Probing the Free Energy Landscape of Organophotoredox Catalyzed Anti-Markovnikov Hydrofunctionalization of Alkenes

Sharath Chandra Mallojjala,† Victor O. Nyagilo,† Stephanie A. Corio, and Jennifer S. Hirschi*  
Department of Chemistry, Binghamton University, Binghamton, NY 13850  
KEYWORDS

ABSTRACT: Experimental $^{13}$C kinetic isotope effects (KIEs) provide unprecedented mechanistic insight into three intermolecular anti-Markovnikov alkene hydrofunctionalization reactions – hydroesterification, hydroamination, and hydroetherification – enabled by organophotoredox catalysis. All three reactions are found to proceed via initial oxidation of the model alkene (anethole) to form a radical cation intermediate followed by sequential nucleophilic attack and hydrogen-atom transfer to deliver the hydrofunctionalized product. A normal $^{13}$C KIE on the olefinic carbon that undergoes nucleophile attack provides qualitative evidence for rate-limiting nucleophilic attack in all three reactions. Comparison to predicted $^{13}$C KIE values obtained from DFT calculations for this step reveals that nucleophile has partial rate-limiting influence in hydroesterification and hydroamination, while the nucleophilic attack is solely rate-limiting in the hydroetherification reaction. The basic additive (2,6-lutidine) activates the nucleophile via deprotonation and is an integral part of the transition state for nucleophilic attack on the radical cation – providing an important design principle for the development of asymmetric versions of these reactions.

The Nicewicz lab has pioneered the development of anti-Markovnikov hydrofunctionalization of alkenes that utilize acridinium salts as photocatalysts.¹ The seminal reports describe intramolecular hydroetherification of alkenols² and intramolecular hydroamination of unsaturated amines (Scheme 1A).³⁴ Following these initial reports, the Nicewicz lab also reported intermolecular anti-Markovnikov hydrofunctionalization of alkenes (Scheme 1B). Specific examples include hydroesterification of alkenes using carboxylic acids,⁵ hydroamination of alkenes using triflyl amines,⁶ and hydrohalogenation of styrenes using mineral acids.⁷ Key to the success of these reactions is the use of catalytic amounts of a base (2,6-lutidine) and a thiol co-catalyst in addition to the photocatalyst.

The proposed mechanism of the intermolecular hydrofunctionalization (using anethole (1) as a model alkene) involves the oxidation of 1 via single electron transfer (SET) by a photoexcited acridinium catalyst (Mes-Acr⁷⁺) to form cation radical intermediate 1⁺ and the reduced acridine radical (Mes-Acr*). This is followed by attack of the nucleophile (Nu-H), resulting in the formation of carbon-centered radical intermediate 4. H-atom transfer (HAT) from the thiol co-catalyst to 4 delivers the anti-Markovnikov product 3 and a thiyl radical (Scheme 1B). The thiyl radical likely oxidizes the Mes-Acr* to Mes-Acr⁺ while forming a thiolate anion. The base, 2,6-lutidine, presumably serves as a proton shuttle between Nu-H and the thiolate anion to regenerate the thiol co-catalyst.

Fundamental mechanistic studies by the Nicewicz group using a battery of photophysical probes provide valuable insight into the elementary steps involved in this catalytic cycle.³⁵ Stern–Volmer analysis reveals that oxidation of alkenes such as anethole (1, $E_{1/2} = 1.34$ V) can occur via SET to either a singlet excited state of Mes-Acr⁺ ($E_{1/2} > +2.0$ V) or a locally excited or charge transfer triplet state ($E^*_{1/2} = +1.45/1.88$ V). Transient absorption spectroscopy supports formation of 1⁺ as a key intermediate in this reaction. Evidence was also obtained for the turnover of the Mes-Acr⁺ by the thiyl radical as the mechanistic event that unites the photoredox and HAT catalytic cycles.

---

**Scheme 1.** Intra- and intermolecular anti-Markovnikov hydrofunctionalization of olefins via organophotoredox catalysis pioneered by the Nicewicz group. Catalytic cycle of intermolecular hydrofunctionalizations investigated in this study.
Key questions regarding the overall mechanism of the intermolecular hydrofunctionalization of alkenes remain unclear (Scheme 1B). 1) What is the overall rate-limiting step? 2) Does the nature of the nucleophile affect the free energy landscape of these reactions? 3) What is the exact nature and timing of the role of 2,6-lutidine in the catalytic mechanism? 4) What are the key features of the transition states of the nucleophilic attack and HAT step?  

