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Chiral Bifunctional Photocatalysts with Aromatic Ketones as Photosensitizers

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Abstract: Because the biological activity of a molecule is directly linked to its three-dimensional configuration, the preparation of chiral compounds is a central discipline in synthetic organic chemistry. With the exploitation of photoredox catalysis that gives access to open-shell (radical) intermediates under mild and sustainable conditions, unprecedented molecular architectures can now be synthesized. However, the parent enantioselective transformations have been developed at a slower pace because suppressing non-catalyzed background reactivities has presented a major hurdle. Designer bifunctional photocatalysts containing a H-bonding motif for substrate recognition and a diaryl ketone as the photosensitizer embedded in a chiral scaffold are useful catalysts in asymmetric radical transformations. Herein, an overview of enantioselective transformations in which this class of catalysts has been successful and future directions are discussed.

Keywords: Asymmetric catalysis · Catalyst design · Photocatalysis

Giuseppe Zuccarello studied chemistry at the University of Basel and at the Swiss Federal Institute of Technology in Zürich (ETH) where he worked on total synthesis of natural products in the group of Prof. E. M. Carreira. He completed his PhD studies in 2020 under the direction of Prof. A. M. Echavarren at the Institute of Chemical Research of Catalonia (ICIQ) working on enantioselective gold(I) catalysis. In the same year he joined the group of Prof. G. C. Fu at the California Institute of Technology as an SNSF Postdoc Mobility fellow focusing on metal-catalyzed cross-couplings. He then returned to his *alma mater* for a postdoctoral stay in the group of Prof. K. Tiefenbacher exploring catalysis in molecular containers before starting his independent career as an SNSF Ambizione fellow at the Swiss Federal Institute of Technology in Lausanne (EPFL) in 2024. His group focuses on enantioselective photochemical transformations and the design of new chiral catalysts.

1. Introduction

We live in a chiral world. By definition, a chiral object is not superimposable on its mirror image. The easiest and closest example are our hands. Our left hand can be regarded as the mirror image of our right hand and at first glance they may seem identical but if we try to superimpose them, we will not be able to do so. This phenomenon is termed chirality or handedness.

Chirality is also found at the molecular level. A chiral organic compound contains a chiral element that can be either planar, axial, helical, or point chiral. Point chirality is often reflected in molecules containing at least one stereogenic carbon center (that is a carbon atom with four different substituents) and the resulting mirror images are termed enantiomers (Fig. 1).

While the atom connectivity of both enantiomers is identical, the different three-dimensional (spatial) arrangement of the molecule can give rise to distinct physical and chemical properties. This is a crucial factor that needs to be considered in drug discovery. The

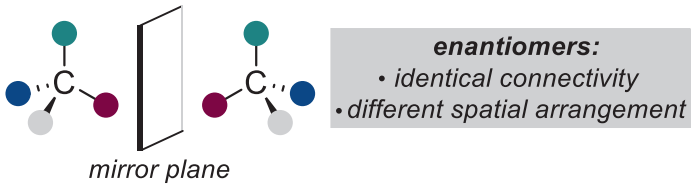

Fig. 1. Two enantiomers are mirror images.

biological properties of a molecule are directly linked to its three-dimensional configuration. A study[1] shows that a high degree of saturation in organic molecules – implying a high number of sp^3-hybridized carbon atoms – imparts molecular and stereochemical complexity that correlate with biological activity[2] in potential leads for drug discovery. Thus, complex chiral molecules provide a higher binding selectivity to the target receptor, ultimately minimizing unwanted side effects. The preparation of such complex molecules requires efficient synthetic methods that allow for high regio- and stereocontrol as even traces of the opposite enantiomer drug can be potentially harmful.

Although nature has provided us with a selection of chiral molecules (chiral pool),[3,4] organic chemists have pursued the synthesis of unnatural chiral scaffolds by selectively accessing one enantiomer of a target product by means of asymmetric catalysis. Despite important progress in the field, outstanding unmet challenges persist. This is also due to the major accomplishments being achieved in ground state (two-electron) transformations whereas controlling enantioselectivity in open-shell transformations (one-electron, radical processes) has proven significantly more difficult. Exploiting the radical domain, however, gives access to unconventional molecular architectures that are otherwise difficult to synthesize and controlling enantioselectivity over those transformations further increases their synthetic value. With the recent advances in photoredox catalysis[5,6] that allows for the mild formation of organic open-shell intermediates, developing enantioselective radical transformations has become

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a central task in synthetic organic chemistry. To achieve this goal novel chiral photocatalysts with unique structural features have recently emerged.[7]

Herein we discuss how chiral bifunctional photocatalysts containing an aromatic ketone as the light-harvesting entity have enabled novel excited state enantioselective transformations and how my group plans to uncover unexplored territory and opportunities in the field of asymmetric photocatalysis capitalizing on similar catalyst designs.

