JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Communication
pubs.acs.org/JACS

A General Approach to Mechanism in Multiproduct Reactions: Product-Specific Intermolecular Kinetic Isotope Effects

Shuhuai Xiang and Matthew P. Meyer*

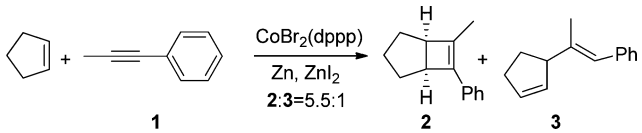
Department of Chemistry and Biochemistry, University of California, Merced, California 95343, United States

Supporting Information

ABSTRACT: Here we report a general method for the measurement of ^{13}C kinetic isotope effects at natural abundance for reactions that yield two or more products concurrently. We use, as an example, a recently reported Co-catalyzed reaction between cyclopentene and 1-phenyl-1-propyne. High-precision intermolecular ^{13}C isotope effects are reported for both the formal [2+2] cycloaddition (major) and Alder−ene (minor) reaction products. Mechanistic possibilities that are in accord with observed isotope effect measurements are discussed.

Kinetic isotope effects (KIEs) have proven invaluable to mechanistic study.[1] Through the efforts of a number of outstanding scientists, the state-of-the-art in isotope effect measurement has improved markedly over the past 20 years.[2] Still, KIE measurement has been mostly limited to reactions that proceed cleanly in high yield (spot-to-spot reactions). This limitation makes it difficult to investigate potentially useful reactions that are in early or intermediate stages of development. In this Communication, we report a method that uses isotopic fractionation in reisolated reactant *and* isotopic partitioning in the product mixture to arrive at high-precision measurements of ^{13}C KIEs at all participating positions for each reaction product. This technique is illustrated using a recently reported cobalt-catalyzed C−C coupling reaction that, under certain conditions, yields both formal [2+2] cycloaddition and Alder−ene products (Scheme 1).[3]

Scheme 1. Moderately Chemoselective Reaction Exhibiting [2+2] Cycloaddition and Alder−Ene Pathways



A product-specific KIE is defined as the ratio of the rate for the formation of a given unlabeled product relative to that for the formation of the same product that is isotopically labeled at a given position. These measurements reflect isotopic fractionation that occurs at both rate- and product-determining steps and can be used to interrogate mechanisms in reactions that have moderate to poor enantio-, diastereo-, regio-, or chemoselectivity. In general, product-specific KIEs are applicable to all products in a reaction that produces multiple products; however, this method is most naturally applied to reactions that have one principal side reaction that erodes yield of the desired product. Product-specific KIEs can be interpreted in terms of the overall intermolecular KIE, which is computed from the isotopic fractionation in reisolated starting material (R/R_0) as a function of fractional conversion (F) as is shown in eq 1.[4] As will be discussed below, patterns of intermolecular

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

KIEs and product-specific KIEs can be used to understand the nature and timing of rate- and product-determining steps in a multiproduct reaction.

First, we define the traditional intermolecular KIE for a given carbon position in the reactant in the conventional way, as described by Singleton (eq 1).[2a] This value reports upon position-specific fractionation that occurs in the reisolated reactant. Isotopic fractionation also occurs in the reaction products. This makes the measurement of product-specific KIEs possible. Traditional intermolecular KIEs are derived from one experimental parameter (fractional conversion) and one reaction observable (relative isotopic fractionation. Fractional conversion (F) can be measured using any suitably quantitative analytical technique.[5] Relative isotopic fractionation in reisolated starting material (R/R_0) is computed for each position as the ratio of peak integral for each position in the reisolated reactant to the peak integral for the corresponding position in stock reactant. The ratio of heavy isotopologue to light isotopologue in unreacted starting material ($F = 0$) and that of starting material taken to a given fractional conversion (F) are given by the ratios R_0 and R, respectively.