We sought to answer these questions utilizing a combination of experimental $^{13}$C kinetic isotope effects (KIEs) and computational studies. Since the olefinic carbon atoms undergo bonding change or rehybridization in each step of the catalytic cycle, experimental $^{13}$C KIEs can provide vital insight into the details of the free energy landscape of the reaction. We report herein, a combined experimental and theoretical study that investigates the general mechanism of intermolecular hydrofunctionalization of alkenes catalyzed by an organophotoredox catalyst.

Figure 1. Experimental $^{13}$C KIEs for three intermolecular hydrofunctionalization reactions of anethole determined via recovered starting material analysis. Key olefinic KIEs are highlighted in orange and standard deviation in the last digit of the measurement is indicated in parenthesis. Also shown are the transition states for nucleophilic attack on the radical cation for each reaction along with predicted $^{13}$C KIEs at the olefinic carbon atoms for comparison with the experimental values.
significant normal KIE on C1 suggests that HAT has a lower barrier than C-Nu bond-formation and has no rate-limiting influence.

For the quantitative interpretation of experimental KIEs, we modeled transition structures for both C-Nu bond-formation and HAT steps using DFT calculations. Geometry optimizations were carried out at three different levels of theory. We observed little functional and basis set dependence on the geometries, and therefore chose M062X/6-31+G(d) 3-10 based on efficiency and precedence in the literature.11 For the energies, we benchmarked five levels of theory against experimental redox potentials of the system and identified oB97X-D/aug-cc-pVTZ12-13 as the most suitable level of theory. A PCM implicit solvation model14-15 was used for all computations to account for solvent effects. Predicted 13C KIEs were obtained from the scaled vibrational frequencies and a Wigner tunneling correction was applied.16-18 A thorough potential energy scan was performed to explore various binding modes for the nucleophiles, lutidine, thiol, and the catalyst. Alternate pathways such as the formation of a thiolene adduct followed by Sₓ2 displacement by the nucleophile were also investigated.

The lowest energy transition structures for C-Nu bond formation for both nucleophiles involve attack of the lutidinium salt of the nucleophile on the radical cation of 1 (TS-Nu2a and TS-Nu2b). Intrinsic reaction coordinate (IRC) calculations confirm that deprotonation of 2a/2b by lutidine occurs prior to the nucleophilic attack. Free energy barriers (ΔG‡) for the nucleophilic addition TSs are 12.9 and 14.8 kcal/mol for TS-Nu2a and TS-Nu2b, respectively (barriers are relative to 1+ 2a/2b). These structures are lower in energy than TSs calculated with no lutidinium counterion present – TS-Nu2a and TS-Nu2b are lower in energy by 9.7 and 3.1 kcal/mol, respectively, than the corresponding TSs without the lutidinium counterion (see Supporting Information Figure S14). The lowest energy transition structures for the HAT step from thiophenol to the carbon-centered radical are significantly lower in energy than nucleophilic addition for both hydrofunctionalizations (ΔG‡ for TS-HAT2a is 6.9 and TS-HAT2b is 10.3 kcal/mol, Figure 2). The lower energy barrier combined with a nominal experimental KIE at C1 indicates that HAT is a facile process. This is consistent with the qualitative interpretation of experimental 13C KIEs indicating that C-Nu bond-formation is likely the rate-determining step in both reactions. If this interpretation is accurate, the predicted KIEs at C1 and C2 for TS-Nu2a and TS-Nu2b should agree with the experimental KIEs determined in the hydroesterification and hydroamination reaction, respectively. However, analysis of the predicted KIEs (Figure 1) reveal values at C2 that are significantly larger than experiment. In the hydroesterification reaction, the experimental KIE at C1 and C2 represents ~40% expression (experimental KIE/predicted KIE)*100) of the predicted KIEs for TS-Nu2a. The discrepancy is slightly less pronounced in the hydroamination reaction, where the experimental KIE at C1 and C2 corresponds to ~60% expression of the predicted KIEs for TS-Nu2b.

A possible explanation for this mismatch between experimental and predicted KIEs at C2 could be that a step prior to nucleophilic attack has partial rate-limiting influence in these reactions. In other words, electron transfer from 1 to Mes-Acr+ to form the radical cation of 1 is kinetically competitive with C-Nu bond-formation.19 A similar discrepancy in experimental and theoretical KIEs was recently observed by Singleton in the photoactive-promoted [2+2] cycloaddition of enones.20 In such a scenario, the experimental KIEs would be a weighted average of the predicted KIEs for SET and the C-Nu bond-forming step, based on the relative free energies of these steps. Predicted KIEs

Figure 2. Reaction coordinate diagram depicting the relative barriers of alkene oxidation, nucleophilic attack, and HAT steps for all three hydrofunctionalization reactions — hydroesterification (blue), hydroamination (purple), and hydroetherification (black). SET is co-rate-limiting in the hydroesterification and hydroamination reactions. Carbon-nucleophile bond formation is solely rate-limiting for intermolecular hydroetherification. The barrier for TS-SET is an average of the estimated SET barriers for hydroesterification and hydroamination as determined from the relative contribution of TS-SET and TS-Nu2a/TS-Nu2b to the experimental KIEs in the respective reactions.
for electron-transfer to form $\text{1}^+$ are near unity (1.003) for both C1 and C2; therefore a weighted average that includes partial rate-limiting electron transfer will have the effect of lowering the KIE for C2.

