

Before discussion of KIEs, we note the distinction between a "rate-determining step"[7] and a "product-determining step".[8] The latter term refers to an irreversible step that controls which of two (or more) possible products are formed in a reaction with multiple competing pathways. It is sometimes also called the "selectivity-determining step". Although the product- or selectivity-determining step can also be the rate-determining step, the product-determining step does not need to be the rate-determining step.[8]

In the first type of KIE experiment, hereafter referred to as Experiment A, two separate rate constants are measured

[*] Dr. E. M. Simmons, Prof. J. F. Hartwig
Department of Chemistry
University of California at Berkeley
Berkeley, CA 94720 (USA)
E-mail: jhartwig@berkeley.edu

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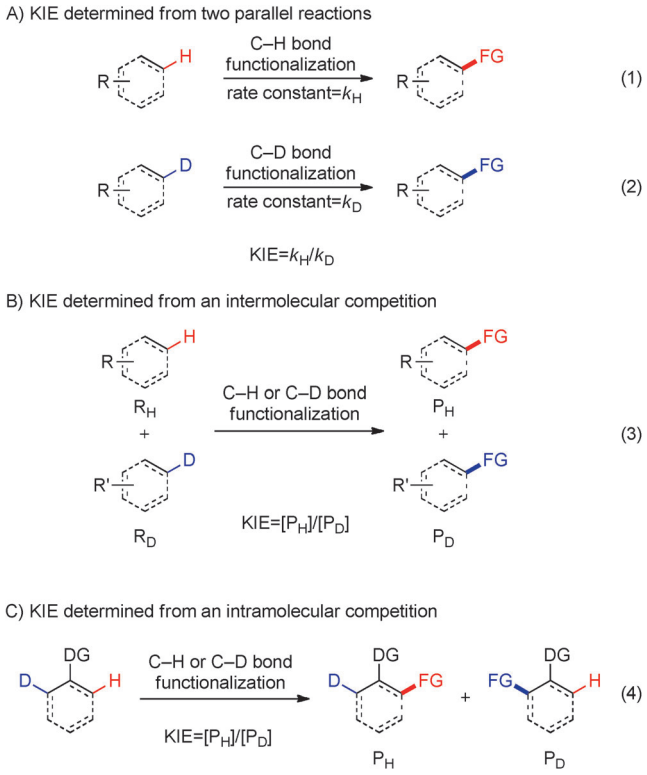
(by NMR spectroscopy, GC, IR spectroscopy, etc.) for two reactions that are conducted separately, one with a substrate containing a C–H bond and one with a substrate containing an analogous C–D bond [Scheme 1 A, Eq. (1) and (2)]. The



Scheme 1. Common deuterium kinetic isotope effect (KIE) experiments A–C.

Eric M. Simmons received his B.A. in 2004 from Tufts University. He earned his Ph.D. in 2009 from the University of California at Berkeley, where he worked on the synthesis of icetexane and cortistatin natural products with Prof. Richmond Sarpong. In 2009, he began postdoctoral studies with Prof. John F. Hartwig at the University of Illinois at Urbana-Champaign, working in the area of iridium-catalyzed C–H bond functionalization.

John Hartwig received his A.B. from Princeton University and his Ph.D. from U.C. Berkeley with Bob Bergman and Richard Andersen. After a postdoctoral fellowship at MIT with Stephen Lippard, he began his independent career at Yale University and became the Irenée P. DuPont Professor in 2004. After five years at the University of Illinois as the Kenneth L. Rinehart, Jr. Professor of Chemistry (2006–2011), he returned to Berkeley in the Henry Rapoport Chair. His group has contributed to cross-coupling reactions, C–H bond functionalization, olefin hydroaminations, and asymmetric allylic substitutions.

relative ratio of these independently determined reaction rate constants (i.e., k_H/k_D) then gives the reported KIE value. The accuracy of the KIE determined by this experiment is limited to the accuracy with which the individual rate constants can be measured, and measurement of the rate constant for a catalytic reaction can be hampered by the presence of induction periods and catalyst decomposition. However, this measurement of the KIE is generally the only one that provides conclusive information on whether the C–H bond cleavage occurs during the RDS of a stoichiometric reaction or the "turnover-limiting step" of a catalytic reaction.