1.1 Photoredox Catalysis as a Tool for Asymmetric Transformations

Although photoredox catalysis is a young branch of organic chemistry, it has found important applications in the synthesis of natural products and pharmaceuticals[8–10] by providing straightforward access to radical reaction pathways that remain otherwise elusive. Upon light irradiation, photocatalysts reach an electronically excited state that can activate ground state organic molecules either *via* energy or single electron transfer.[11,12] Thereby, open-shell intermediates can be accessed under mild conditions. Photoredox catalysis is an attractive technology to implement future green and sustainable processes[13] as the only required energy source are photons and the light absorbing species (photocatalyst) can be employed in substoichiometric amounts.[14,15] Thus, harsh thermal activation can be avoided.

Controlling enantioselectivity in reactions proceeding through open-shell intermediates is a rather recent and difficult goal in synthetic organic chemistry. While numerous racemic radical transformations have been developed, the development of asymmetric versions has been less rapid. Achieving high enantioselectivities in radical transformations is an outstanding challenge due to the short lifetime and high reactivity of the putative intermediates. Successful strategies have relied on pairing photoredox catalysis with established activation modes for ground state asymmetric transformations[16,17] such as organocatalysis,[18] transition metal catalysis,[19] and enzyme catalysis to forge C–C and C–X (X = N, O) bonds. Alternatively, specialized (almost unique) chiral-at-metal[20] or chiral bifunctional[21] photocatalysts are required to suppress competing background reactivity in enantioselective radical processes.[22]

2. Chiral Bifunctional Photosensitizers

Early examples of enantioselective light-mediated reactions relied on the use of chiral sensitizers where chirality was expected to be transferred within transient excited-state interactions. However, the observed enantioselectivities were usually low due to the lack of interaction between the chiral photocatalyst and the substrate during the stereochemistry determining step. In view of this limitation, bifunctional catalyst designs have emerged in which a photosensitizer is embedded in a chiral scaffold bearing hydrogen bond donors for substrate fixation (Fig. 2).

This general catalyst design can achieve high enantioselectivities provided that the substrate is organized in a chiral microenvironment forming a tight catalyst-substrate complex and the photochemical activation of the bound substrate is faster (because it is closer) than the activation of the unbound one.

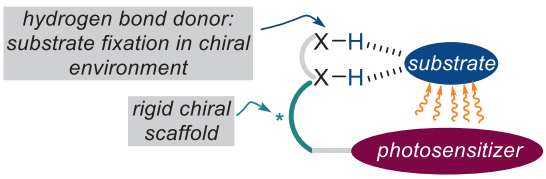
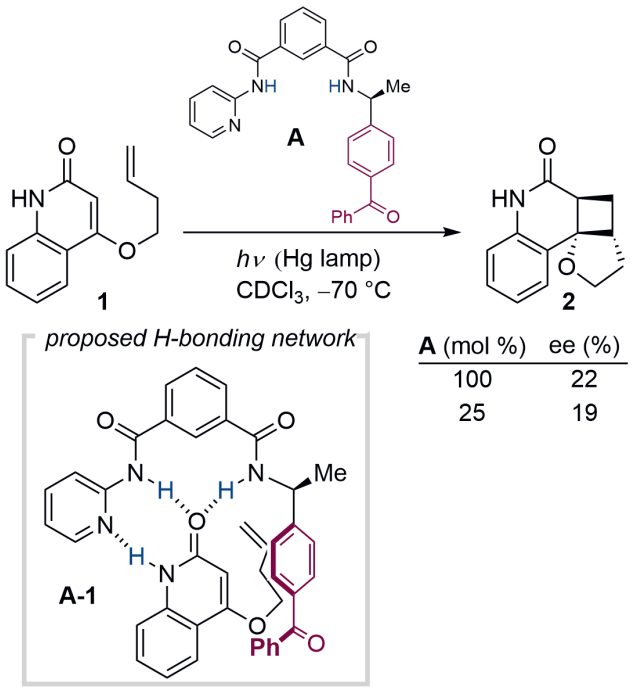


Fig. 2. General bifunctional photocatalyst design. Formation of catalyst-substrate complex.