Our results thus far are consistent$^{23}$ with a partially rate-limiting mechanistic scenario — the higher barrier for TS-$\text{Nu}_{2b}$ (14.8 kcal/mol) compared to TS-$\text{Nu}_{2a}$ (12.9 kcal/mol) makes nucleophilic attack more rate-limiting for hydroamination as compared to hydroesterification, consistent with the increased KIE expression for hydroamination (~60%) relative to hydroesterification (~40%). To further validate this interpretation of our experimental KIEs, we decided to determine $^{13}$C KIEs for the intermolecular hydroetherification of 1 with methanol (2c) as the nucleophile. We hypothesize that since 2c is an inferior nucleophile compared to deprotonated 2a/2b, C-Nu bond-formation would become solely rate-limiting, resulting in full expression of experimental KIEs. Nucleophilic addition of methanol was originally reported by Nicewicz as a sole example of intermolecular hydroetherification in the seminal paper described earlier.$^{2}$ We made one modification to the originally reported procedure by adding 25 mol% 2,6-lutidine to this reaction to prevent the formation of thiouene side product as well as to maintain consistency with the experimental conditions used for hydroesterification and hydroamination.$^{22}$

Gratifyingly, $^{13}$C KIEs of 1.028 and 1.006 were observed at C2 and C1, respectively, for the reaction of 1 with 2c — values that correspond to >90% expression of the $^{13}$C KIE predictions for TS-$\text{Nu}_{4a}$, the transition structure for lutidine-activated nucleophilic attack of methanol on $\text{1}^+$ (Figure 1, $\Delta G^i = 21.1$ kcal/mol). Unlike 2a/2b, where deprotonation by lutidine occurs prior to the nucleophilic attack step, TS-$\text{Nu}_{2b}$ is a transition structure where the two steps — deprotonation and nucleophilic attack — occur as a concerted event (confirmed by IRC calculations).

Finally, we used Marcus theory to estimate the barrier for electron transfer from 1 to Mes-Acr$^{+*}$ to generate the radical cation $\text{1}^{++}$. Since alkene oxidation is a common step for all three hydrofunctionalizations, we estimated the effective redox potential for the catalyst species to be ~1.83 V based on the % expression of the $^{13}$C KIEs at C2 and the calculated SET barrier from Marcus theory. The four-point approximation was used to calculate the inner sphere reorganization energies and a modified two sphere model was applied to the outer sphere reorganization energies. From this analysis, we found that $\Delta G^i_{\text{SET}}$ is ~0.2 kcal/mol uphill from 1 + Mes-Acr$^{+*}$ (~13.9 kcal/mol relative to 1$^{+*}$ + Mes-Acr$^+$, the arbitrary zero in Figure 2). We emphasize that the calculation of this free energy surface is only possible by estimation of the effective redox potential of the photoexcited catalyst species from the expression of the KIEs, highlighting the importance of a combination of kinetic experiments and computations to probe the energy surface of these reactions.$^{26}$ It must be noted that SET can occur from different combinations of photoexcited states of the catalyst as long as the average redox potential is ~1.83 V (See Supporting Information for detailed discussion).

A composite free energy profile (Figure 2), for all three hydrofunctionalization reactions of anethole, is consistent with (a) partial rate-limiting alkene oxidation (TS-SET, $\Delta G^i = -13.9$ kcal/mol) and nucleophilic attack for both hydroesterification (TS-$\text{Nu}_{2a}$, $\Delta G^i = 12.9$ kcal/mol) and hydroamination (TS-$\text{Nu}_{2b}$, $\Delta G^i = 14.8$ kcal/mol), and (b) sole rate-limiting influence of TS-$\text{Nu}_{2c}$ ($\Delta G^i = 21.1$ kcal/mol) in the hydroetherification reaction, as previously hypothesized. The HAT step is facile in all three hydrofunctionalization reactions — lending strong support to the qualitative interpretation of our experimental KIEs. This free energy profile presents an experimentally validated unified model that provides comprehensive insight into the rate- and selectivity-determining factors for intermolecular hydrofunctionalization reactions enabled by organophotoredox catalysis.

