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Enantioselective counter-anions in photoredox catalysis: The asymmetric cation radical Diels-Alder reaction

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ABSTRACT

Control of absolute stereochemistry in radical and ion radical transformations is a major challenge in synthetic chemistry. Herein, we report the design of a photoredox catalyst system comprised of an oxidizing pyrilium salt bearing a chiral *N*-triflyl phosphoramide anion. This class of chiral organic photoredox catalysts is able to catalyze the formation of cation radical-mediated Diels-Alder transformations in up to 75:25 e.r. in both intramolecular and intermolecular examples.

1. Introduction

In recent years, research in the field of photoredox catalysis has resulted in the development of numerous, powerful new transformations for organic synthesis that are complementary to reactions proceeding by two electron processes.[1] A central challenge in the field is the development of methods to conduct these reactions in an asymmetric manner, as access to enantiopure products is critical for the development of new bioactive compounds. However, photoredox catalysis is distinct from other common modes of catalysis in a way which makes developing enantioselective reactions especially challenging. Namely, after the key electron (or energy) transfer event occurs between substrate and catalyst, the two are no longer necessarily associated in solution. Subsequent bond-forming steps can therefore take place off-catalyst, which poses a challenge to traditional methods for asymmetric induction, such as introducing chiral ligands to the catalyst. Success in this field therefore requires engineering systems in which the activated substrate is necessarily associated with an element of chirality during the enantiodetermining step of the reaction. Several key advances have recently been made in this area, though reports remain sparse (Scheme 1).

The state of the art in this field includes MacMillan's use of chiral enamine catalysis, which affords excellent stereocontrol in reactions with electron-deficient radical partners.[2] The Yoon group has developed a dual photoredox/Lewis acid catalyst system that enables enantioselective [2 + 2] cycloaddition reactions, as well as radical conjugate addition reactions.[3] The Meggers group has developed a chiral-at-Iridium complex capable of acting both as a Lewis acid and photoredox catalyst for similar conjugate addition reactions.[4] The Knowles group has demonstrated absolute stereocontrol in ketyl radical chemistry, enabled by a key proton-coupled electron transfer event to generate the reactive species that is coordinated to a chiral Brønsted acid catalyst.[5] Additionally, enzymatic processes have recently been shown to be compatible with photoredox catalysis and allow for enantioinduction.[6] These methods have proven to be very powerful, and share many common features. In each case, the reactions proceed by a mechanism in which the starting material is reduced by the photoredox catalyst in order to arrive at the desired reactive intermediate. The substrates for these reactions also all contain functional groups, specifically carbonyls, which serve as sites for association with the chiral co-catalyst, via either covalent or non-covalent interactions.

An archetypal example of a reaction that operates via this manifold is the cation-radical Diels-Alder reaction (Scheme 2). This transformation was initially reported by Bauld[7] using ground-state one-electron oxidants, and has been greatly expanded upon through photoredox manifolds in recent years by the Yoon group

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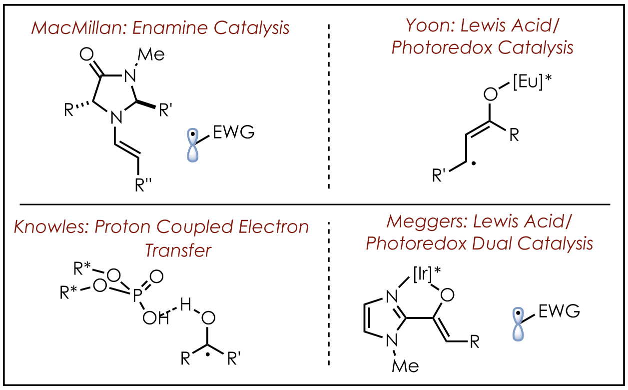
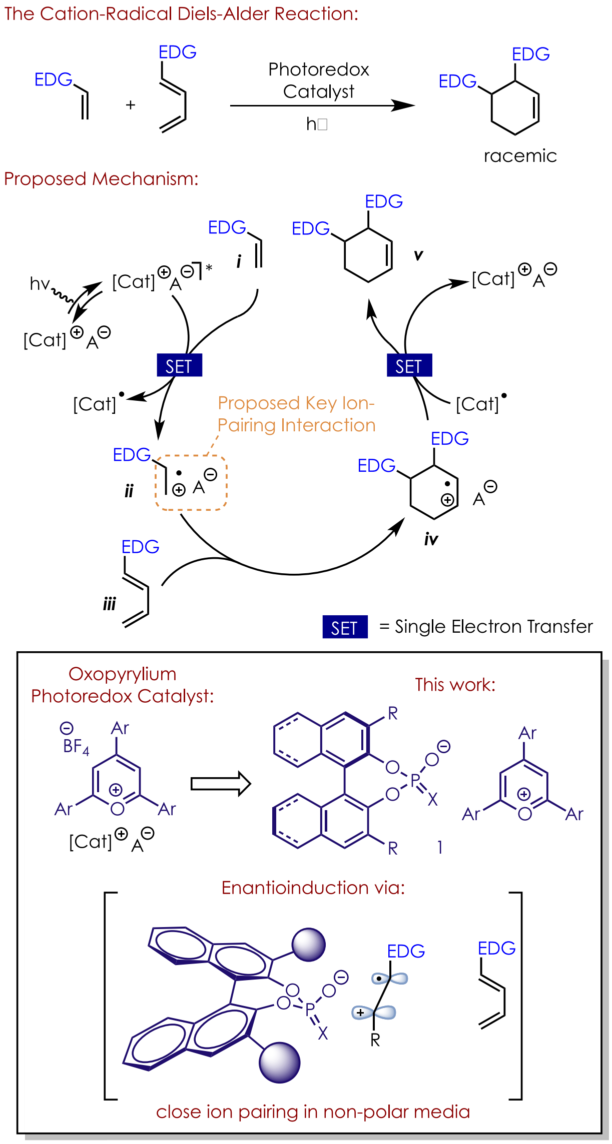


