Organic Synthesis Away from Equilibrium

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An emerging area of study in catalysis and sustainable chemistry

The great majority of organic transformations are thermal processes which occur on a single potential energy surface. Due to microscopic reversibility, thermal processes are limited to transforming higher energy starting materials into lower energy products. A significant goal for the field of synthetic organic chemistry in the years to come is to devise strategies that decouple reaction direction from reaction thermochemistry and to employ these strategies to develop reactions and processes that proceed against a thermodynamic bias and thus cannot be achieved using any conventional methods.

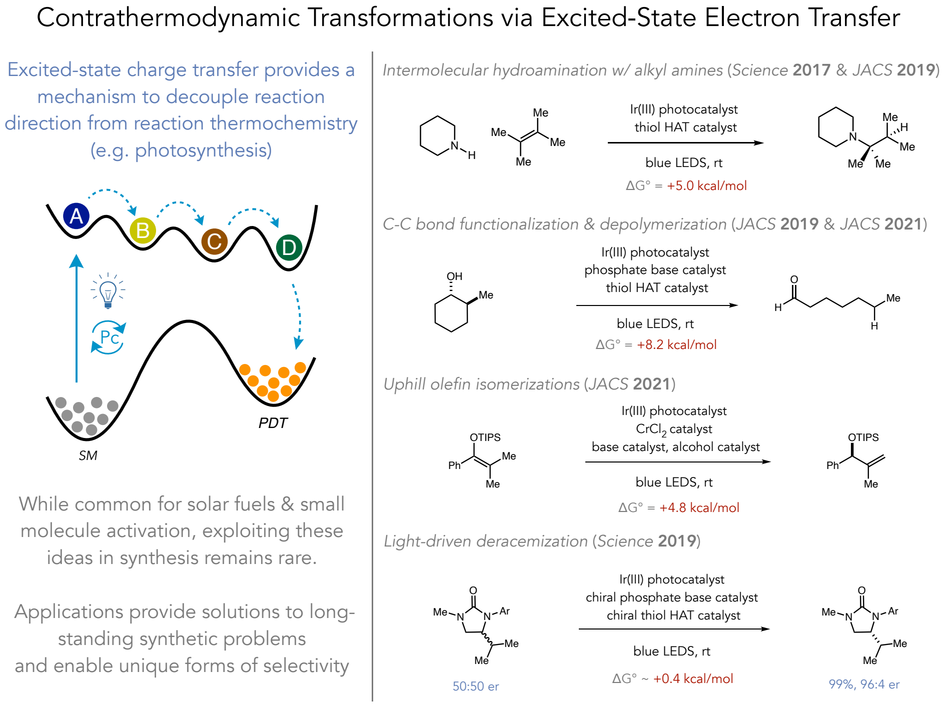
Toward this goal, significant advances have been made through the use of photoredox catalysis. One of the most interesting and enabling aspects of photoredox chemistry is the ability of these methods to drive organic reactions ‘uphill’ in opposition to a thermodynamic bias. Drawing parallels to solar fuels chemistry, photoexcitation events provide an exogenous driving force that offsets the otherwise unfavorable energetics of the bond forming and bond breaking steps, allowing access to products that are formally higher in energy than the starting materials. However, for synthetic applications these reaction manifolds also exhibit unique kinetic benefits. Specifically, as all the reaction pathways proceeding from the initial excited state are thermodynamically favorable, the partitioning between potential pathways is kinetically controlled and fully decoupled from the ground-state thermochemistry of the resulting products – even for systems that are dynamic. These attributes create an exciting prospect for catalysis where chemists can, in principle, use molecular catalysts to kinetically select for any accessible product state in a dynamic system irrespective of the system’s ground-state thermochemical preferences. The applications of these ideas in synthesis have begun to be explored and developed in recent years. Important contributions have been made by a number of groups, including Thorsten Bach, Alison Wendlandt, David MacMillan, Aiwen Lei, and Ryan Gilmour.[1–5] In the sections below I will highlight some of my lab’s contributions to this area and thoughts on where these advances may lead in the future.

