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Snapshots of some topics of interest of recent notable advances in chemistry:

- The catalytic activity of ruthenium complexes: some recent advances
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Snapshots of some topics of interest of recent notable advances in chemistry

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The Catalytic Activity of Ruthenium Complexes: Some Recent Advances

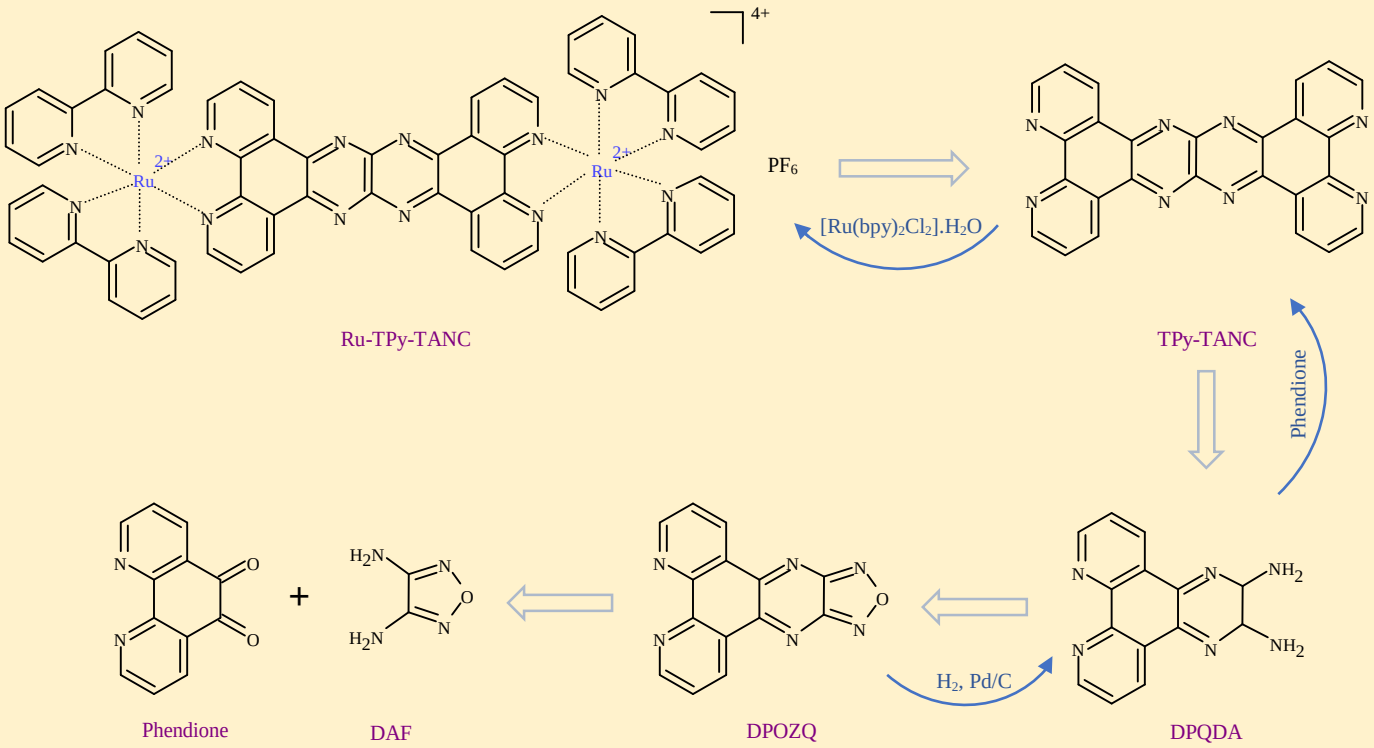
Ruthenium complexes have emerged as a powerful catalyst with significant recent advances in terms of their synthesis and applications to a variety of organic and electrochemical reactions; synthesis of natural and biologically active compounds; and valorization of renewable resources as platform chemicals for polymer. This snapshot highlights few examples of the recent advances of ruthenium-catalyzed processes, exhibiting their catalytic activities as well as their synthetic procedures.

KEYWORDS: ruthenium, transition metals, chiral ligands.

Ruthenium (Ru) is involved in a variety of reactions serving as a catalyst. The catalytic activity of ruthenium-catalyzed processes arises from Ru as a transition metal and the acquired asymmetric induction exerted by the chiral ligands coordinated to the metal. These ligands control the binding of reactants and their subsequent process paths through a combination of steric and electronic interactions. This snapshot aims to inform the reader about some of the significant role of Ru-catalyzed processes reported recently in the literature.