Scheme 1. Asymmetric photoredox catalysis – prior art.



Scheme 2. The cation radical Diels-Alder reaction and current work.

and others.[8] The reaction is powerful due to its ability to enable Diels-Alder reactions between pairs of electron-rich dienes and dienophiles. The transformation begins with the one-electron oxidation of the electron-rich dienophile **i** (Scheme 2). The dienophile is now rendered electrophilic (**ii**), and readily undergoes cyclization with diene **iii**, giving intermediate **iv**. One-electron reduction of this intermediate furnishes the final product **v**, and also serves to either turn over the catalyst, or propagate the reaction via a chain mechanism.[9]

Pyrylium salts are a class of organic photoredox catalysts that are strong one-electron photooxidants and are known catalysts for this transformation.[10] Being cationic in nature, they also bear a non-coordinating anion, such as a tetrafluoroborate (BF_4) anion. Based on the proposed mechanism for the reaction, if it were to be run in a relatively non-polar solvent, then presumably the BF_4 anion would become paired with the cation radical intermediates of the reaction (**ii** and **iv**) after electron transfer occurs. This led us to consider whether an ion pairing interaction between a radical cation intermediate and chiral counterion could be used to control the absolute stereochemistry of these types of reactions (Scheme 2). In a single example reported by Schuster, low levels of enantioinduction (15% ee, yield not given) were observed in a cation-radical Diels-Alder reaction promoted by a neutral, axially-chiral cyanoarene photosensitizer, lending support to this hypothesis.[11] Moreover, a recent report utilizing an acridinium photooxidant showed enantioinduction in a hydrofunctionalization reaction using a chiral anion.[12]

We therefore set out to develop a new class of organic photoredox catalysts, in which a pyrylium-based photooxidant is paired with a chiral anion, and ascertain whether these compounds could be used to control the absolute stereochemistry of the cation radical Diels-Alder reaction. The design of this catalyst system is especially appealing, as the goal of ion pairing directly with the radical-cation intermediates circumvents the need for chelating functional groups, such as carbonyls, to be present in the substrates.

2. Results and discussion

At the outset of the project, we hypothesized that the chiral anion would need to be sufficiently non-nucleophilic in nature in order to avoid directly reacting with either the photo-oxidant or charged intermediates. We focused our attention on anions derived from chiral Bronsted acids, due to their tunable steric and electronic properties.[13] They have also been successfully employed as chiral anions in a number of previously reported transformations.[14] Triaryl pyryliums were chosen as the photooxidant due to their easily tunable high excited state reduction potentials, mono-cationic nature, and prior use as catalysts in Diels-Alder reactions.[10]

We found that the preparation of the desired oxopyrylium salts could be accomplished in a very straightforward manner. A precursor ene-dione molecule was found to undergo an acid promoted cyclization to the oxopyrylium when heated in the presence of an appropriate chiral Bronsted acid. This strategy proved general and allowed us to construct our library of chiral catalysts. Furthermore, the salts have proven to be highly stable and can be stored on the bench top for extended periods of time.

A series of catalysts were evaluated bearing different counteranion structures with triene **2a** as the substrate (Table 1). In general, anions derived from *N*-trifylphosphoramides afforded the desired Diels-Alder adduct whereas chiral phosphate anions did not, possibly due to the higher nucleophilicity of the latter species. We also found that sterically demanding groups were necessary at the 3,3′-positions of the BINOL-derived anions, with triphenylsilyl groups ultimately proving most effective. We attribute this success to two factors: in addition to creating a highly demanding chiral environment, the bulky nature of the triphenylsilyl groups may also further decrease the effective nucleophilicity of the anion, thereby enhancing reactivity. Toluene proved uniquely effective as a solvent during an initial screen. Conversion was observed in