The second type of experiment, Experiment B, involves an *inter*molecular competition between two different substrates in the same reaction flask [Scheme 1 B, Eq. (3)]. Often, the substrates that are suitable for this type of experiment are the same as those employed in Experiment A. Thus, the major difference between Experiments A and B is whether the two substrates are contained in two different reaction vessels or in the same vessel. In Experiment B, the two substrates are both present in excess in the same vessel and compete for reaction with a limiting amount of a second reaction partner. Rather than being determined by comparing two reaction rate constants (i.e., k_H/k_D) measured separately, the KIE is calculated from the relative amount of products formed by the functionalization of a C–H versus a C–D bond (i.e., P_H/P_D), or alternatively, extrapolated from the relative amount of unreacted starting materials recovered at the end of the reaction. Because both substrates are present in the same flask, this method requires just one measurement and ensures that the C–H and C–D bond functionalizations both occur under exactly the same conditions, without inadvertent variation in conditions because of experimental error. Moreover, the ratio of reactants and products can be measured with much greater precision than individual rate constants. However, this experiment does not provide the same information as Experiment A on whether or not C–H bond cleavage occurs during the rate-determining step of a reaction. The absence of an isotope effect would show that C–H bond cleavage does not occur during the rate-determining step, but the observation of a primary isotope effect does not provide evidence that C–H bond cleavage occurs during the rate-determining step.

The third type of experiment, Experiment C, is conceptually similar to Experiment B but involves an *intra*molecular competition between functionalization of a C–H bond and a C–D bond in a single substrate [Scheme 1 C, Eq. (4)]. In many (but not all) cases, the substrates employed in this experiment possess a directing group that is positioned between the C–H and C–D bonds. As is the case for Experiment B, the KIE is calculated from the relative amount of products formed from the functionalization of a C–H versus a C–D bond (P_H/P_D). Experiment C is usually simple to conduct, typically gives precise data, and has been cleverly applied to probe the steps that occur after the RDS of metal-mediated C–H bond cleavage processes.[9] The lack of a kinetic isotope effect from Experiment C rules out the potential that C–H bond cleavage occurs during the rate-determining step. Thus Experiment C can provide a simple means to show that C–H bond cleavage is not rate-determin-

ing, but the observation of a KIE from this experiment does not indicate that C–H bond cleavage must occur during the rate-determining step of a reaction.

With the preceding overview of the three most common experiments used to measure H/D KIE values as a backdrop, a number of common mechanistic scenarios for C–H bond functionalization processes will be presented with simplified energy diagrams (Figure 1). We will then show whether a primary isotope effect would be expected to be observed for the three types of experiments for the different mechanistic scenarios. Although the scenarios illustrated in Figure 1 encompass the relative rates of the different steps of many C–H bond functionalization processes, it is not feasible to present in this essay an analysis of every possible set of relative rates. Instead, we seek to use certain cases to emphasize some of the basic principles for determining conclusions from isotope effects that should allow one to analyze situations that do not fall within the scenarios treated here.

The energy axis for the diagrams in Figure 1 is Gibbs free energy. When using such diagrams to explain relative rates for different steps of a reaction, one must appreciate the differences between the various energy units often used for such diagrams, and one must consider that the relative energies of reaction components change over the course of a reaction. An energy surface calculated by theoretical methods typically corresponds to the standard state (1 M, 1 atm, etc.). Thus, thermodynamic parameters generated from such studies are the "standard enthalpy" $\Delta H°$ or the "standard free energy" $\Delta G°$. Of course, the energies of the intermediates and transition states determined by such calculations rarely correspond directly to values under the experimental reaction conditions.