![Experimental $^{13}$C KIEs for intermolecular hydroesterification reaction](image_url)

**Figure 3.** Experimental $^{13}$C KIEs for intermolecular hydroesterification reaction of (a) an alkene with lower redox potential (isosafrole, top) using Mes-Acr$^+$ as catalyst, and (b) of anethole using a more sterically hindered photocatalyst (t-Bu-Mes-Acr$^+$, bottom).

To further probe the energy surface of this reaction, we envisioned that a reaction involving an alkene with a lower oxidation potential or a more efficient photocatalyst could alter the rate-limiting influence of alkene oxidation, resulting in an increased expression of KIEs in the hydroesterification reaction (Figure 3). Gratifyingly, determination of $^{13}$C KIEs for isosafrole (1a, an alkene with .14 V lower oxidation potential than 1) in the hydroesterification reaction resulted in a $^{13}$C KIE at C2 of ~1.026. This corresponds to ~80% expression of the predicted KIE at C2 for 1a (predicted C2 KIE = 1.031), suggesting a reduced rate-limiting influence of TS-SET for this alkene. A second experiment involved the hydroesterification of 1 with the more robust, second-generation Nicewicz photocatalyst (t-Bu-Mes-Acr$^+$).$^{1,27}$ Despite the faster rate of reactions utilizing t-Bu-Mes-Acr$^+$, there is no statistical difference in the experimental KIEs (Figure 3) when compared with corresponding reactions run with Mes-Acr$^+$ (Figure 1). These results demonstrate that the free energy profile for both photocatalysts remains the same, and the faster kinetic profile observed for t-Bu-Mes-Acr$^+$ must be due to the prolonged viability of the catalyst as originally hypothesized by Nicewicz.$^{27,28}$

In conclusion, we have conducted a mechanistic evaluation of intermolecular alkene hydrofunctionalization reactions developed in the Nicewicz lab. The key finding from experimental $^{13}$C KIEs determined for anethole is that alkene oxidation and
nucleophilic attack are kinetically competitive in the hydroxysterification and hydroamination reactions, while nucleophilic attack is solely rate-limiting in the hydroetherification reaction. The 2,6-lutidine base is likely involving in the transition state for nucleophilic attack, which is the selectivity-determining step of the reaction. This suggests that utilization of a chiral base could enable enantioselective catalysis in these reactions. This is a rare example of experimental validation of the atomistic features of the transition state geometry of a photoredox reaction. In addition, the combination of \(^1^C\) KIEs and theoretical calculations provides unique insight into the complexities of the mechanistic landscape involved in photoredox catalysis by probing SET as well as steps involving bonding changes at carbon. We anticipate that our findings will lead to similar investigations into other areas of photoredox catalysis and provide a valuable complement to existing photophysical tools for mechanistic evaluation of photoredox reactions.

ASSOCIATED CONTENT

Supporting Information
The Supporting Information is available free of charge on the ACS Publications website.

AUTHOR INFORMATION

Corresponding Author
*Jennifer S. Hirschi – Department of Chemistry, Binghamton University, Binghamton, New York 13902, United States. ORCID: 0000-0002-3470-0561.

Email: jhirschi@binghamton.edu

Present Addresses
Sharath Chandra Mallojjala – Department of Chemistry, Binghamton University, Binghamton, New York 13902, United States. ORCID: 0000-0003-0446-792X.

Victor O. Nyaglo – Department of Chemistry, Binghamton University, Binghamton, New York 13902, United States.

Stephanie A. Corio – Department of Chemistry, Binghamton University, Binghamton, New York 13902, United States.

Author Contributions
‡These authors contributed equally.

ACKNOWLEDGMENT

Financial support for this work was provided by Binghamton University startup funds and the National Institutes of Health under R15 GM142103 (J.S.H.). J.S.H and M.S.C acknowledge support from the XSEDE Science Gateways Program (allocation IDs CHE180061 and CHE210031), which is supported by the National Science Foundation grant number ACI-1548562.

REFERENCES


19. Alternatively, self-exchange between 1 and 1* could also be kinetically competitive with C-Nu bond-formation but this was unlikely based on the computed barrier for self-exchange versus SET involving the photocatalyst. (see SI)

21. A co-rate limiting scenario involving HAT and nucleophilic attack can be ruled out based on the computed free energy barriers. Moreover, no combination of HAT and nucleophilic attack KIEs yield the experimentally observed KIEs.

22. In the absence of 2,6-lutidine, NMR analysis of the hydroetherification reaction revealed the formation of a thiolene intermediate which was eventually converted to the hydroetherification product. Addition of 2,6-lutidine significantly accelerates the reaction and eliminates the formation of the thiolene product. The calculated barrier for $\Delta G^\ddagger$ for the addition of methanol without lutidine is 6.5 kcal/mol higher in energy, consistent with the significant rate acceleration observed experimentally.


26. See SI for a detailed discussion on the computed SET barriers and the approximations involved.