Finally, the desired enantioselective transformation should occur faster than substrate dissociation.

In 2003, Krische[23] introduced this conceptual catalyst design with **A** containing H-bond donors/acceptors and benzophenone as the photosensitizer (Scheme 1). The catalyst performance was studied in the photochemical [2+2] photocycloaddition of quinolone **1** to obtain cycloadduct **2**. The catalyst loading could be lowered to 25 mol% and only a marginal drop in enantiomeric excess is observed showing that the photocycloaddition of the bound substrate takes place faster than the unbound one due to binding-induced accelerated energy transfer. Because a Job plot showed quantitative formation of the **A-1** complex through H-bonding interactions with association constant K_a = 2.5 ± 0.2, the observed low enantioselectivities are attributed to the poor enantiodifferentiation provided by the chiral scaffold of **A**.

Following the same conceptual catalyst design, Bach introduced chiral bifunctional photosensitizers **B-D** (generally diaryl ketones) derived from Kemp's triacid. This class of catalysts



Scheme 1. [2+2] Photocycloaddition catalyzed by Krische's chiral bifunctional sensitizer **A**.

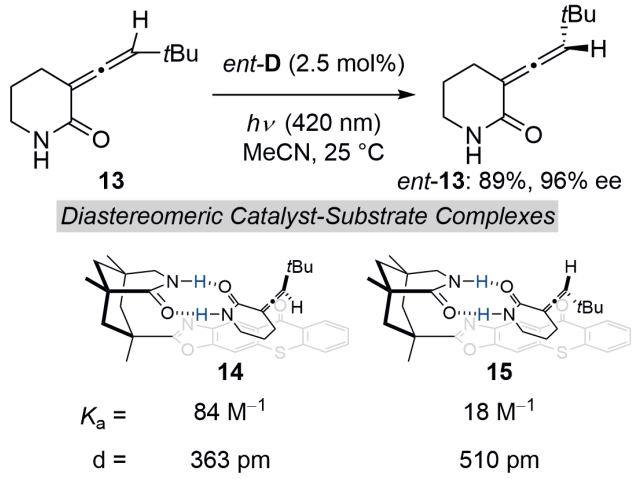
can fix amide substrates in a chiral environment *via* H-bonding (Scheme 2).[24] To date this class of catalysts has proven efficient in numerous enantioselective photochemical reactions.[25] The rigid cyclohexane backbone limits the degree of rotation and the photosensitizer provides additional steric congestion, eventually leading to high facial differentiation.

Catalyst **B**, the first of this kind, promotes the formation of **4** through an enantioselective spirocyclization of an α-amino radical, which is generated by light-mediated hydrogen atom abstraction from **3** (Scheme 2A).[26] Recently, catalysts of this type containing a benzophenone photosensitizer have been employed in photochemical deracemization reactions *via* hydrogen atom transfer (HAT).[27] For reactions proceeding *via* energy transfer such as photochemical intra-[28,29] and intermolecular[30] [2+2] cycloadditions, the benzophenone sensitizer in **B** was replaced with the xanthone sensitizer in catalyst **C** (Scheme 2B). With catalyst **C**, the intramolecular cycloaddition of quinolone **1** previously studied by Krische[22] gave the desired product in good yields and excellent enantioselectivities. For the intermolecular cycloaddition of 2-pyridone **5** a large excess of acetylenedicarboxylate **6** (50