To predict the RDS for a process conducted in the laboratory, one must consider the free energy of each intermediate at the temperature and either pressure or concentration of the reaction conditions (in this case, the enthalpy and free energy values are ΔH and ΔG). Moreover, one must appreciate that the concentration of reactants and intermediates are often different for different experiments and even change during the same reaction as the reactants are consumed. Thus, the rate-determining step of a reaction can be different for the same reaction conducted under different conditions and can change during the reaction without changing the elementary steps by which the reaction proceeds or the rate constants for individual steps.[1]

With these features of reaction coordinate diagrams in mind, we will analyze the conclusions that can be drawn, in general, from different measurements of KIEs. In the first and arguably simplest mechanistic scenario depicted in Reaction Coordinate 1 of Figure 1, the C–H bond cleavage step is irreversible and is the RDS of the overall process. In this case, one would certainly expect to observe a KIE from each of the three types of experiments described.

In the second scenario shown as Reaction Coordinate 2 of Figure 1, the C–H bond cleavage step is irreversible, but this step occurs after an RDS that does not involve the substrate that ultimately undergoes C–H bond cleavage. The RDS of such a reaction could involve ligand dissociation or reductive elimination from a metal complex, the formation of a metal-

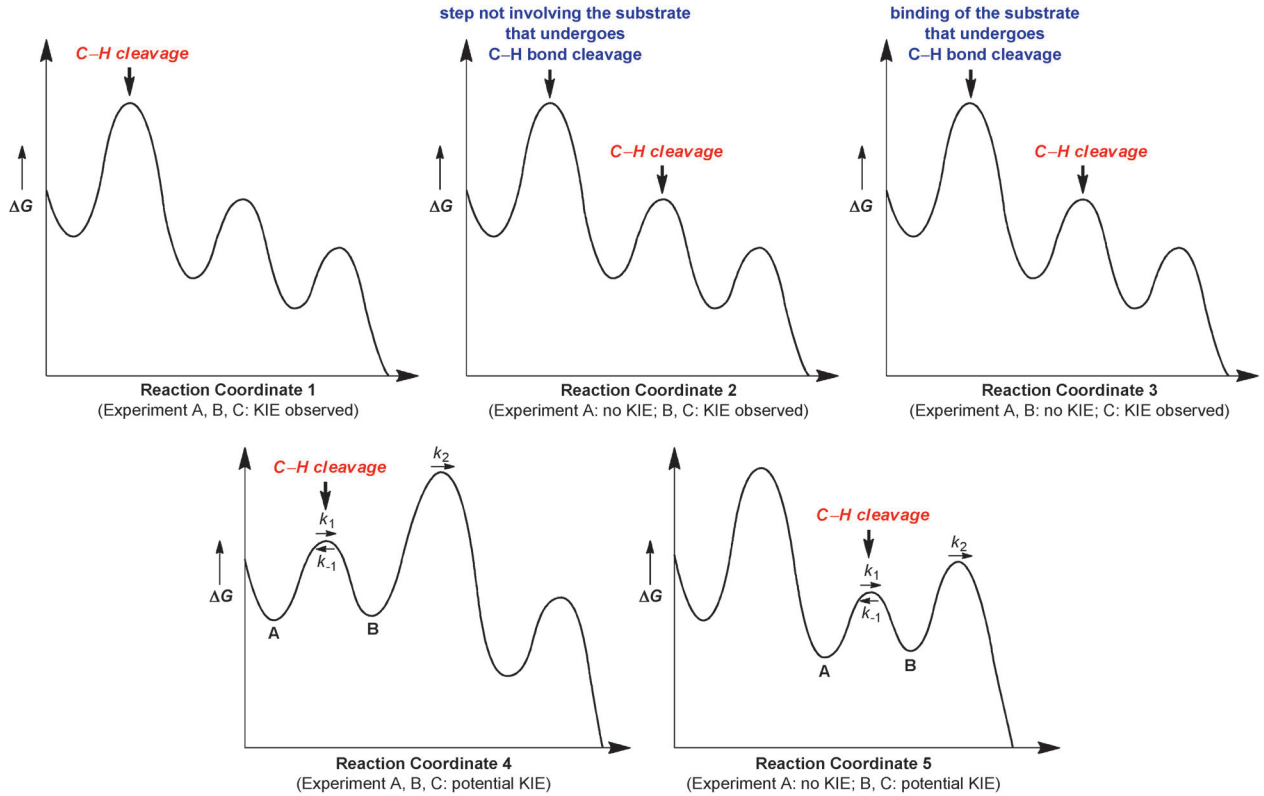


Figure 1. Representative mechanistic scenarios and expected KIE for Experiments A–C.