1. Ru-mediated solubility of bis-bidentate ligand in organic solvents

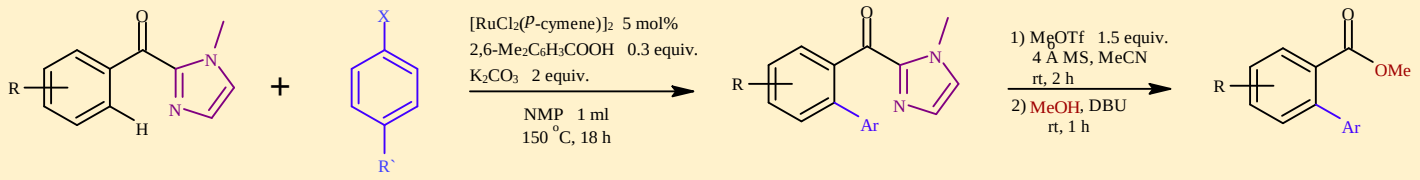
Acenes are polycyclic aromatic hydrocarbons, which can often be used effectively as semiconductors. In particular, *N*-heteroacenes with four nitrogen atoms exhibits reversible two-step/two-electron redox waves in its cyclic voltammograms (CVs) and behaves as organic n-type semiconductors. In this context, Kamebuchi *et al.*[1] reported a bis-bidentate ligand (TPy-TANC), which is a *N*-heteroacene with four fused pyridine rings at both ends of the TANC (5,6,11,12-tetraazanaphthacene). This ligand is poorly soluble in most common organic solvents, which was impossible to obtain CVs on this ligand. However, the incorporation of Ru (II) ions with this ligand to form a dinuclear Ru(II) complex had improved solubility, and enabled to investigate its electrochemistry. The CV of this Ru-TPy-TANC complex showed fully reversible four-step/six-electron redox behavior (Scheme 1).



Scheme 1. Synthesis of the ligand and the Ru complex.[1] Phendione: 1,10-Phenanthroline-5,6-dione; DAF: diaminofurazan; DPOZQ: dipyrido[3,2-*f*:2′,3′-*h*][1,2,5]oxadiazolo[3,4-*b*]quinoxaline; DPQDA: dipyrido[3,2-*f*:2′,3′-*h*]quinoxaline-2,3-diamine; TPy-TANC: tetrapyrido[3,2-*a*:2′,3′-*c*:3′′,2′′- *j*:2′′′,3′′′-*l*][5,6,11,12]tetraazanaphthacene; Ru-TPy-TANC: $[(bpy)_2Ru^{II}(TPy\text{-}TANC)Ru^{II}\text{- }(bpy)_2](PF6)_4$.

2. Ru-catalyzed C-H functionalization reactions

Ru-based catalysts are involved in a variety of organic reactions. Ru-catalyzed *ortho*-C-H arylation of 2-aroyl-imidazoles with aryl halides were synthesized by Wang and Chatani (Scheme 2).[2] The feature of this pathway allowed the imidazole moiety to function both as a masked ester (or amide) and a directing group for C-H activation. The arylated final products could be easily converted into the corresponding esters and amide.



Scheme 2. Ru(II)-catalyzed C-H arylation of 2-aroyl-imidazoles with aryl halides.[2] R or R′ = a variety of functional groups; X = Br or Cl.

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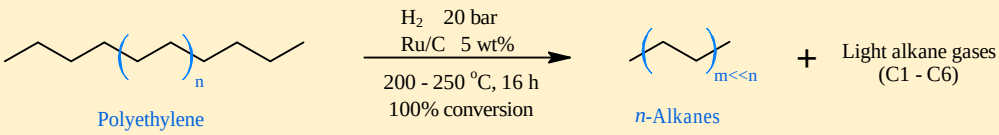
3. Ru/C-catalyzed selective depolymerization of polyolefin waste to liquid alkanes

Plastic waste adversely affects the Earth's environment and causing damage to our ecosystem. Plastic is slow to degrade owing to its chemical structure. It is made from polyolefins, which they are produced from polyethylene (PE) or polypropylene (PP). Recycling of plastic waste requires strong catalyst in order to selective polyolefin depolymerization via breaking the strong sp^3 C−C bonds in PE.

Román-Leshkov and co-workers[3] demonstrated the selective depolymerization of PE (average *M*w ~ 4000 Da) via hydrogenolysis to processable liquid *n*-alkanes with yields of up to 45% under mild conditions (200 °C, 20 bar H_2, 16 h) in the absence of solvent using Ru nanoparticles supported on carbon (5 wt%) compatible with gaseous products containing light alkane gases (C_1-C_6) (Scheme 3). At 250 °C, CH_4 was produced in near stoichiometric yields. In addition, the hydrogenolysis of long chain, low-density polyethylene (LDPE) and a postconsumer LDPE plastic bottle to produce C7−C45 alkanes was also achieved over Ru/C.