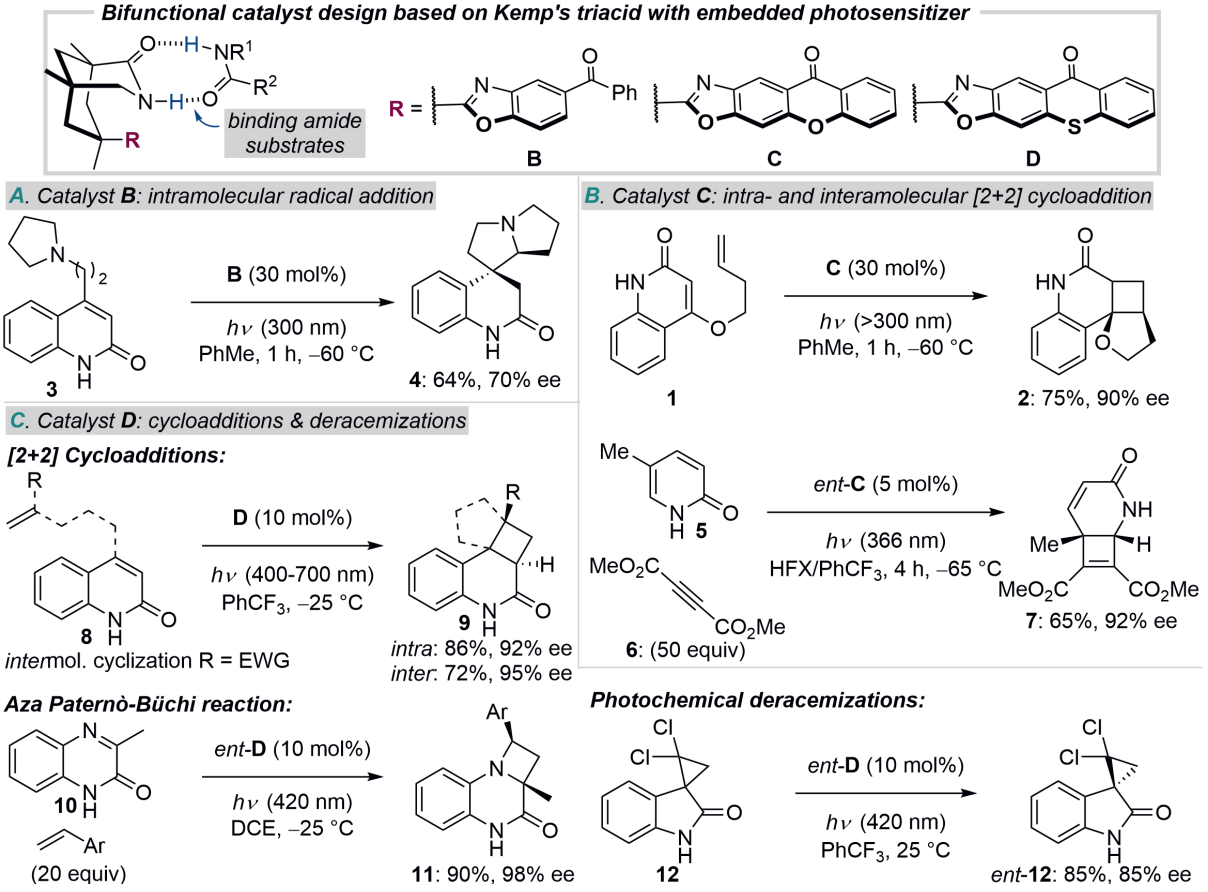
equiv.) is necessary to ensure that cycloadduct **7** forms before substrate dissociation.[30] Although xanthone photocatalyst **C** and quinolone **1** absorb at the same wavelength, the xanthone moiety has a bigger extinction coefficient and thus absorbs nearly all the photons, suppressing major background reactivity of any unbound substrate. Nonetheless, catalyst **C** absorbs high energy UV light, and the absorption overlap with the substrate still limits its general use in catalysis with a broad collection of substrates. Moreover, xanthone catalyst **C** is affected by decomposition *via* HAT (*e.g.* with the solvent). In contrast, the thioxanthone photosensitizer in catalyst **D** absorbs light in the visible range and is less prone to undergo HAT (Scheme 2C). Bach has demonstrated that catalyst **D** is highly versatile in different enantioselective transformations. The intra-[31,32] and intermolecular[33] [2+2] cycloadditions of quinolones **8** with alkenes occur efficiently and give the corresponding cycloadducts **9** under visible light irradiation. Similarly, quinoxalinones like **10** engage in intermolecular aza Paternò-Büchi reactions to access fused ring systems such as **11**.[34] Once again, in intermolecular reactions, the alkene is required to be present in excess to prevent background reactivity taking place if the substrate dissociates from the catalyst before the desired enantioselective cyclization. Catalyst **D** also promotes photochemical deracemizations.[35–37] This class of transformations is emerging as a promising strategy to obtain enantioenriched products from racemic mixtures, exploiting the excited state surface potential.[38,39] For example, the deracemization of racemic spiro-cyclopropyl oxindole **12** is performed in the presence of *ent*-**D** to obtain the corresponding enantioenriched compound *ent*-**12**. Mechanistic studies showed that deracemization occurs through the formation of a non-chiral triplet 1,3-diradical intermediate.[35]

Catalyst *ent*-**D** has been shown to be an efficient catalyst in photochemical deracemizations of racemic allenes containing secondary[40,41] and primary[42] amides as the recognition motif for the chiral catalyst. The deracemization of allene **13** containing secondary amide is realized through selective sensitization of one enantiomer (Scheme 3).