oxo species, or the oxidative addition of a C–X bond that is not part of the molecule containing the C–H bond. Because the RDS does not involve C–H bond cleavage, the overall rate of the reaction will be unchanged by the replacement of a C–H bond with a C–D bond, and no significant KIE would be measured when Experiment A is conducted. However, the subsequent C–H bond cleavage step is irreversible and, therefore, will give rise to a KIE value for other types of experiments. Because Experiments B and C measure a difference in product distribution that results from a difference in the rate of an irreversible C–H bond-cleavage step, these experiments will give rise to a product ratio reflecting a 1° KIE, even though the C–H bond cleavage does not occur during the rate-determining step of the overall process. In other words, the C–H bond-cleavage in this scenario occurs in the step that is product-determining,[8] but this step is not rate-determining.[7]

In the third scenario shown as Reaction Coordinate 3 of Figure 1, the C–H bond cleavage step is irreversible and occurs after the RDS, but the RDS involves a reaction of the substrate possessing the C–H bond that undergoes functionalization, and the initial, irreversible reaction of this substrate occurs without cleavage of the C–H bond. In such a scenario, the RDS could be the formation of a π complex with the aromatic ring of a substrate that undergoes subsequent aromatic C–H bond functionalization, or the oxidative addition of a C–X bond that is part of the substrate containing the C–H bond that undergoes subsequent functionalization. In this case, no significant KIE would be measured when Experiment A is conducted because the RDS does not involve C–H bond cleavage. Similarly, a 1° KIE would not be observed when Experiment B is conducted because irreversible binding of the substrate that contains the C–H bond does not involve cleavage of the C–H bond. In other words, the substrate-binding step is the product-determining step in Experiment B because this step determines whether a C–H or C–D bond ultimately undergoes functionalization, and this step is insensitive (or weakly sensitive) to isotopic substitution. In contrast, a KIE would be observed when Experiment C is conducted because two different hydrogen isotopes are present in the same molecule in equal environments after the substrate-binding step. The subsequent, irreversible C–H bond cleavage step is now the product-determining step in Experiment C, and C–H or C–D bond functionalization will occur with different rates.

In the fourth scenario shown in Reaction Coordinate 4 of Figure 1, the C–H bond cleavage step is reversible, and occurs before the RDS of the overall process. Because the C–H bond cleavage step is reversible, a large 1° KIE will not be observed for any of three experiments. However, an isotope effect could still be observed in each of these experiments if the equilibrium concentration of the species that reacts in the RDS is significantly affected by the substitution of a C–H bond for a C–D bond. This scenario is best appreciated by considering the rate law for such a reaction:

$$\frac{d[P]}{dt} = k_2[B] = \frac{k_1 k_2[A]}{k_{-1} + k_2} \quad (1)$$

For the sake of simplicity, we take into account only intermediate B, which undergoes the irreversible step of the reaction mechanism. The RDS in this scenario is step 2, and the rate for this step is given by $k_2[B]$. However, the concentration of intermediate B depends on the forward and reverse reaction rate constants k_1 and k_{-1}, both of which would be expected to be affected by isotopic substitution because these individual steps involve C–H bond cleavage and formation, respectively. Consequently, the observed rate for a reaction that is represented by this scenario could occur with a KIE because the rate law for the overall reaction contains two rate constants that are likely to be sensitive to H/D substitution. If the k_{-1} step is much faster than the k_2 step, as would be expected under the conditions shown in Reaction Coordinate 4, the observed kinetic isotope effect results from an equilibrium isotope effect on the first step. (If the k_{-1} step is much slower than the k_2 step, then the scenario shown in Reaction Coordinate 1 in Figure 1 applies, and the measured KIE results from the KIE for the first step as discussed earlier.) If the k_{-1} and k_2 steps occur with similar rates, then the observed KIE does not directly correspond to either the value of the equilibrium isotope effect for the first step or the KIE of the k_1 step, and will have a value between the two.