Isotopic substitution at positions that undergo bonding changes in the product-determining step of a reaction can alter product ratios. It is this factor that can make product-specific KIEs distinct from each other and from traditional intermolecular KIEs. Our general procedure involves no more effort than that reported by Singleton. Quantitative ^{13}C NMR spectra are obtained for stock reactant and the reaction mixture obtained after taking the reaction to moderate levels of conversion ($F = 0.70-0.80$). NMR spectra are obtained using inverse-gated decoupling and relaxation times of $5-7\times T_1$. Integrals are taken from appropriately phased spectra using integration regions of 3×fwhm (full width at half-maximum peak height) spanning each side of the peak maximum. These

Received: December 17, 2013
Published: April 2, 2014

   dx.doi.org/10.1021/ja412827c | J. Am. Chem. Soc. 2014, 136, 5832−5835

measurements yield ^{13}C-dependent product ratios. ^{12}C-labeled product ratios used in the denominator of eq 2 can be

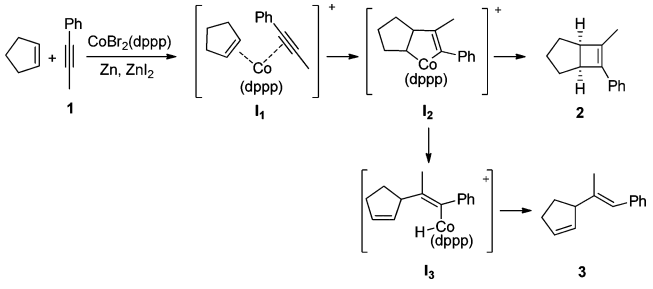
$$\mathrm{KIE}(\mathbf{2}) = \mathrm{KIE}_{\mathrm{Inter}}\frac{([^{13}\mathbf{2}] + [^{13}\mathbf{3}])/[^{13}\mathbf{2}]}{([^{12}\mathbf{2}] + [^{12}\mathbf{3}])/[^{12}\mathbf{2}]} \quad (2)$$

estimated using ^{1}H NMR or by using quantitative ^{13}C NMR integrations at a position that is unlikely to experience fractionation. This practice of choosing an unfractionated position is equivalent to the choice of an internal standard position in the Singleton method. The product-specific KIE corresponding to a given position on **2** is computed using eq 2 for the reaction shown in Scheme 1. Likewise, one can compute the product-specific KIE for **3** by permuting the labels for products **2** and **3** in eq 2. This procedure can, in principle, be easily generalized to a reaction with n products $\{P_{1\ldots n}\}$ (eq 3).

$$\mathrm{KIE}(\mathbf{P}_j) = \mathrm{KIE}_{\mathrm{Inter}} \times \frac{\left(\sum_{i=1}^{n}[^{13}\mathbf{P_i}]\right)/[^{13}\mathbf{P_j}]}{\left(\sum_{i=1}^{n}[^{12}\mathbf{P_i}]\right)/[^{12}\mathbf{P_j}]} \quad (3)$$

To demonstrate the power of product-specific ^{13}C KIEs, we have selected a recently developed Co-catalyzed C−C coupling of current interest that yields [2+2] cycloaddition and Alder−ene products in an approximately 5.4:1 ratio (Scheme 1). Our choice of this reaction is motivated by three primary considerations. First, cobalt-catalyzed C−C couplings comprise an area of intense methodology development where competing reaction pathways frequently erode yield.[6,7] Second, few experimental studies have been leveraged toward understanding Co-catalyzed C−C couplings. Finally, product-specific KIEs provide a means to test the hypothesis put forth by Hilt et al. that the [2+2] cycloaddition and Alder−ene products derive from a common intermediate (Scheme 2).[3]

Scheme 2. Putative Mechanism for the Coupling of Cyclopentene and 1-Phenyl-1-propyne Catalyzed by $CoBr_2$(dppp)



The standard intermolecular ^{13}C KIEs are shown in Figure 1A. Product-specific ^{13}C KIEs are shown in Figure 1B. What becomes obvious first is that the intermolecular KIEs that are computed from the fractionation (R/R_0) in the reisolated 1-phenyl-1-propyne are quite similar to those measured for both the major [2+2] cycloaddition pathway and the Alder−ene pathway. The statistical errors in these measurements are substantial, but there are three mitigating factors that render this technique one of high potential. First, increasingly sensitive NMR spectrometers promise to enhance the precision of quantitative NMR measurements needed to compute the values

