CHEMISTRY

Getting excited about cycloadditions

Photoactivation to long-lived triplet excited states enables cycloadditions with heteroarenes

By **Valerie A. Schmidt**

Synthetic chemists use photochemistry to achieve challenging or unusual chemical transformations, but not all compounds are photoactive. Photosensitization is a process by which a molecule that is incapable of efficiently absorbing a particular wavelength of light directly is promoted to its triplet excited state (T_1) by an intermolecular triplet energy transfer from a photosensitizer, which is a compound that ideally has a large extinction coefficient, rapid rate of intersystem crossing, and a long-lived T_1. A particular advantage of photosensitization is that distinctive reactivity profiles not accessible through ground states become facile from corresponding excited states (*1*). The use of photosensitizers in chemical synthesis has paralleled the rise in popularity and use of various photoredox catalysts (*2*). On page 1338 of this issue, Ma *et al.* (*3*) report a photosensitized dearomative [4 + 2] cycloaddition that converts simple, unsaturated building blocks into products of increased molecular complexity using visible light.

Cycloaddition reactions are one of a limited number of fundamental reaction types that exemplify several ideals of chemical synthesis and that have divergent reactivity when carried out under thermal versus photochemical conditions. These reactions have the ability to bring together multiple molecular fragments in a convergent manner and can create several new covalent bonds with well-established predictability and often with control over the chemo-, regio-, and diastereoselectivity of the addition products. As a result of their utility in the synthesis of complex molecules and their well-studied mechanistic pathways, cycloadditions have been a cornerstone for demonstrating key principles in organic chemistry classes for many years. Notably, [4 + 2] cycloadditions require two unsaturated reaction components that trade two double (π) bonds for two single (σ) bonds to form a six-membered ring structure. The first unsaturated component, known as the "diene," contains two π bonds connected by a single σ bond.

Arenes similarly contain alternating double bonds (as a result of conventions of chemical structure drawing), but their use in cycloaddition reactions presents additional challenges as a result of their increased stabilization conferred by aromaticity. Although aromatic compounds are a diverse, abundant set of chemical building blocks, these flat molecules are limited in their three-dimensional structural complexity and, for applications as pharmaceutical agents, possible interactions with biological receptors (*4*). Thus, the development of new synthetic methods that may simultaneously take advantage of abundant arene starting materials while increasing stereochemical and functional group density is highly attractive.

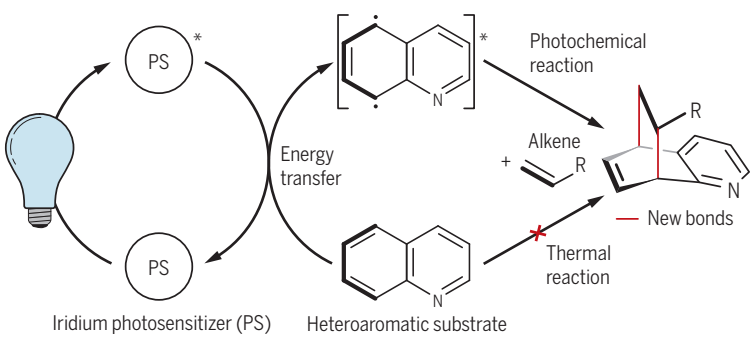
Several heteroarenes, such as furans and pyrroles, have long been used as "dienes" in [4 + 2] cycloadditions to produce multicyclic, bridged compounds, enabled largely by their lower degree of aromaticity created by electronegative oxygen and nitrogen atoms in their rings, compared with more stabilized all-carbon arenes such as benzene. Whereas thermally promoted dearomative cycloadditions of benzene, pyridine, or quinoline are plagued with challenges caused by high kinetic barriers and unfavorable thermodynamic profiles, photochemical activation has been successfully used (*5*).

Given that pyridine is one of the most commonly found nitrogen heterocycles in drugs approved by the U.S. Food and Drug Administration (*6*), synthetic strategies to access them from readily available starting materials is an attractive conceptual approach. Ma *et al.* chose to combine established photosensitizing reactivity of octahedral iridium photocatalysts with Lewis and Brønsted acid T_1 energy-lowering coordination (*7*) to activate azaarenes and direct excellent chemo-, regio-, and stereoselective dearomative [4 + 2] cycloadditions with a range of functionalized terminal olefins (see the figure). In this process, the valuable heteroarene is retained in the product, and molecular complexity is increased with full atom economy.

Given nature's ability to perform highly complex and energetically demanding photochemical processes, there are likely few limits to chemical transformations that can be enabled by photochemistry. With increased interest in rational design and application of triplet energy transfer catalysts that has been facilitated by continued advances in computational chemistry (*8*, *9*), it is likely that we are at the earliest stages of seeing the bright future photosensitization has in store for chemical synthesis. ■

Acting like a diene

Aromatic molecules are usually too stable to serve as conjugated diene substrates (which contain two double bonds separated by one single bond) in cycloadditions through thermal routes. Ma *et al.* show that energy transfer from an iridium photosensitizer allows heteroaromatics (azaarenes) to react with alkenes bearing a functional group R.



GRAPHIC: JOSHUA BIRD/*SCIENCE*

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