In the fifth scenario shown as Reaction Coordinate 5 of Figure 1, the C–H bond cleavage step is reversible, but occurs after the RDS of the overall process. In this case, a large 1° KIE will be not observed for any of three experiments because the C–H bond cleavage step is reversible. Furthermore, no isotope effect will be observed for Experiment A, which measures only relative rates, because the step involving C–H bond cleavage occurs after the RDS. However, a small isotope effect could be observed from Experiments B and C, which both measure product distributions, because the substitution of a C–H bond for a C–D bond can alter the equilibrium concentration of the species that reacts in the step that is product- or selectivity-determining (but not rate-determining), as described for Reaction Coordinate 4 of Figure 1.

The analyses just presented can be applied to catalytic reactions, but one must appreciate the differences between catalytic and stoichiometric reactions. Catalytic reactions operate under steady-state conditions within which the rates (not rate constants) for each step are equal. On this basis, it has been argued[10] that there is no single step that is "rate-determining", although the IUPAC definition of "rate-controlling step"[7] does not preclude its usage in such a context. In either case, the transition state involving the largest overall change in free energy is often referred to as the "turnover-limiting" or "turnover-determining"[10] transition state (TDTS), and the microscopic step that is associated with the TDTS is often termed the "turnover-limiting step".[11] Similarly, the intermediate present in the highest concentration is considered to be the resting state, or "turnover-determining intermediate",[10] of the catalytic cycle. It is also important to note that the starting point for each catalytic cycle is lower in energy than that of the previous cycle by an amount equal to the change in free energy of the reaction (ΔG_R).[10] Finally, because the concentrations of the reactants and products change over time, the step that is turnover

limiting can change as the reaction progresses. These additional complexities must be considered when analyzing catalytic reactions, but these features of a catalytic reaction do not allow a primary KIE value measured from Experiments B and C to imply that C–H bond cleavage occurs during the turnover-limiting step of a catalytic cycle.

To illustrate this point, consider a reaction that proceeds by the simplified catalytic cycle illustrated in Figure 2, for

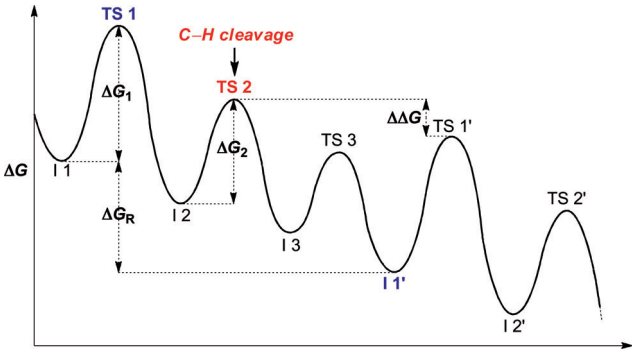


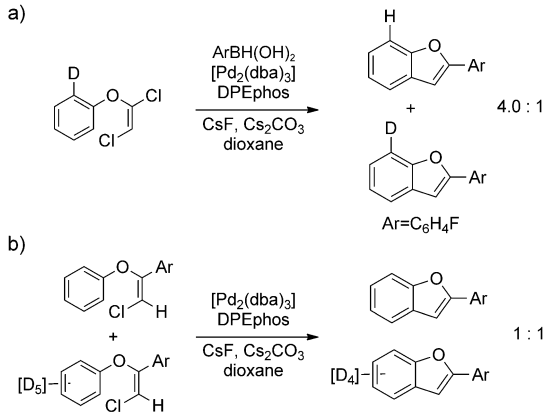
Figure 2. A catalytic cycle with a fast, irreversible C–H bond cleavage step. I = intermediate, TS = transition state.

which the individual steps correspond to those presented in Reaction Coordinate 2 with the second step involving C–H bond cleavage. In the scenario shown in Figure 2, step 1 is turnover-limiting because the corresponding transition state (TS 1) involves the largest overall change in free energy (ΔG_1). The resting state of the cycle is the intermediate that immediately precedes this step (I 1), because it is the lowest-energy species on the reaction coordinate before the TDTS.