Scheme 3. The hydrogenolysis of polyethylene (average M_W ~ 4000 Da)

The high hydrogenolysis activity of Ru-based catalysts allowed for highly active depolymerization of PE into liquid *n*-alkanes, and pure CH_4 compatible with natural gaseous products, which could be used as fuels, chemicals, or synthons for the next generation of infinitely recyclable polymers.

4. Transfer of Ru-complex unit to biomolecules through ligand exchange strategy

Organometallic Ru complexes play an important role in protein matrixes. They can serve as inhibitor towards several enzymes, and have the potentiality to use as antibody-drugs. One of the strategies applied to covalent conjugation of a synthetic molecule into a protein, is to employ cysteine (Cys) residues in the protein as a conjugation site owing to reactivity of its nucleophilic functional group under physiological conditions. However, the conjugation of cysteine thiols to the transition metal complexes results often in unpredicted side reactions, causing critical issues. Relatedly, Jatmike *et al.*[4] have demonstrated that based on ligand exchange strategy, the transfer of (NHC)-Ru complex unit onto biomolecules (including peptides and proteins) can be achieved with reducing side reactions. Furthermore, they explained that Ru complexes with an electron-withdrawing group in the ligand should be employed in order to increase the efficiency of the metal complex transfer. Such Ru complex transfer reactions for proteins cannot be accomplished without alkene moieties proving that Ru-olefin interactions trigger the Ru complex transfer reactions (Scheme 4).

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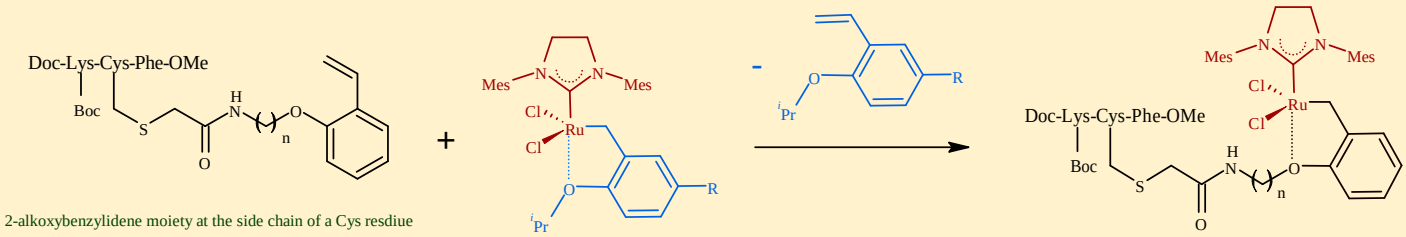

n =2; 3

R = H, NO_2, $CH_2N^+Me_3Cl^-$

Scheme 4. Transfer of the Ru complex from Hoveyda-Grubbs-type complex to a tripeptide.[3]

Conclusion

These examples have revealed the extraordinarily activity of Ru-based catalysts, indicating that the reactivity and selectivity in Ru-catalyzed reactions can be controlled by selecting suitable ligands of the complex catalysts.

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Some Recent Trends in Mitochondria

Beyond their role of energy supply, mitochondria are envisaged to be organelles implicated in many diseases. So many questions thus arise, for example: how can one monitor the physiological states of mitochondria to predict the outcome of diseases, or the response to a therapeutic treatment? This snapshot reflects a sample of the recent advances in this area.

KEYWORDS: mitochondria, nanothermometry, prodrug activation, Mito-TEMPO.

Mitochondria are the "energy factory" of the cell as they produce most of the energy in the form of ATP that the cell needs. They participate in critical central metabolic pathways and are fully integrated into the intracellular signaling networks that regulate diverse cellular functions. This snapshot illustrates three elegant publications addressing important issues, namely, how to monitoring mitochondrial thermal dynamics; how a redesign of structurally bioorthogonal reagents can lead to their transformation into organelle-specific probes; and to what extent can Mito-TEMPO impact the initiation phase of hepatocarcinogensis.

1- Monitoring *in situ* mitochondrial thermal dynamics

Mitochondria provide energy to the living cells through the oxidative phosphorylation process to synthesize ATP, and the other released energy, as a byproduct of active metabolism, dissipates in the form of heat. Thus, the variation of the mitochondria temperature reflects the cellular metabolism status, which is related to homeostasis and energy balance. Di *et al.*[1] have reported an upconversion nanoparticle-based thermometer that allows the *in situ* thermal dynamics monitoring of mitochondria in living cells. Their strategy is based on the use of upconversion nanoparticles (UCNPs), which they are nanophotonic particles that can absorb two or more incident photons of relatively low energy and convert them into one emitted photon with higher energy.