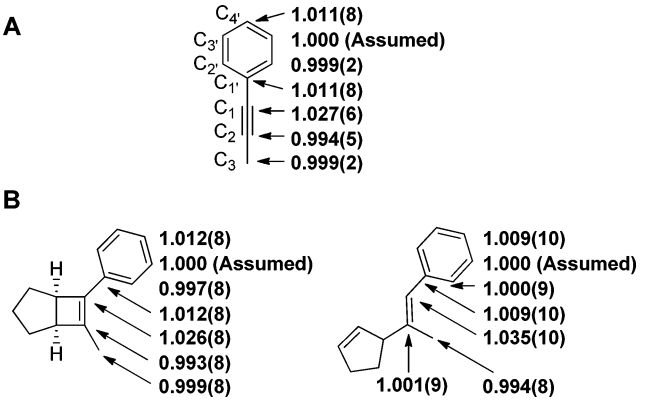


Figure 1. (A) Conventional intermolecular ^{13}C KIEs and (B) product-specific ^{13}C KIEs for the coupling of cyclopentene and 1-phenyl-1-propyne catalyzed by $CoBr_2$(dppp). Standard error is shown in parentheses.

in Figure 1. Second, the two-product reaction shown in Schemes 1 and 2 is inherently challenging, yielding somewhat large product ratios. Reactions exhibiting smaller product ratios are inherently less challenging. Finally, product-specific KIEs amplify the information content over conventional KIE measurements. In cases where a common intermediate is formed in the rate-determining step, product-specific KIEs reflect the product of intermolecular KIEs and the ratio of KIEs for the product-determining step. In cases where the rate- and product-limiting steps are concurrent, the conventional intermolecular KIE is a weighted average of the intrinsic KIEs for the formation of both products. As a consequence, such measurements allow for the exclusion of a greater number of mechanistic possibilities.

Among possible scenarios that the results in Figure 1 make unlikely are (1) formation of different regioisomers of $\mathbf{I_2}$ leading to products **2** and **3**, (2) synchronous C−C and Co−C bond formation during rate-limiting formation of $\mathbf{I_2}$, and (3) rate-limiting π-complex ($\mathbf{I_1}$) formation. The first scenario would yield conventional KIEs at the C1 and C2 positions of **1**, with product-specific KIEs separately localized at either C1 or C2 in the event of a highly asynchronous transition state. In the event of a synchronous transition state, product-specific KIEs would be present at both C1 and C2 for both products, with values that bracket the conventional intermolecular KIE. Synchronous rate-limiting formation of $\mathbf{I_2}$ followed by product-determining steps would yield both conventional and product-specific KIEs at both C1 and C2, with differences in the product-specific KIEs reflecting the ratio of isotope effects for the formation of both products. Finally, rate-limiting formation of $\mathbf{I_1}$ would likely yield diminutive conventional KIEs at both C1 and C2, with product-specific KIEs once again reflecting the ratio of KIEs for the two distinct product-determining steps. While information on the product-determining step is limited to the ratio of the KIEs for the two processes, this ratio communicates information about the relative bond strengths of forming and breaking bonds in the product-determining transition states. Given the high information content inherent in the simultaneous measurement of conventional and product-specific KIEs, these values hold great potential for use in conjunction with isotope effect predictions from computed transition structures.

As with any mechanistic method, reductive reasoning can only allow us to exclude mechanistic possibilities. In the context

dx.doi.org/10.1021/ja412827c | J. Am. Chem. Soc. 2014, 136, 5832−5835

of a mechanistic model, we can abductively reason within the constraints of the experimental data. Within the context of the mechanism in Scheme 2, we can draw some conclusions about the nature of putative rate- and product-determining steps in the reaction shown in Scheme 1. The insignificant intermolecular KIE at the C2 position suggests a highly asynchronous transition state leading to $\mathbf{I_2}$, with bond formation between the C1 position in the alkyne and one of the vinylic centers in cyclopentene lagging behind formation of the two Co−C bonds in the cobaltacyclopentene intermediate. Houk et al. have shown that, in cases of concerted, asynchronous transition states, positions that experience earlier bond formation exhibit larger isotope effects than positions in which bonding changes occur later.[8] The notion that C−C bonding lags behind C−Co bond formation is reinforced by computational optimizations of analogous transition structures for the conversion of bisalkyne cobalt complexes to the corresponding cobaltacyclopentadiene complex.[9,10]

