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An alkene, a photon, and a catalyst walk into a bar; Zaitsev wasn't invited

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Isomerization reactions represent a powerful class of synthetic transformations. These processes allow chemists to assemble molecules with robust bond-forming reactions then fine-tune key structural features of the molecule including functional group position and stereochemistry. Accordingly, expanding the breadth of selective isomerization tools has the potential to substantially streamline chemical synthesis.

Alkene isomerization is among the most classic and broadly employed classes of positional isomerization reactions. Manipulation of alkene position within a molecule is particularly appealing because there is a vast array of powerful reactions to both generate and transform alkenes. However, while mechanistically diverse strategies have been established that promote selective isomerization of alkenes, these are driven by the thermodynamic stability of the final isomeric product relative to the starting alkene. Endergonic alkene isomerization reactions (Figure 1, top) have remained, perhaps unsurprisingly, elusive. Based on the principle of microscopic reversibility, any thermal driving force sufficient to overcome the forward barrier is necessarily sufficient to drive the reverse reaction. As a consequence, thermally promoted processes can provide, at best, a Boltzmann distribution of products with poor enrichment in the targeted less stable product. The development of new strategies to drive the selective isomerization of alkenes to less stable isomers would represent an enabling synthetic technology.

In principle, photochemistry offers an appealing mechanistic opportunity to access products higher in energy from their corresponding starting materials without balancing this energy with sacrificial chemical reagents. Consumption of photons offers a sizable thermodynamic driving force (40–70 kcal/mol) and thus enables transformations that are uphill with respect to the bonds formed and broken. While examples of photosensitized stereochemical alkene isomerization date back over half a century, driving such processes across a wider scope of substrates remains an area of immense contemporary interest (Figure 1, middle). In the past several years, Gilmour and coworkers have developed an array of photosensitization methods to convert diverse (*E*)-alkenes to their less stable (*Z*)-alkene isomers [1]. Additionally, photocatalytic systems have recently been designed to drive other endergonic transformations, such as deracemization of chiral allenes [2] and cyclic ureas [3] as well as carbohydrate epimerization [4]. Each of these pioneering reports represents advances in endergonic stereochemical isomerization. Endergonic positional isomerization, however, poses unique challenges as it requires the removal of a functional group and subsequent reinstallation at a less favorable site. Previously reported approaches to promote positional alkene isomerization in a contra-thermodynamic fashion have been limited to a narrow range of specific substrate classes [5–8], leaving general strategies to promote these synthetically attractive processes underdeveloped.

Recently, the Knowles and Wendlandt groups independently disclosed generalizable photochemical strategies to promote the contra-thermodynamic positional isomerization of alkenes with exquisite selectivity in a recent pair of back-to-back reports (Figure 1, bottom) [9,10]. While both methods proceed through allylic radical intermediates, they operate via two different mechanistic paradigms. As a result, the two reaction systems are controlled by distinct factors, excel in different contexts, and are ideal complements to one another.

In the Knowles work, the allylic radical intermediate is accessed via photocatalytic alkene oxidation followed by deprotonation of the nascent radical cation. The transient allylic radical formed by this process is subsequently trapped by a chromium cocatalyst to generate an allylchromium intermediate. Regioselective protodemetalation of this species leads to the isomerized product. The product is then inert to further photochemical oxidation due to a more positive oxidation potential, which lies beyond the oxidation potential window of the photoredox catalyst. Intriguingly, the crux of this strategy is still grounded in the thermodynamic parameters of the products relative to the starting materials. However, rather than the product distribution being dictated by relative alkene stability, this catalytic system is controlled by their relative oxidation potentials.

By contrast, the catalytic system developed by Wendlandt and coworkers leverages the excited state of a decatungstate photocatalyst to generate the allylic radical intermediate through hydrogen atom abstraction. This allylic radical intermediate is again selectively intercepted by a metal co-catalyst, in this case cobalt. However, rather than releasing the desired product through protonation, hydrogen atom delivery to the allyl cobalt species occurs by a regiospecific S_H2' mechanism to liberate the isomerized alkene product. Deuterium labeling experiments conclusively exclude the possibility of hydrogen atom abstraction from the allylbenzene