Because of lanthanide-doped UCNPs are characterized by their unique nanophotonic characteristics; long-term biosensing; biological compatibility; and low cytotoxicity, the researchers have synthesized a series of UCNPs@copolymer, UCNPs@PEG, and UCNPs@TPP nanosensors to realize their goal. The employed trivalent lanthanide ions were yttrium(III); ytterbium (III); and erbium (III), which they exhibit a temperature-dependent luminescence. These functionalized UCNPs are designed to be specific to the target organelle through modification of UCNPs surface with a cross-linked polymer network. A di-block copolymer ($PEGMEMA_{80}$-*b*-$EGMP_3$) **1** was applied to avoid aggregation of UCNPs in the cell culture medium, then further modified with 4Arm-PEG-NH_2 to allow the mitochondria-targeting moiety, and finally conjugated with (3-carboxypropyl)-triphenylphosphonium bromide (TPP) **2** to be covalently functionalized onto UCNPs (Figure 1). These hydrophilic cross-linked coating layers can firmly anchor onto the surface of positively

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charged UCNPs and keep UCNPs stable in the intracellular environment, as well as facilitate the nanoparticles to penetrate into cell cytoplasm and mitochondria.

The results revealed that the upconversion nanothermometers can efficiently target mitochondria, displaying their reaction-time and thermal dynamics profiles under different physiological and chemical stimuli. The UCNPs@TPP conjugate allowed to monitor the glucose-, lipid-, Ca^{2+}-, and FCCP-dependent thermodynamics in the mitochondria within living HeLa cells. In addition, UCNPs@TPP has proven to be a powerful tool for analyzing how the mitochondria metabolism activates and maintains cellular homeostasis in living cells.

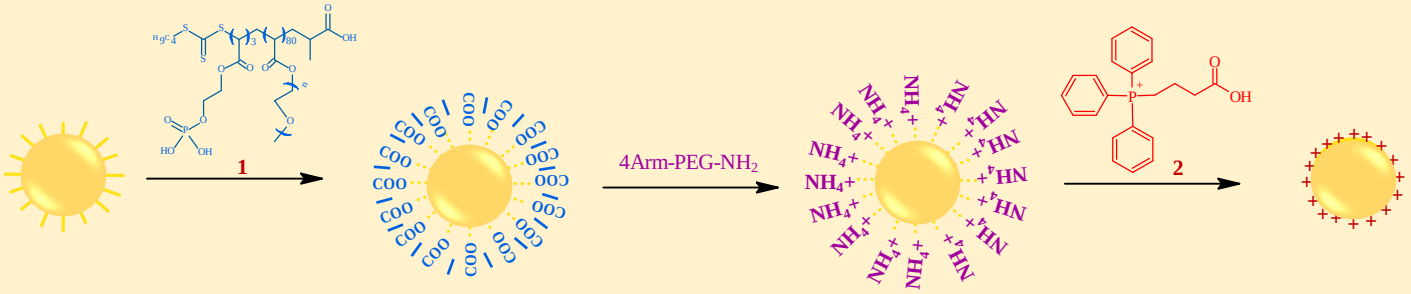

Figure 1. Schematic illustration of the mitochondria-targeted probes with cross-linked polymer layers and TPP.

This nanothermometers would pave the way for potential applications of studying in situ vital processes related to mitochondrial metabolism pathways and interactions between organelles.

2- Structurally redesigned bioorthogonal reagents for mitochondria-accumulation

Toward the delivery of therapeutics targeting mitochondria and their subsequent release, it is important to overcome the complexity of the cellular environment (a large negative membrane potential with $\Delta\Psi$ approximately −180 mV). Vrabel and co-workers[2] have developed structural fine-tuning of 1,2,4,5-tetrazines, enabling their redesign into mitochondriotropic reagents (Figure 1). The structural features of these bioorthogonal tetrazine reagents constitute the combination of a positive, delocalized charge and sufficient lipophilicity, leading to their spontaneous accumulation in the mitochondria. the authors reported that the optimized mitochondriotropic tetrazines are not toxic at working concentrations as determined on different cell lines and one-cell mouse embryos.

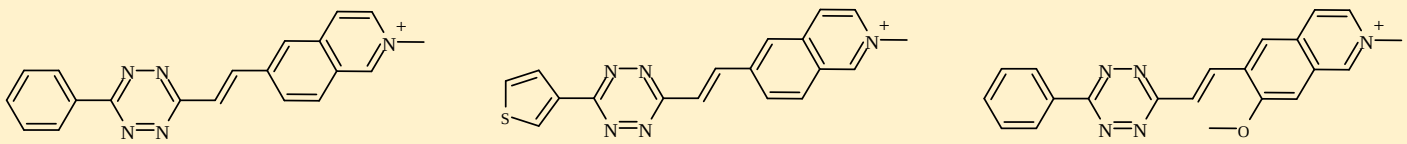

Figure 1. Chemical structures of 1,2,4,5-tetrazines, that showed optimal accumulation in mitochondria.