Because the energy barrier for step 1 is significantly higher than the barrier for step 2 (i.e., $\Delta G_1 \gg \Delta G_2$), the rate constant for step 2, which corresponds to the C–H bond-cleavage step, will have a minimal influence on the overall rate of the reaction.[10] In this case, no significant KIE would be observed when Experiment A is conducted because the rate constant that is affected by the presence of H or D is a minor contributor to the overall rate of the reaction. Thus, one would correctly conclude from Experiment A that C–H bond cleavage does not occur in the TDTS (i.e., TS 1). However, the C–H bond cleavage step is irreversible (the barrier for regeneration of I2 from I1′ is higher than the barrier for conversion of I1′ to I2′). Because the C–H bond cleavage step is irreversible, Experiments B and C will both give rise to a KIE value for a 1° KIE, even though the C–H bond cleavage step contributes only minimally to the overall rate of reaction.

Thousands of kinetic isotope effects have been measured,[3] and hundreds of KIE values have been obtained during mechanistic studies of reactions catalyzed by transition-metal complexes.[6] Because the purpose of this essay is to increase the awareness of the factors one should consider when designing an experiment involving the measurement of a KIE and to be cautious about conclusions one draws from such an experiment, an extensive survey of examples and applications of KIE measurements is outside the scope of this essay. A review of KIE measurements in reactions of organometallic hydrides in C–H activation reactions was published several years ago.[6b,12] However, to provide a brief illustration of the major points raised in this essay we have selected four results from recent papers showing the difference in KIE values that can be obtained from different experiments on catalytic reactions.

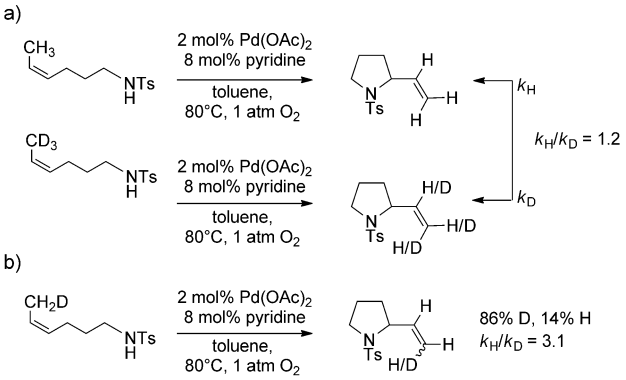
The first example involves an intramolecular direct arylation of an arene with a vinyl chloride to form benzofuran derivatives.[13] As shown in Scheme 2a, the reaction of



Scheme 2. A comparison of intramolecular versus intermolecular KIE values reported by Geary and Hultin.[13]

a substrate containing one deuterium in the *ortho* position gives rise to a k_H/k_D value of 4.0. Many authors have concluded from similar intramolecular competition experiments that C–H bond cleavage occurs in the rate- or turnover-limiting step. However, reaction of a mixture of the two substrates in Scheme 2b, one fully protiated and one fully deuterated at the reactive *ortho* positions, gives rise to a k_H/k_D value of 1. This second experiment shows that C–H bond cleavage cannot occur during the turnover-limiting step. Instead, the C–H bond cleavage occurs after an irreversible oxidative addition of the C–Cl bond.