The two substrate enantiomers form diastereomeric catalyst-substrate complexes **14** and **15** with different association constants (K_a = 84 M^{-1} *vs* 18 M^{-1}). The stronger binding enantiomer is excited selectively and more efficiently to its triplet state because the allene can be placed closer to the sensitizer (quantum yield: **Φ** = 0.52 ± 0.03, distance sensitizer-allene: 363 pm *vs* 510 pm). The triplet allene decays forming both enantiomers resulting in the enantioenrichment of the weaker binding one, *ent*-**13**.



Scheme 3. Photochemical deracemization of allenes, d = allene-photosensitizer distance.



Scheme 2. Application of Bach's bifunctional photosensitizer derived from Kemp's triacid.

Despite the broad applicability of chiral bifunctional sensitizers **B-D** derived from Kemp's triacid, the substrates need to contain an amide functional group to provide high binding affinity with the catalysts.[43] To broaden the scope of substrates and explore a wider chemical space,[44] different classes of bifunctional photocatalysts maintaining the same conceptual design have emerged.

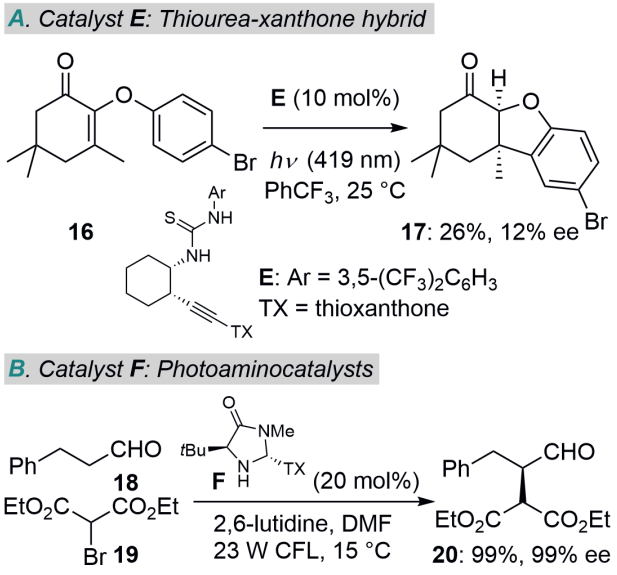
The Bach group incorporated the thioxanthone sensitizer in a thiourea with a chiral backbone giving bifunctional catalyst **E** that was tested for the 6π-photocyclization[45] of the 2-aryloxycyclohex-2-enones **16** (Scheme 4A).[46] However, cycloadduct **17** was only obtained with modest results under unoptimized reaction conditions.

In 2018, Alemán introduced the bifunctional photoaminocatalyst **F** merging thioxanthone and a chiral imidazolidinone organocatalyst in the same structure (Scheme 4B).[47] This catalyst showed excellent performance in the α-alkylation of aldehyde **18**. In contrast to previous examples discussed herein, the excited state of the thioxanthone moiety undergoes single electron reduction (rather than energy transfer) of alkyl bromide **19** generating an alkyl radical that adds to the enamine intermediate (formed upon condensation of the aldehyde substrate and catalyst **F**) to give alkylation product **20**.