It is somewhat surprising that subsequent fractionation, from the partitioning of $\mathbf{I_2}$ between $\mathbf{I_3}$ and **2**, is not more substantial at the C1 position. In the context of the mechanism in Scheme 2, this means that the product-determining steps, however distinct, do not fractionate differentially at the C1 position to an appreciable degree. This may be just a consequence of both pathways leading from $\mathbf{I_2}$ having very early transition states. Alternatively, product determination could be decided at the transition state connecting $\mathbf{I_3}$ and **3** for the Alder−ene pathway. This would mean that two reductive eliminations ($\mathbf{I_2} \rightarrow \mathbf{2}$ and $\mathbf{I_3} \rightarrow \mathbf{3}$) would compete in product determination, likely resulting in similar fractionation.

Some considerations must be borne in mind regarding the proposed intermediate, $\mathbf{I_2}$. The most convincing evidence for the formation of a cobaltacyclopentene intermediate in Co-catalyzed reactions between alkenes and alkynes comes from X-ray structures of isolated metallacycles resulting from the stoichiometric reaction of Co(I)−alkyne complexes with alkenes.[11] These structures are analogous to cobaltacyclopentadiene intermediates isolated along the Co-catalyzed cyclotrimerization pathway.[12,13] Density functional calculations also identify these metallacycles as intermediates.[9,10,14] Thus, metallacycles like $\mathbf{I_2}$ seem quite plausible as on-pathway intermediates in the mechanism depicted in Scheme 2. The results in Figure 1 hint at a nuanced understanding of structural characteristics of a putative cobaltacyclopentene intermediate. Significant fractionation at the C1′ aromatic carbon suggests either direct bonding of this position to the metal center or geometrically imposed destruction of conjugation between the aryl ring and the C1 position during the rate-determining step. Unfortunately, computational efforts to explore the formation of cobaltacyclopentene and cobaltacyclopentadiene intermediates have been concerned primarily with model structures lacking complex substitution patterns, so no precedent for this type of interaction exists. The only known X-ray structure for a cobaltacyclopentene does not possess an interaction of this type; however, the only phenyl substituent ring is out of plane with the π-system in the C=C double bond internal to the complex.[11] The origin of the isotope effect at the C1′ position remains an open question, but the existence of such an effect implies that the structural and electronic properties of the transition structure leading to $\mathbf{I_2}$ are more complex than might be supposed by considering the mechanism as drawn in Scheme 2.

Intermolecular KIEs report on relative rates of conversion between individual isotopologous molecules. Intramolecular KIEs report on internal isotopic competition within a molecule where the isotopic label breaks an element of symmetry. Intermolecular ^{13}C KIEs could be measured for the cyclopentene fragment in this reaction. However, given the σ_v symmetry element within cyclopentene, intramolecular KIEs are perhaps more illuminating. Intramolecular KIEs report upon the process that irreversibly breaks a symmetry element, but downstream fractionation from product partitioning can give rise to KIEs that are not immediately interpretable.[15−17] In the present case, we can interrogate intramolecular KIEs that result from the rate-determining step by exploring the weighted average of ^{13}C integrations in the Alder−ene and [2+2] cycloaddition product (eq 4). Doing this yields the intramolecular KIEs resulting from desymmetriztion of cyclopentene in the formation of $\mathbf{I_2}$ (Figure 2). Intramolecular

$$\mathrm{KIE}_{\mathrm{Intra}}(a') = \frac{([\mathbf{2}]/[\mathbf{3}])\int \mathbf{2} - a + \int \mathbf{3} - a}{([\mathbf{2}]/[\mathbf{3}])\int \mathbf{2} - a' + \int \mathbf{3} - a'} \qquad (4)$$

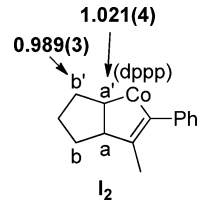


Figure 2. Intramolecular KIEs for the rate-determining step leading to the common intermediate, $\mathbf{I_2}$.