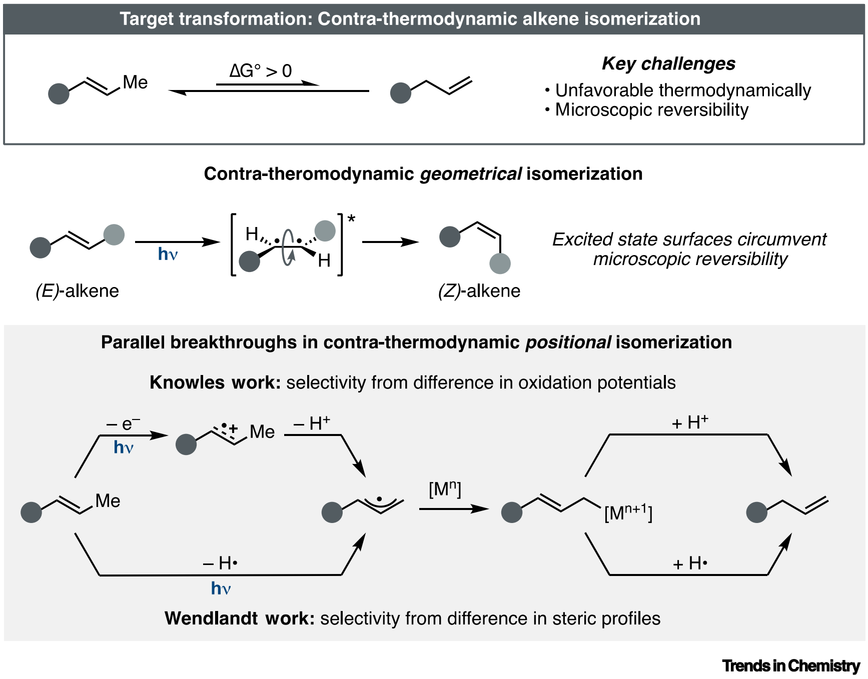

Figure 1. Overview of contra-thermodynamic alkene isomerization.

products, illustrating that the product is not susceptible to reverse reaction. The authors posit that both the photochemical hydrogen atom abstraction and the cobalt trapping steps are sensitive to substrate steric parameters and contribute to the high selectivity observed across diverse substrate classes.

Together these new processes are remarkably effective across a variety of alkene substrate classes (Figure 2). Both methodologies promote the isomerization of various vinylarene substrates out of conjugation to allylbenzene products. Of note, vinylarene starting materials bearing both electron-donating and electron-withdrawing groups were transformed to the corresponding allylbenzene isomer under the two mechanistic manifolds. Both methods demonstrate excellent functional group tolerance, including the isomerization of vinyl heterocycles. Wendlandt and coworkers systematically examined reactivity for the deconjugation of vinylarenes with respect to the alkene substitution pattern. They found that di-, tri-, and tetrasubstituted substrates were all amenable to isomerization; however, the highest yields were observed for tetrasubstituted alkenes. Both methodologies were also amenable to the selective isomerization of conjugated dienes to their unconjugated counterparts.

A major appeal of having multiple mechanistically distinct approaches to any synthetic process is that the strengths and weaknesses of each approach are likely to differ. In this case, while vinylarene and diene substrates are isomerized using both methods, further examination of alkene substrate classes revealed a high level of complementarity in the scope of the two new catalytic manifolds.

In the oxidation triggered isomerization method from the Knowles group, exceptionally electron-rich alkenes, such as enol ethers and enamides, are ideal substrates due to their ease of oxidation relative to their deconjugated products. Additionally, the oxidation-potential-based selectivity allows practitioners to maximize chemoselectivity through the selection of a photocatalyst with the minimum requisite oxidizing ability. Remarkable functional group tolerance is illustrated throughout the report. While conjugated alkenes constitute the majority of the scope, isolated alkene substrates with significantly higher oxidation potentials, such as isolated tetrasubstituted alkenes, are quantitatively isomerized when a more-oxidizing photocatalyst is employed.

The hydrogen atom abstraction induced isomerization process advanced by the Wendlandt group appears to fundamentally alter the electronic requirements for the alkene substrates relative to the oxidation-based approach. This hydrogen atom abstraction process promotes the isomerization of electron-deficient alkene substrates, such as enones, to their deconjugated counterparts. Furthermore, trisubstituted alkenes, which are energetically demanding for direct oxidation to their radical cation congeners, were selectively isomerized to their less substituted isomers. The addition of these two alkene classes allows the Wendlandt approach to transform naturally abundant feedstocks into valuable new alkene building blocks. They leveraged this strategy to convert a terpene feedstock to a key intermediate in the total synthesis of (–)-cyclonerodiol, streamlining the prior synthesis by eliminating conciliatory redox interconversions.

Overall, we are excited to see that not only are the mechanisms of action distinct for the two reactions but also the origins of the contra-thermodynamic selectivity appear to differ as well. Knowles has illustrated how catalytic systems can be designed to be controlled by specific thermodynamic parameters, even at the cost of overall product stability. By contrast, Wendlandt's system induces selectivity for the less stable alkene isomer based on kinetic sensitivity to steric parameters.

