

ORIENTED ELECTRIC FIELDS IN NON-REDOX ORGANIC REACTIVITY

Reported by Casey Olen

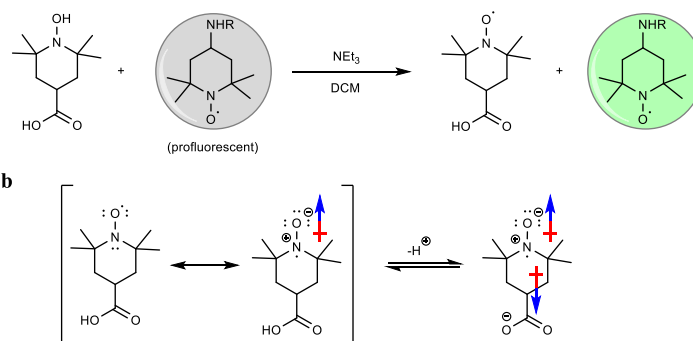
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INTRODUCTION

Electric fields have recently emerged as a means of controlling reactivity in non-redox chemical processes. This seminar will present an overview of the physical organic principles guiding applications of oriented external electric fields (OEEFs), local electric fields (LEFs), and interfacial electric fields (IEFs) in synthesis, and will outline the current state of the art in using electric fields for electrostatic (i.e. non-redox) catalysis. Applying an electric field to catalyze a reaction requires the field to be oriented along the reaction coordinate.¹ Properly oriented electric fields facilitate electronic reorganization from a reactant-like to a product-like state by enhancing the relative resonance contributions of ionic valence bond isomers. Effectively exploiting this technique for synthesis depends on fixing the reactants in a conformation that is non-orthogonal to the electric field vector, a challenging organizational requirement.

LOCAL ELECTRIC FIELDS: EARLY INSPIRATION FROM ENZYMATIC SYSTEMS

Nature exploits properly oriented LEFs^a for enzymatic catalysis. The enzyme ketosteroid isomerase catalyzes the isomerization of a δ,γ -unsaturated ketone to an α,β -unsaturated ketone at an especially high catalytic rate. Unusual spectral shifts in the substrate are observed when bound to the enzyme, which have been quantified and attributed directly to a strong LEF produced by polar moieties within the active site.² Taking inspiration from Nature, Coote *et al.* have employed LEFs in synthetic organic chemistry (Scheme 1a).³ They demonstrated that a proximal carboxylate anion enhances the rate of radical H-abstraction from the O–H bond of an *N*-hydroxylpiperidine. Reaction rate dependence on pH-switchable deprotonation of the carboxyl moiety is attributed to the stabilization of the product by the electric field of the anion (Scheme 1b).

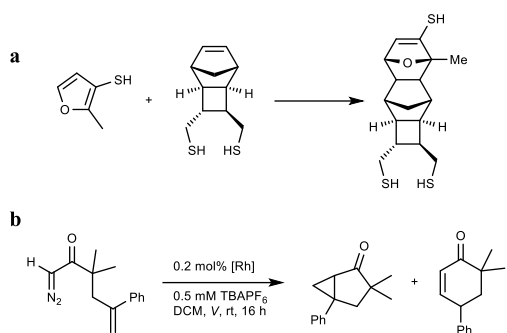


Scheme 1: (a) LEF-catalyzed H-bond abstraction. (b) Deprotonation stabilizes minor resonance structure.

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ORIENTED EXTERNAL ELECTRIC FIELDS IN ORGANIC SYNTHESIS

OEEFs obviate the need to covalently incorporate an LEF within the reactant. The difficulty in orienting single molecules within an electric field is a major obstacle to this approach. The scanning-



Scheme 2: (a) STM-BJ catalyzed cycloaddition. (b) isomeric product ratio depends on voltage bias V .

tunneling microscopy break junction (STM-BJ) technique provides a controlled system in which this challenging organizational requirement is met, while simultaneously permitting determination of the chemical identity of the reactant and resulting product.⁴

STM-BJ has been applied to catalyze the Diels–Alder reaction between a norbornyl-type olefin and a furan-derived diene (Scheme 2a).⁵ The observed increase in reaction rate is

directly proportional to the magnitude of the voltage bias applied across the STM junction, indicating rate acceleration by the resulting electric field. Shaik *et al.* have shown *in silico* that an OEEF can also induce enantioselectivity in the Diels–Alder reaction.⁶ STM-BJ has been used to catalyze a hetero-Diels–Alder, aromatization cascade reaction.⁷ When applied to the *cis/trans* isomerization reaction of a [3]cumulene, STM-BJ produced a synthetically useful amount of the *trans*-isomer in a product ratio that outperformed both thermal and photochemical isomerization methods.⁸

HARNESSING ELECTRIC FIELDS FOR PRACTICAL NON-REDOX SYNTHESIS

STM-BJ, while convenient for orienting reactants, is expensive and difficult to scale. Various attempts have been made to adapt OEEFs to catalysis in electrochemical cells. Avoiding dielectric breakdown in such systems proved critical in preventing the mechanistic shift from electrostatic catalysis to electrochemical redox processes. Coote *et al.* have demonstrated that such mechanistic shifts can occur when adapting the STM-BJ catalyzed homolytic cleavage of alkoxyamines to an electrochemical cell.⁹ Matile *et al.* have demonstrated an electric field-dependent rate enhancement in the 1,4-addition of malonic acid half thioester to β -nitrostyrene.¹⁰ In addition, Kanan *et al.* have demonstrated IEF catalysis controls the product ratio in rhodium-carbene insertions into π bonds (Scheme 2b).¹¹

LIMITATIONS AND FUTURE DIRECTIONS

The prospects for applying electric fields in non-redox organic synthesis are bright despite current difficulties, including scaling the orientation of reactants, and avoiding dielectric breakdown in the reaction medium. Moving past STM-BJ to LEF and IEF approaches is an area of active research. Further experimental demonstrations of regio- and enantioselective electric field control are required to recapitulate the *in silico* predictions described thus far.

(1) Shaik *et al.* *J. Am. Chem. Soc.* **2020**, 142, 12551–12562. (2) Boxer *et al.* *Science*. **2014**, 346, 1510–1513. (3) Coote *et al.* *Chem. Sci.* **2015**, 6, 5623–5627. (4) Nikiforov, M. *MRS Bull.* **2003**, 28, 790–792. (5) Coote *et al.* *Nature*. **2016**, 531, 88–91. (6) Shaik *et al.* *J. Am. Chem. Soc.* **2018**, 140, 13350–13359. (7) Hong *et al.* *Sci. Adv.* **2019**, 5, 1–8. (8) Venkataraman *et al.* *Nat. Commun.* **2019**, 10, 1–7. (9) Coote *et al.* *J. Am. Chem. Soc.* **2018**, 140, 766–774. (10) Matile *et al.* *J. Am. Chem. Soc.* **2017**, 139, 6558–6561. (11) Kanan *et al.* *J. Am. Chem. Soc.* **2013**, 135, 11257–11265.