My recent research contributions

In recent years our lab has reported a number of methods that make use of excited-state redox events to drive reactions away from equilibrium (Figure 1). Our first report in this area was on the development of intermolecular hydroaminations of unactivated olefins with secondary alkyl amines.[6] Under visible light irradiation, an excited state chromophore oxidizes an amine substrate to its corresponding aminium radical cation, which then readily reacts with alkene reaction partners. This protocol constructs valuable tertiary alkyl amine products with complete anti-Markovnikov regioselectivity. Notably, many of these hydroamination products are less thermodynamically favored than their corresponding olefin and amine starting materials, which makes them inaccessible through conventional ground-state catalysis. Recently, we have extended this protocol to the selective synthesis of secondary amines via direct intermolecular hydroamination of primary alkyl amines and simple olefins with minimal generation of over-alkylated tertiary amine products.[7]

We have also described a catalytic protocol for C–C bond cleavage with simple aliphatic alcohols that mediates redox-neutral isomerizations of cyclic aliphatic alcohols to linear carbonyl compounds.[8] In these reactions, the alcohol O–H bonds is homolytically activated via excited-state proton-coupled electron transfer. The resulting alkoxy radical intermediates undergo intramolecular C–C β-scission to provide fragmented carbonyl products, which are generally higher in energy than their corresponding alcohol starting materials. We have further advanced this chemistry for the development of photocatalytic methods for depolymerization of native lignin and high molecular weight hydroxylated polyolefins.[9,10]

We have also applied the ideas above for the contra-thermodynamic positional isomerization of internal olefins into terminal olefins.[11] In this work, stepwise oxidation and deprotonation of a more substituted and more thermodynamically stable olefin substrate is mediated by an excited-state oxidant and a Brønsted base to afford an allylic radical. This radical is captured by a Cr(II) co-catalyst to furnish an allylchromium(III) intermediate that undergoes *in situ* protodemetalation with methanol, affording an isomerized and less thermodynamically stable alkene product with high regioselectivity. The higher oxidation potential of the less substituted olefin isomer renders it inert to further reaction with the excited-state oxidant, enabling it to accumulate in solution over the course of the reaction. A similar light-driven method that proceeds by a distinct mechanism was also reported by Wendlandt and coworkers.[12]



Contrathermodynamic Transformations via Excited-State Electron Transfer

Excited-state charge transfer provides a mechanism to decouple reaction direction from reaction thermochemistry (e.g. photosynthesis)

While common for solar fuels & small molecule activation, exploiting these ideas in synthesis remains rare.

Applications provide solutions to long-standing synthetic problems and enable unique forms of selectivity

Fig. 1. Examples of light-driven contrathermodynamic transformations in synthesis enabled by excited-state electron transfer.

Lastly, we have applied these ideas in out-of-equilibrium catalysis to asymmetric synthesis. In particular we have developed, in collaboration with Professor Scott Miller, a light-driven deracemization reaction wherein a racemic urea substrate undergoes spontaneous optical enrichment (upto 94% ee and 95% yield) simply upon visible light irradiation in the presence of three distinct molecular catalysts.[13] Excellent enantioselectivity is achieved for the homolysis and reformation of a stereogenic C–H bond through orchestrated movements of an excited-state electron, proton, and hydrogen atom. Remarkably, this system establishes a stable, non-equilibrium distribution of urea enantiomers without any use of stoichiometric chemical reagents. It is notable that a number of other light-driven deracemization technologies have been reported in recent years, including seminal contributions from the group of Bach.[1]

Outlook

These approaches will create new possibilities and efficiencies in synthesis. The results above show that a variety of canonical, redox-neutral reaction types (additions, eliminations, isomerizations, etc) can be driven away from their equilibrium positions using excited-state electron transfer based mechanisms. This framework can potentially be extended to a large number of reaction classes, providing a platform to drive known transformations in reverse, introduce dynamic behavior into otherwise static systems, and access reaction products that cannot be achieved using conventional thermal methods. Moreover, the use of visible-light excitation obviates the needs to use stoichiometric chemical reagents to provide a reaction's driving force, thus limiting the production of waste and increasing the sustainability of the developed technologies.

A particularly exciting direction for this area extends the ideas presented in the deracemization work discussed above. Specifically, as these technologies advance one could imagine a new paradigm where stereocomplex target molecules could be made as stereo-random mixtures and then edited post-synthetically to adjust all the stereochemical relationships.[2,3,13] Moreover, this could be achieved with catalyst-controlled selectivities that are not subject to thermodynamic constraints. While such an idea would have seemed distant or perhaps impossible several years ago, it is increasingly clear that such strategies are tractable. If successful, this approach points to a fundamentally distinct way of thinking about stereoselective synthesis with potential impacts at the level of retrosynthetic analysis. Taken together, the prospects for this area appear bright and it will be exciting to see what progress can be made in the years to come.

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