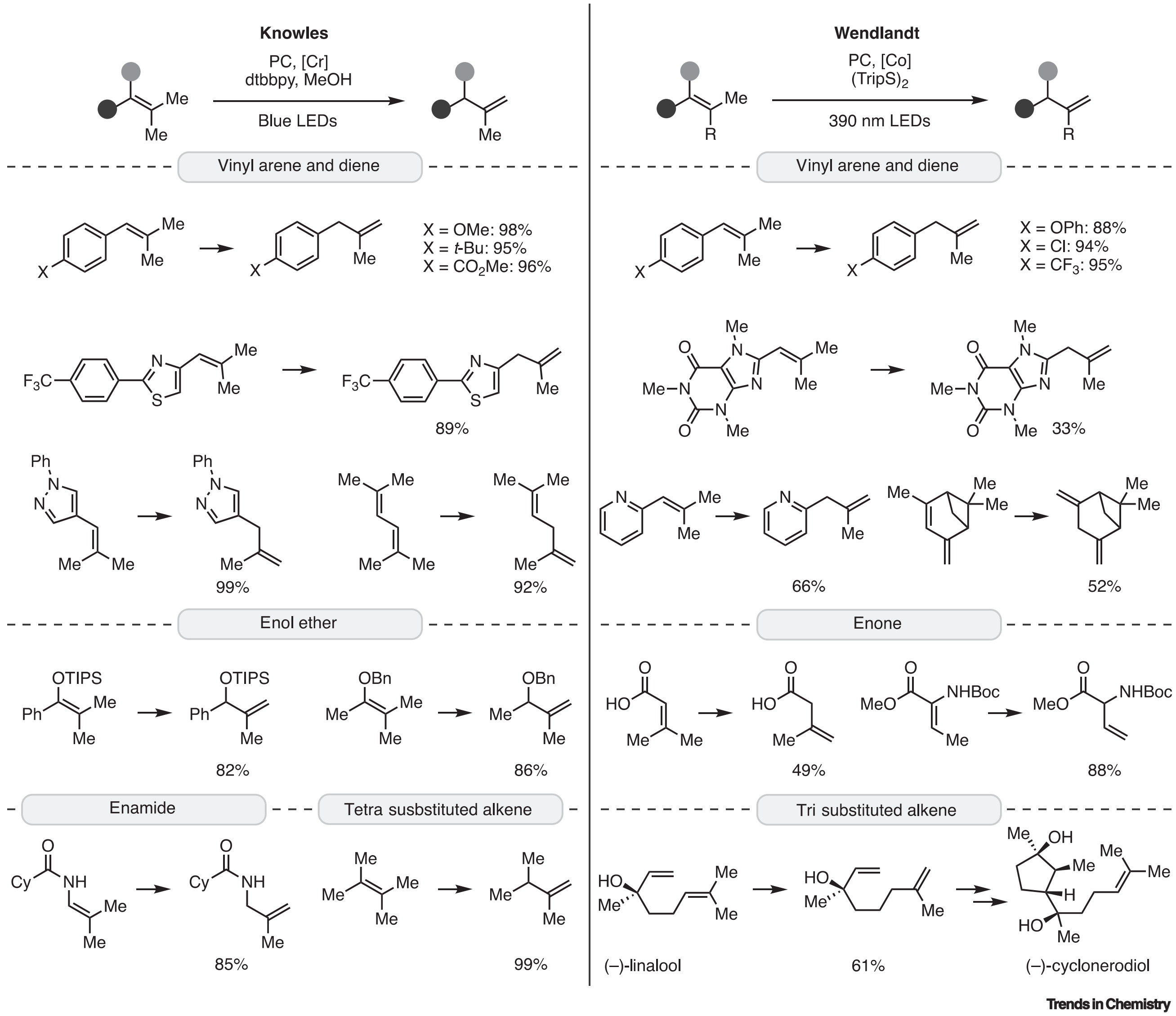

Figure 2. Selected scope entries. See [9,10]. Abbreviations: LED, light emitting diode; PC, photocatalyst.

Looking forward, we envision that these new reactions pose a wide range of new questions to explore. For example, three questions caught our attention. (i) What other parameters, besides oxidation potential and steric profile, might be leveraged for contra-thermodynamic selectivity? (ii) Can molecules be isomerized towards particularly unstable isomers rather than away from stable conjugated systems? (iii) Can a system be designed to provide high contra-thermodynamic selectivity in cases where a multitude of less stable isomers would be feasible to form? We expect that these reports will lay the foundation to answer these questions – and many more – as chemists continue to design diverse approaches to drive positional isomerization processes against a thermodynamic bias.

In summary, these two reports represent breakthrough strategies to promote positional alkene isomerization beyond the constraints of thermodynamic stability. Excitingly, due to the distinct mechanistic approaches employed by the Wendlandt and Knowles groups, most alkene substrate classes can now be isomerized to a less stable isomer. With the addition of these strategies to the synthetic toolbox, alongside existing alkene isomerization reactions, we are nearing a complete set of precision tools to enable synthetic chemists to move and rearrange alkenes at will.

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Declaration of interests

No interests are declared.

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