KIEs are relative by definition and are the inverse of the relative integrations at corresponding positions. The values shown in Figure 2 bolster the argument for a common intermediate preliminary to product determination. A significant intramolecular KIE at the Co−C bonding position arising from cyclopentene also supports the notion of a highly asynchronous transition state. Intramolecular KIEs measured for each product are compound KIEs that arise from fractionation at both the rate- and product-determining steps. These values will be reported and discussed later in a more comprehensive full paper on the detailed mechanism studied here.

In conclusion, we have demonstrated a new mechanistic method that significantly expands the reach of KIEs as a quantitative tool in organic chemistry. Results from the work presented herein consider mechanistic scenarios for the $CoBr_2$(dppp)-catalyzed C−C coupling reaction between cyclopentene and 1-phenyl-1-propyne shown in Scheme 1. Product-specific KIEs are applicable to chemo-, regio-, diastereo-, and enantioselective reactions. In general, the inherently large chemical shift dispersion in ^{13}C NMR spectra is sufficient to acquire accurate regioisomeric and diastereomeric product ratios. Of course, the method presented here is not limited to ^{13}C KIEs. Deuterium KIEs can also be determined using this methodology; however, the small chemical shift dispersion inherent to ^{1}H and ^{2}H NMR can make integration difficult in a sample containing reactant(s) and products. This limitation can be circumvented by using ^{13}C NMR as a detection method and making use of the isotope effects caused by ^{2}H substitution upon ^{13}C NMR chemical shifts. Because of the limited

dx.doi.org/10.1021/ja412827c | J. Am. Chem. Soc. 2014, 136, 5832−5835

sensitivity of ^{13}C NMR, product-specific ^{2}H KIEs are practically limited to analyses using labeled compounds. Measurement of product-specific KIEs in reactions that yield two enantiomeric products requires the presence of an external source of chirality and is the focus of current work in our laboratory.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures for measuring KIEs; raw NMR integration data; derivation of eq 2. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

mmeyer@ucmerced.edu

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the National Science Foundation (CHE-1058483).

■ REFERENCES

(1) Recent monographs and reviews: (a) Kohen, A., Limbach, H.-H., Eds. *Isotope Effects in Chemistry and Biology*; CRC Press: Boca Raton, FL, 2005. (b) Wolfsberg, M.; Hook, W. A.; Paneth, P. *Isotope Effects in the Chemical, Geological and Bio Sciences*; Springer: London, 2010. (c) Giagou, T.; Meyer, M. P. *Chem.—Eur. J.* **2010**, *16*, 10616−10628. (d) Meyer, M. P. *Adv. Phys. Org. Chem.* **2012**, *46*, 57−120. (e) Simmons, E. M.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2012**, *51*, 3066−3072.

(2) Some examples: (a) Singleton, D. A.; Thomas, A. A. *J. Am. Chem. Soc.* **1995**, *117*, 9357−9358. (b) Lewis, B. E.; Schramm, V. L. *J. Am. Chem. Soc.* **2003**, *125*, 4785−4798. (c) Lee, J. K.; Bain, A. D.; Berti, P. J. *J. Am. Chem. Soc.* **2004**, *126*, 3769−3776. (d) Murkin, A. S.; Tyler, P. C.; Schramm, V. L. *J. Am. Chem. Soc.* **2008**, *130*, 2166−2167. (e) Chan, J.; Lewis, A. R.; Gilbert, M.; Karwaski, M.-F.; Bennet, A. J. *Nat. Chem. Biol.* **2010**, *6*, 405−407. (f) Pabis, A.; Kaminski, R.; Ciepielowski, G.; Jankowski, S.; Paneth, P. *J. Org. Chem.* **2011**, *76*, 8033−8035. (g) Chan, J.; Tang, A.; Bennet, A. J. *J. Am. Chem. Soc.* **2012**, *134*, 1212−1220. (h) Manning, K. A.; Sathyamoorthy, B.; Eletsky, A.; Szyperski, T.; Murkin, A. S. *J. Am. Chem. Soc.* **2012**, *134*, 20589−20592. (i) Wong, K. Y.; Gu, H.; Zhang, S.; Piccirilli, J. A.; Harris, M. E.; York, D. M. *Angew. Chem., Int. Ed.* **2012**, *51*, 647−651. (j) Vetticatt, M. J.; Desai, A. A.; Wulff, W. D. *J. Org. Chem.* **2013**, *78*, 5142−5152.