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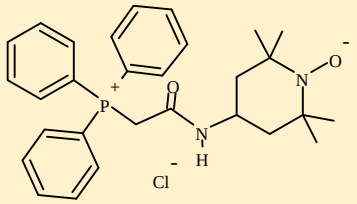
3- Mito-TEMPO modulated initiation phase of hepatocarcinogensis

Mito-TEMPO is a mitochondria-targeted superoxide dismutase mimetic with superoxide and alkyl radical scavenging properties. Shetty *et al.*[3] investigated targeting mitochondrial oxidative stress during initial stages of haptocarcinogenesis as an effective strategy to prevent hepatocellular carcinoma. Mito-TEMPO pre-treatment animals injected by *N*-nitrosodiethylamine (NDEA) revealed that Mito-TEMPO protected them from the damaging effects of NDEA. NDEA metabolism resulted in a significant increased intracellular and mitochondrial ROS generation with concomitant increase in lipid peroxidation (LPO) formation.



Mito-TEMPO

Mito-TEMPO effectively scavenged NDEA-induced ROS generation and reduced lipid peroxidation formation. A remarkable improvement was also observed in the activity of mitochondrial complex I, complex II, malate dehydrogenase and normalization of mitochondrial membrane potential.
These results suggested that mito-TEMPO had significant impact on the initiation phase of hepatocarcinogensis.

Conclusion

With the increasing growth in the diagnosis and treatment paradigm targeting mitochondria, rapid access could be possible to a wide variety of new therapies with promising potential, and novel approaches to prevent the progression of a variety of diseases associated with this organelle.

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Samples of Research Progress on Photocatalysis & Light-promoted Reactions

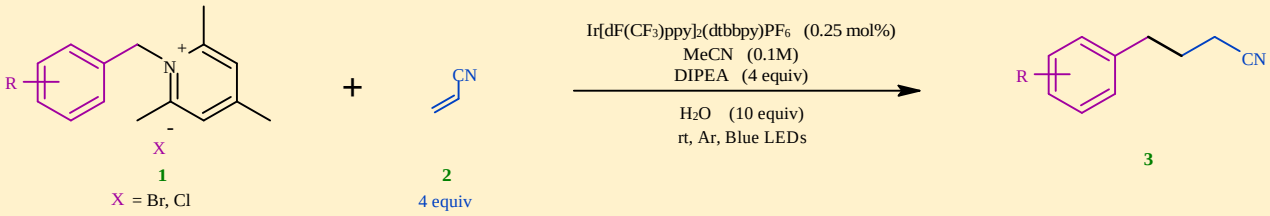
Photocatalysis constitutes a key role in both energy generation and environmental remediation applications. To design visible light-active photocatalysts with low charge carriers' recombinatiom rate; inexpensive cost and reusability, organic compounds are considered versatile materials to achieve such a goal. This snapshot highlights some recent advances in this field.

KEYWORDS: photocatalysis, photsystems, azoalkanes, hydroquinone.

Photocatalysis is a process for converting photonic energy derived from solar irradiation to chemical energy by using a photocatalyst. Through the absorption of light, catalysts or substrates are activated by photons or light radiation followed by electron-transfer processes to or from reactants performing the oxidation and reduction reactions. Semiconductor nanoparticles-based heterogeneous photocatalysis is an effective technology and demonstrated its potential applications for solving environmental contamination. This snapshot highlights some of recent advanced publications addressing interesting issues including how to control the variation in reduction potential of molecules with greater structural sensitivity; generating hydrogen evolution from hydroquinone derivatives; and an analysis of the photophysics reactivities and streoselectivity of denitrogenation of bicyclic azoalkanes.

1- Collidinium salts serving as efficient photoredox catalysis

Photocatalysis has the potential to generate radicals in a controlled fashion *via* absorption of a photon. Some organic substrates (such as aryl halides and pseudohalides) can be reductively activated through single electron transfer (SET). This is related to the relatively low-lying unoccupied π^* orbitals, which facilitate intramolecular electron transfer to the C-X σ^* orbitals resulting in mesolytic fragmentation to form halide ion and carbon-centered radical. However, the rates of radical anion fragmentation of some substrates with greater structural sensitivity (such as benzylic halides) suffer from considerable variation in reduction potential, and hence, limiting their wide application. Rathnayake and Weaver[1] have demonstrated that the use of commercially available collidinium salts **1** to replace the halides can serve as an electron capture motif that normalize the variable redox potentials across substrates (Scheme 1). These radical precursors have proven to be effective with a broad scope.