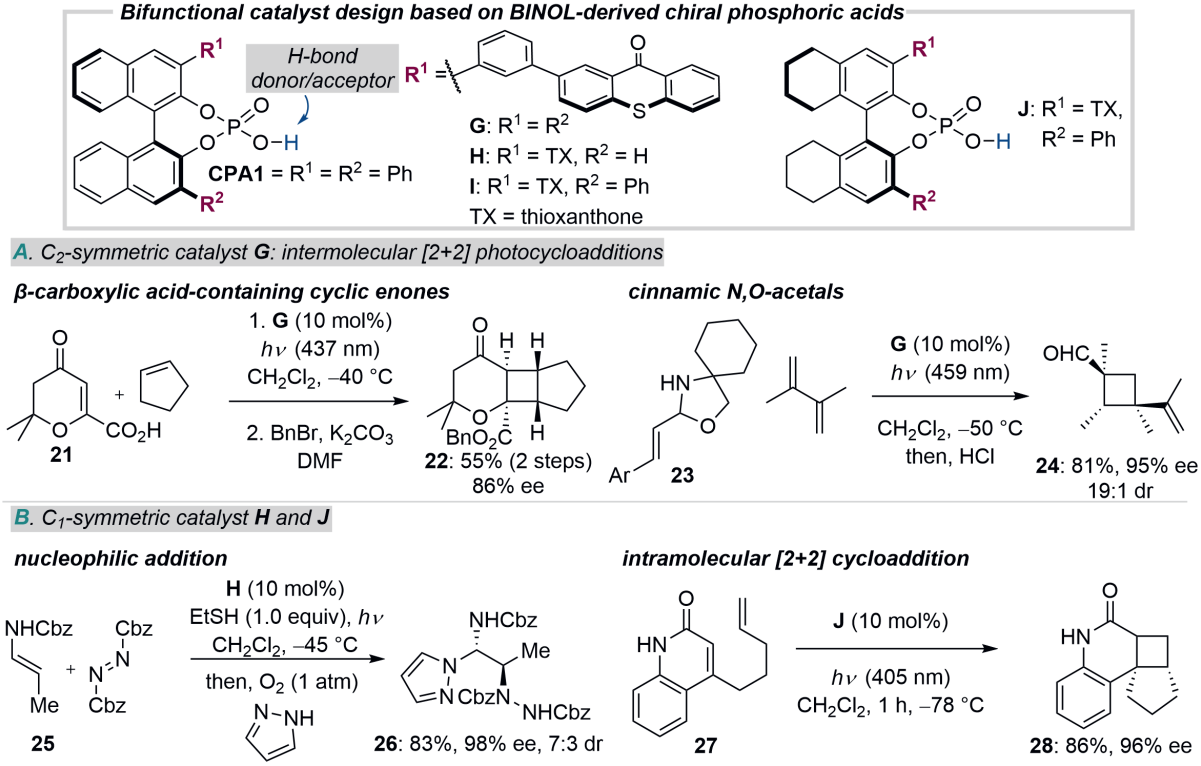
Incorporating photoactive aromatic ketones in binaphthol (BINOL)-derived chiral phosphoric acids (CPAs), a class of privileged[48] organocatalysts can give synthetically useful bifunctional photocatalysts. Bach[49] and Masson[50] independently reported chiral C_2- and C_1-symmetric BINOL-derived bifunctional phosphoric acids **G-J** in 2020 (Scheme 5). For this class of catalysts, the substrate recognition also relies on H-bonding interactions but the need for amide substrates, required for catalysts **B-D**, is overcome.

Bach employed phosphoric acid **G** with a *meta*-phenyl-tethered thioxanthone at the 3,3'-position of the binaphthyl backbone in the intermolecular [2+2] photocycloaddition of β-carboxylic acid-containing cyclic enone **21**, leading to cycloadduct **22** in good yield and enantioselectivity (Scheme 5A, left).[48] NMR studies showed that the carboxylic acid in **21** is required to ensure a strong interaction with the phosphoric acid catalyst. The same group applied bifunctional catalyst **G** in the enantioselective intermolecular [2+2] cycloaddition of N,O-acetals **23**, derived from β-aryl-substituted cinnamic aldehydes, with alkenes to give chiral cyclobutane aldehydes such as **24** (Scheme 5A, right).[51] During catalysis, catalyst **G** protonates the N,O-acetal forming an iminium intermediate which is hydrogen-bonded to the chiral counterion.

The triplet energy of the iminium intermediate (213 kJ mol^{-1}) was determined to be lower than that of catalyst **G** (235 kJ mol^{-1}) allowing for an exothermic energy transfer. Masson used C_1-symmetric catalyst **H** for the synthesis of the chiral 1,2-diamine **26** in good yield and selectivity from enecarbamate **25** (Scheme 5B, left).[50] However, the enantioselective step is a



Scheme 4. A) Thiourea-xanthone hybrids **E**; B) Photoaminocatalysts **F**.