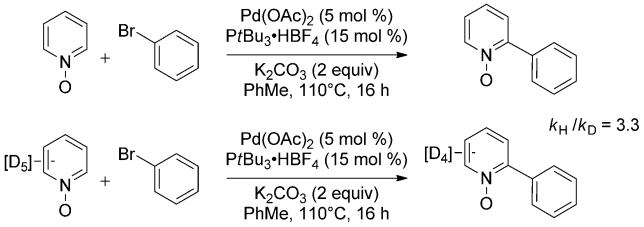
A second example involves a palladium-catalyzed allylic amination process.[14] As shown in Scheme 3a, an intermo-



Scheme 3. A comparison of intramolecular versus intermolecular KIE values reported by Stahl and co-workers.[14]

lecular competition reveals a small, perhaps secondary, isotope effect whereas the partially labeled substrate in Scheme 3b reveals a larger primary isotope effect. These data show that C–H bond cleavage (by β-hydrogen elimination) occurs as part of the mechanism of the reaction, but cannot be part of the turnover-limiting step.

A third example[15] reveals an experiment appropriately selected to determine if C–H bond cleavage is the turnover-limiting step of a direct arylation reaction. The reaction of bromobenzene with pyridine *N*-oxide shown in Scheme 4

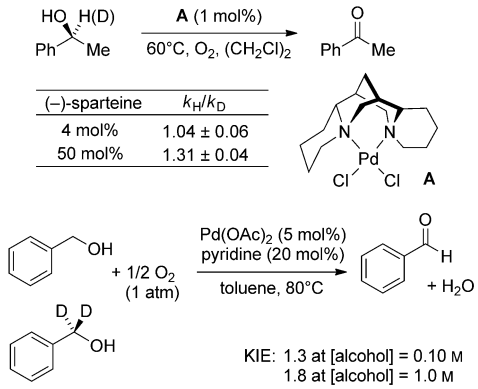


Scheme 4. KIE measurement from two parallel reactions reported by Fagnou and co-workers.[15]

could occur by rate-limiting oxidative addition, C–H bond cleavage, or reductive elimination. If the authors had measured the isotope effect by conducting an intermolecular competition between pyridine-*N*-oxide and [D_5]-pyridine-*N*-oxide or an intramolecular competition by conducting the reaction of 2-deuteropyridine-*N*-oxide, the result would have shown whether C–H bond cleavage occurs during the mechanism of the reaction, but would not have shown whether C–H bond cleavage occurs during the turnover-limiting step. (A comparison of the isotope effects from the latter two experiments has been successfully used to distinguish irreversible C–H bond cleavage from irreversible binding of an arene during the C–H bond functionalization step of a catalytic carboamination.[9b]) Thus, the authors measured rate constants from two separate, side-by-side reactions, one of pyridine-*N*-oxide and one of [D_5]pyridine-*N*-oxide. The KIE of 3.3 observed from this comparison then showed that C–H bond cleavage occurred during the turnover-limiting step.

Other examples reveal the peril faced when drawing conclusions from a kinetic isotope effect measured under a single set of conditions. For example, the KIE for the oxidation of the protio versus deuterio benzyl alcohols in Scheme 5 shows that the presence or absence of a measurable KIE and the magnitude of the measured KIE can depend on the concentration of sparteine base[16] or the concentration of alcohol.[17] Thus, the proper experiment must be chosen, and this experiment should be run under a variety of conditions or under the conditions of the system about which one wishes to gain mechanistic information.

In summary, we have presented in this essay a reminder of the limitations of some of the experiments used most commonly to measure kinetic isotope effects for processes involving C–H bond functionalization. Specifically, we have shown that the KIE experiment that allows one to conclude



Scheme 5. KIE measurements at different reactant concentrations reported by a) Sigman and co-workers[16] and b) Steinhoff and Stahl.[17]

that C–H bond cleavage occurs during the rate-determining step of a reaction is the measurement of the rates or rate constants of two independent reactions with two substrates, one containing a C–H bond and one containing a C–D bond. We hope that this presentation will assist in the selection of experiments to conduct when seeking information on whether C–H bond cleavage occurs during the "rate-determining"[7] or "turnover-limiting"[10] step of a metal-mediated C–H bond functionalization process.

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[8] The IUPAC Gold book definition of "product-determining step" (http://old.iupac.org/goldbook/P04862.pdf) is as follows: "The step of a stepwise reaction, in which the product distribution is determined. The product-determining step may be identical to, or occur later than, the rate-controlling step on the reaction coordinate.".
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