Scheme 1. Electron capture by collidinium salts as nucleophilic displacement of halides.

2- Photocatalytic Hydrogen evolution from hydroquinone derivatives

Photosystems are functional and structural units of protein complexes involved in photosynthesis, and are found in the thylakoid membranes of plants, algae and cyanobacteria. There are two photosystems, photosystem I (PSI) and photosystem II (PSII) and both contain photosynthetic reaction centers, which they are enzymes that use light to proceed multistep charge-separation reactions. PSI use ferredoxin-like iron-sulfer cluster proteins as terminal electron acceptors. Whereas PSII are used to oxidize H_2O through the oxidizing equivalents generated at their donor side, while the reducing equivalents accumulated at their acceptor side are used to reduce plastoquinone (PQ) in a quinone pool to form plastoquinol (PQH_2) as shown in the overall solar-driven reaction by eq. 1.

$$2H_2O + 2PQ \xrightarrow{h\nu} O_2 + 2PQH_2 \quad (1)$$

Hong *et al.*[2] reported a new functional model of PSI, in which PQH_2 analogues were oxidized to PQ analogues, accompanied by H_2 evolution (eq.2).

$$PQH_2 \xrightarrow{h\nu} PQ + H_2 \quad (2)$$

Photo-irradiation of a deaerated acetonitrile (MeCN) solution containing hydroquinone derivatives (X-QH_2) as a hydrogen source, 9- mesityl-10-methylacridinium ion (Acr^+ -Mes) as a photoredox catalyst, and a cobalt(III) complex, $Co^{III}(dmgH)_2pyCl$ (dmgH = dimethylglyoximate monoanion; py = pyridine) as an efficient redox catalyst resulted in the evolution of H_2 and formation of the corresponding *p*-benzoquinone derivatives (X-Q) quantitatively (Scheme 2).

Acr^+ -Mes serves as a photosynthetic reaction center model, undergoing photoinduced electron transfer (ET) to produce charge-separated (ET) state, which shuttles an electron to oxidize hydroquinone derivatives and to reduce $Co^{III}(dmgH)_2pyCl$ at the same time to form hydroquinone radical cation derivatives and $[Co^{II}(dmgH)_2pyCl]^-$, respectively. These radical cation derivatives are deprotonated to form semiquinone radical derivatives, which undergo either hydrogen-atom transfer or a proton-coupled electron transfer to $[Co^{II}(dmgH)_2pyCl]^-$ to produce a cobalt(III) hydride complex, $[Co^{III}(H)(dmgH)_2pyCl]^-$, which react with a proton to evolve H_2.