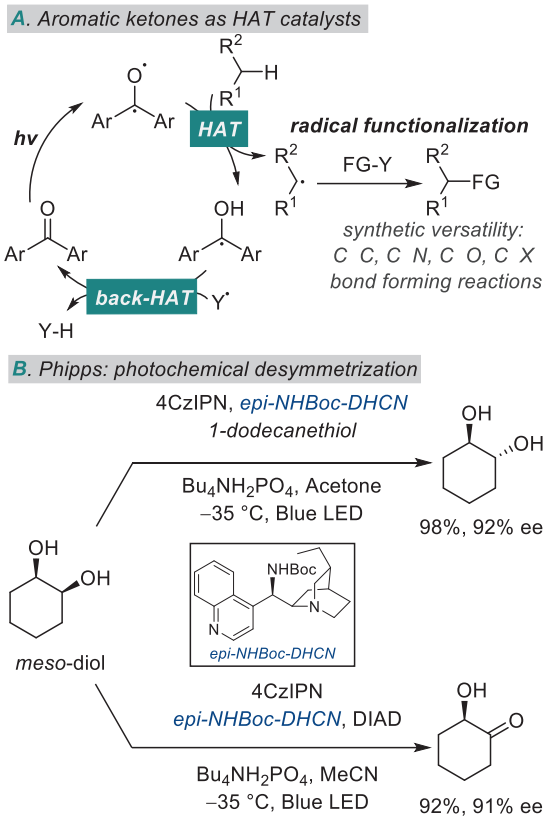
Scheme 5. A) C_2-symmetric bifunctional CPAs in catalysis; B) C_1-symmetric CPAs in catalysis.

nucleophilic addition to an intermediate imine that is previously formed under photochemical conditions. Thus, the enantioselective step does not involve open-shell intermediates. Indeed, the reaction proceeds in comparable 90% enantioselectivity in a dual catalytic system with **CPA1** and thioxanthone, albeit with a modest 21% yield thereby validating the use of bifunctional catalyst **H**. Later the Masson group introduced further variations of their catalysts and tested them for catalytic performance. However, only catalyst **I** gave **26** with comparable results (66%, 97% *ee*, 3:1 *dr*).[52]

In 2022, Takagi reported that C_1-symmetric bifunctional catalyst **J** with a chiral H8-BINOL backbone and thioxanthone as the sensitizer is a competent catalyst in the intramolecular [2+2] cycloaddition of **27** to give **28** in excellent yield and enantioselectivity (Scheme 5B, right).[53] A Job plot analysis established the formation of a 1:1 catalyst substrate complex *via* dual hydrogen bonding.

3. Conclusions and Outlook

With the growing interest in controlling enantioselectivity in radical transformations, the design of novel chiral catalysts becomes desirable. Herein, we have shown that bifunctional photocatalysts with an H-bonding entity for substrate recognition and a light-harvesting aromatic ketone as the photosensitizer embedded in a chiral scaffold have shown great potential in numerous transformations, spanning from radical additions and photocycloadditions to photochemical deracemizations. To date, the most general catalysts are derived from Kemp's triacid and axially chiral BINOL-derived phosphoric acids. Nonetheless, most transformations are initiated by energy transfer from the triplet excited state of the photosensitizer to the bound substrate. While this is an important class of transformations, upon light irradiation the photoexcited triplet state of aromatic ketones can also undergo hydrogen atom abstraction[54,55] generating carbon-centered radicals that further react with a suitable partner in an overall net C(sp^3–H) functionalization (Scheme 6A).



Scheme 6. A) Aromatic ketones as HAT catalysts; B) Photochemical desymmetrizations of *meso*-1,2-diols.

In the case where a bifunctional photocatalyst, reminiscent to the ones discussed in this review, is employed for the C(sp^3–H) functionalization of a prochiral substrate, the C–H abstraction is expected to occur enantioselectively resulting in a photochemical desymmetrization. This concept has been recently introduced by Phipps in the context of enantioselective photochemical isomerizations[56] and oxidations[57] of *meso*-1,2-diols (Scheme 6B). Because of the great synthetic potential of bifunctional photocatalysts, our newly established research team is currently exploiting such photocatalysts to probe innovative photochemical desymmetrizations and access biologically relevant stereochemically complex molecules.

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