(3) Hilt, G.; Paul, A.; Treutwein, J. *Org. Lett.* **2010**, *12*, 1536−1539.

(4) Melander, L. *Isotope Effects on Reaction Rates*; The Ronald Press: New York, 1960.

(5) It should be noted that the bulk fractional conversion, *F*, may only be used as shown in eq 1 when the isotopic label is present at only trace levels. When substantial amounts of labeled material are used in competitively measured KIE experiments, fractional conversion for competing isotopomers or isotopologues must be considered explicitly. A full derivation is given in the following: West, J. D.; Meyer, M. P. *J. Am. Chem. Soc.* **2008**, *130*, 7816−7817.

(6) A recent review: Hess, W.; Treutwein, J.; Hilt, G. *Synthesis* **2008**, 3537−3562.

(7) Some recent examples: (a) Chang, H.-T.; Jayanth, T. T.; Wang, C.-C.; Cheng, C.-H. *J. Am. Chem. Soc.* **2007**, *129*, 12032−12041. (b) Schmidt, A.; Hilt, G. *Org. Lett.* **2013**, *15*, 2708−2711. (c) Bohn, M. A.; Schmidt, A.; Hilt, G.; Dindaroğlu, M.; Schmalz, H.-G. *Angew. Chem., Int. Ed.* **2011**, *50*, 9689−9693. (d) Arndt, M.; Dindaroğlu, M.; Schmalz, H.-G.; Hilt, G. *Synthesis* **2012**, *44*, 3534−3542. (e) Wei, C.-H.; Mannathan, S.; Cheng, C.-H. *J. Am. Chem. Soc.* **2011**, *133*, 6942−6944. (f) Wei, C.-H.; Mannathan, S.; Cheng, C.-H. *Angew. Chem., Int. Ed.* **2012**, *51*, 10592−10595.

(8) Storer, J. W.; Raimondi, L.; Houk, K. N. *J. Am. Chem. Soc.* **1994**, *116*, 9675−9683.

(9) Hardesty, J. H.; Koerner, J. B.; Albright, T. A.; Lee, G.-Y. *J. Am. Chem. Soc.* **1999**, *121*, 6055−6067.

(10) Gandon, V.; Agenet, N.; Vollhardt, K. P. C.; Malacria, M.; Aubert, C. *J. Am. Chem. Soc.* **2006**, *128*, 8509−8520.

(11) Wakatsuki, Y.; Aoki, K.; Yamazaki, H. *J. Am. Chem. Soc.* **1979**, *101*, 1123−1130.

(12) McAlister, D. R.; Bercaw, J. E.; Bergman, R. G. *J. Am. Chem. Soc.* **1977**, *99*, 1666−1668.

(13) Wakatsuki, Y.; Nomura, O.; Kitaura, K.; Morokuma, K.; Yamazaki, H. *J. Am. Chem. Soc.* **1983**, *105*, 1907−1912.

(14) Agenet, N.; Gandon, V.; Vollhardt, K. P. C.; Malacria, M.; Aubert, C. *J. Am. Chem. Soc.* **2007**, *129*, 8860−8871.

(15) Grdina, B.; Orfanopoulos, M.; Stephenson, L. M. *J. Am. Chem. Soc.* **1979**, *101*, 3111−3112.

(16) Singleton, D. A.; Szymanski, M. J. *J. Am. Chem. Soc.* **1999**, *121*, 9455−9456.

(17) Giagou, T.; Meyer, M. P. *J. Org. Chem.* **2010**, *75*, 8088−8099.