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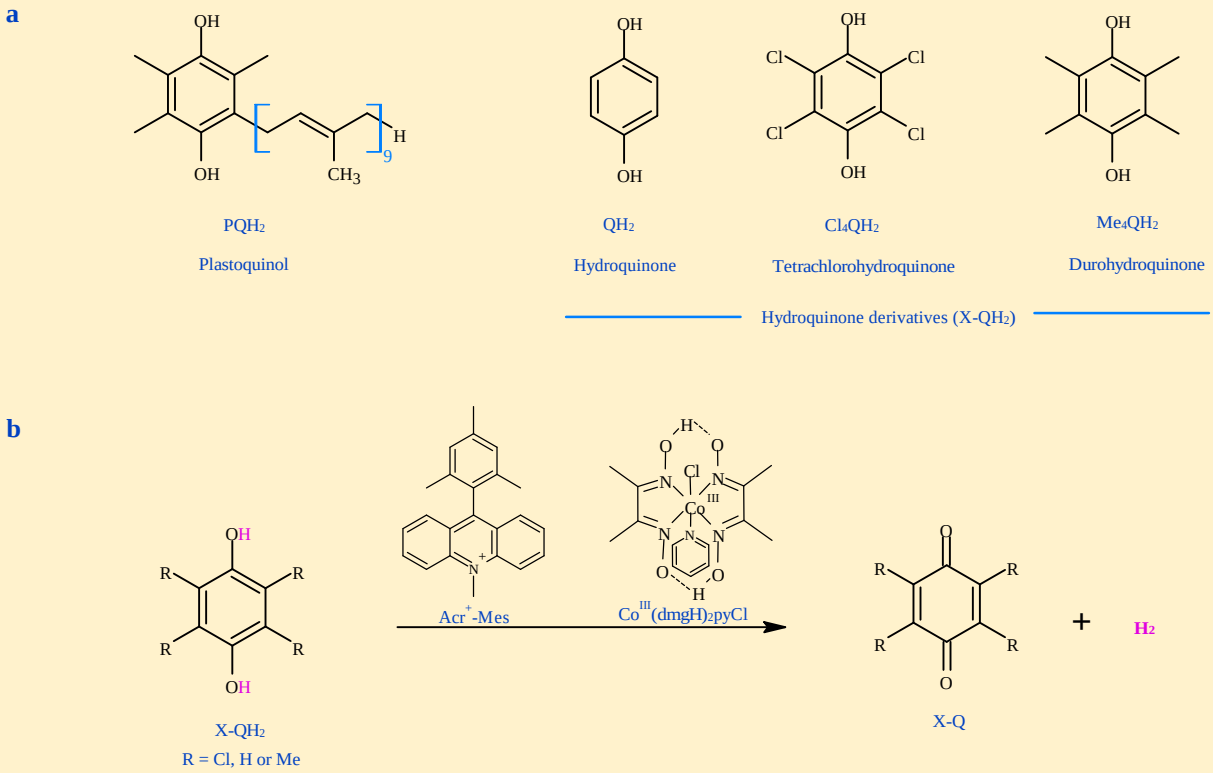
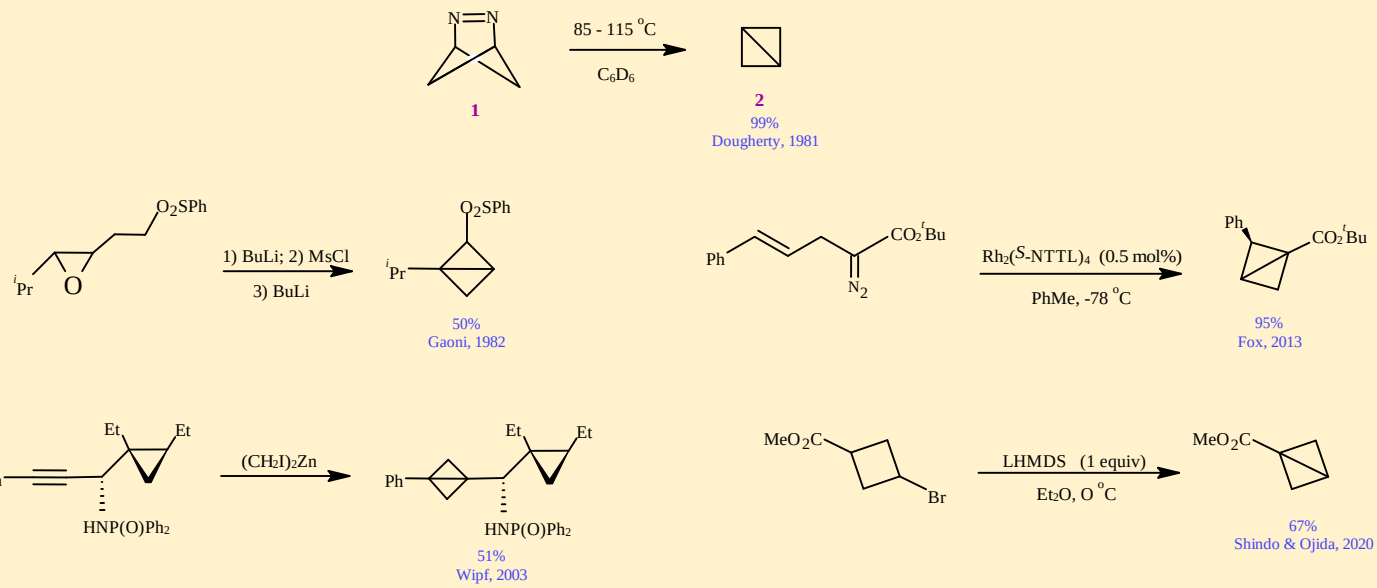


Scheme 2. Chemical structures of plastoquinol (PQH_2) and hydroquinone derivatives ($X\text{-}QH_2$).

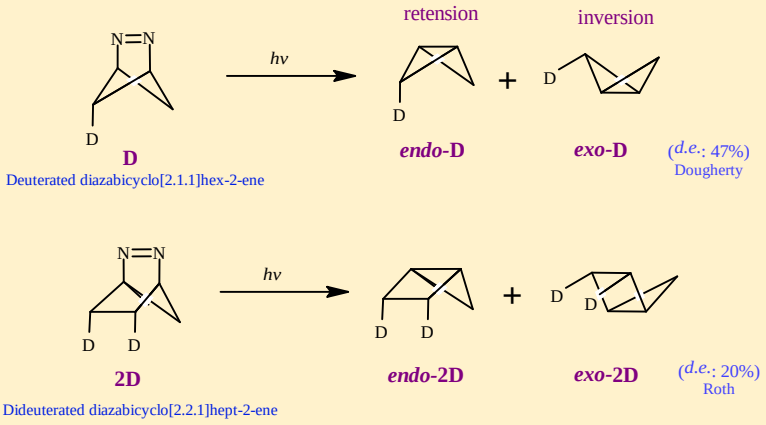
3- Light-promoted synthesis of stereoenriched bicyclo[1.1.0]butanes

The light-promoted denitrogenation of bicyclic azoalkanes affords functionalized, stereoenriched bicyclo[1.1.0]butanes. For example, diazabicyclo[2.1.1]hex-2-ene **1** yields bicycle[1.1.0]butane **2** under thermal condtions (Scheme 1). The privileged bicyclo[1.1.0]butane is the most strained carbon-based bicycle with the strain energy ~ 66 kcal/mol. It possesses a central $\sigma_{C\text{-}C}$ bond, that bends the plane of two cyclopropanes, exposing the *p*-orbitals which can function as nucleophiles or electrophiles. Scheme 1 depicts the synthetic pathways of bicyclo[1.1.0]butane and the derivatives.



Scheme 1. Preparation of bicyclo[1.1.0] butane.

Several diverse studies have been explored to investigate the diastereoselective denitrogenation of cyclic azoalkanes toward carbon-based bicycles, which offered qualitative rationale for the stereoselectivity (Scheme 2). Lopez and co-workers[3] revisited these reactions with multireference calculations and non-adiabatic molecular dynamics (NAMD) simulations to provide a detailed analysis of the photophysics, reactivities, and unexplained stereoselectivity of a series of diazabicyclo[2.1.1]hexenes.



Scheme 2. Diastereoselectivity in the direct photolysis of cyclic azoalkanes.

They employed complete active space self-consistent field (CASSCF) calculations with an (8,8) active space and ANO-S-VDZP basis set; the CASSCF energies were corrected with CASPT2 (8,8)/ANO-S-VDZP. They

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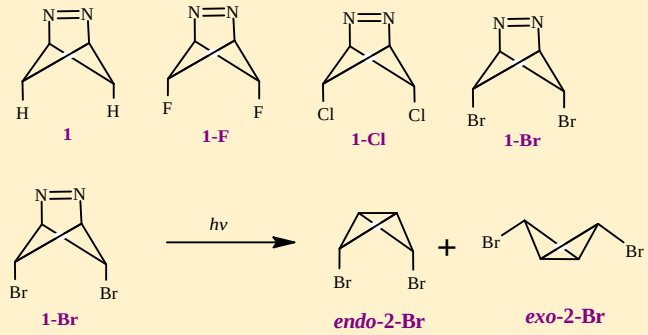
demonstrated that the nature of the electronic excitation is n → π* and ranges from 3.77 to 3.91 eV for the diazabicyclo[2.1.1]hexenes of **1**, **1-F**, **1-Cl**, and **1-Br** (Scheme 3). The minimum energy path calculation of **1-Br** showed stepwise C−N bond breaking and characterized a minimum energy crossing point that favors "double inversion".



Scheme 3. Proposed denitrogenation of 1,3-dihalogenated diazabicyclo[2.1.1]hexa-2-ene.

They identified competing complete stereoselective and stereochemical scrambling pathways. The stereoselective pathways feature concerted bicyclobutane inversion and N_2 extrusion. The stereochemical scrambling pathways involve N_2 extrusion followed by bicyclobutane planarization, leading to stereochemical scrambling. The predicted diastereomeric excess (*d.e.*) almost exactly matches the experiment (calc. *d.e.* = 46% vs exp. *d.e.* = 47%). Their NAMD simulations for **1-F**, **1-Cl**, and **1- Br** predicted a *d.e.* of 94−97% for the double inversion products. They concluded that halogenation significantly perturbs the potential energy surface (PES) toward the retention products due to hyperconjugative interactions. The $n_C \rightarrow \sigma^*_{C-X}$, $_{X = F, Cl, Br}$ hyperconjugative effect leads to a broader shoulder region on the PES for double inversion demonstrating its crucial role on the increased stereoselectivity for halogenated diazabicyclo[2.1.1]hexenes.

Conclusion

These snapshots reflect new approaches to solve a number of challenges, which have facilitated a variety of characteristic reactions and expanded the range of utility for photocatalysis. Such fruitful achievements in this ever-widening field would allow rapid access to a wide variety of many other reactions with promising sustainable applications in the environment.

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