

Enantioselective Excited-State Photoreactions Controlled by a Chiral Hydrogen-Bonding Iridium Sensitizer

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ABSTRACT: Stereochemical control of electronically excited states is a long-standing challenge in photochemical synthesis, and few catalytic systems that produce high enantioselectivities in triplet-state photoreactions are known. We report herein an exceptionally effective chiral photocatalyst that recruits prochiral quinolones using a series of hydrogen-bonding and π – π interactions. The organization of these substrates within the chiral environment of the transition metal photosensitizer leads to efficient Dexter energy transfer and effective stereoinduction. The relative insensitivity of these organometallic chromophores towards ligand modification enables the optimization of this catalyst structure for high enantiomeric excess (ee) at catalyst loadings as much as 100-fold lower than the optimal conditions reported for analogous chiral organic photosensitizers.

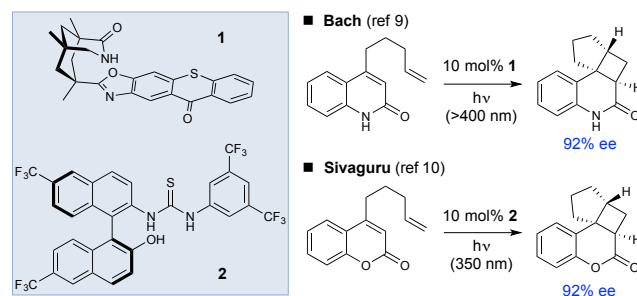
INTRODUCTION

Organic molecules in their electronically excited states undergo reactions that differ significantly from those of ground-state, closed-shell intermediates. The distinctive transformations available via excited-state chemistry have motivated the development of the field of synthetic photochemistry throughout the past century.¹ However, control over the stereochemistry of excited-state reactions remains a considerable challenge with few practical solutions, particularly using modern asymmetric catalytic approaches.² This difficulty is attributable to the short lifetimes and generally high reactivity of electronically excited organic intermediates, which challenge the ability of exogenous chiral catalysts to intercept and to modulate their subsequent reactions. Thus, successful strategies for highly enantioselective photocatalytic reactions have only been reported within the past decade, and applications of photochemical reactions to the synthesis of structurally complex, stereochemically well-defined organic molecules have remained quite limited.

Recently, there has been a renewed interest in photocatalytic synthesis centered largely on the remarkable photochemical properties of visible-light-absorbing transition metal complexes exemplified by Ru(bpy)₃²⁺ and Ir(ppy)₃.³ Many of the photophysical characteristics of these coordination compounds compare favorably to those of classical organic sensitizers, including their long excited-state lifetimes, their high intersystem crossing quantum yields, and their robust chemical stability. Recent investigations have led to the development of a range of new, highly enantioselective photocatalytic methods.⁴ Almost all of these new asymmetric catalytic photochemical transformations, however, have been photoredox reactions,⁵ in which the propensity of photoexcited chromophores to participate in electron-transfer reactions is exploited to produce radical or radical ion intermediates. Thus, these reactions can be characterized as “secondary” photoreactions, in which bond formation occurs from

photogenerated intermediates in their ground-state electronic configurations, rather than from excited-state molecules.⁶

Scheme 1. Previous Reports of Enantioselective [2+2] Photocycloadditions using Chiral Organic Sensitizers



Fewer strategies are available for controlling the stereochemistry of “primary” photoreactions, which are defined as transformations where the bond-forming events arise directly from electronically excited intermediates.^{6,7} To date, only a handful of systems have been able to deliver high ee’s in primary photoreactions at reasonably low concentrations of chiral catalyst (e.g., >80% ee at <10 mol%).⁸ Arguably the most well-established of these are chiral hydrogen-bonding organic photosensitizers developed by Bach⁹ and Sivaguru,¹⁰ both of which feature photosensitizing chromophores functionalized with a hydrogen-bonding moiety that orients a polar, achiral organic substrate within the stereocontrolling environment of the chiral photosensitizer (Scheme 1). Notably, the photocatalytic moieties in both systems are organic chromophores. In the past five years, several laboratories, including our own, have studied transition metal photocatalysts as sensitizers for a variety of triplet-state reactions (e.g., cycloaddition,^{9,11} aziridination,¹² isomerization,¹³ cross-coupling,¹⁴ and formal C–H amination¹⁵). An important feature of this work is the

tunability of the transition metal photocatalyst. While the photophysical properties of organic chromophores can often be sensitive to small structural perturbations,¹⁶ transition metal photocatalysts have proven to be substantially more robust towards modification, and a large family of octahedral ruthenium(II) and iridium(III) complexes bearing extensively modified ligand sets generally serve as excellent photocatalysts.¹⁷

Most of these Ru and Ir photocatalysts feature helical, metal-centered chirality, although they are typically utilized in racemic form. We wondered if this intrinsic chiral information could be exploited to control excited-state photoreactions. Meggers has designed a family of chiral-at-metal coordination complexes that provide high ee's in a remarkably broad range of transformations.¹⁸ These include non-photochemical reactions in which the chiral metal complexes serves principally as a chiral structural scaffold; bidentate L₂-type ligands bearing hydrogen-bonding¹⁹ or basic amine moieties²⁰ are introduced as catalytic functional groups. More recently, Meggers has also shown that Lewis acidic bis(acetonitrile) iridium(III) complexes can be effective enantioselective catalysts for photocatalytic reactions.²¹ In these processes, the metal complex typically plays a dual role as both a chiral Lewis acid as well as a photoredox catalyst, which has resulted in the development of a range of enantioselective reactions involving photogenerated radical intermediates. However, the use of chiral enantiopure organometallic complexes as triplet energy transfer photocatalysts has not yet been reported.²²

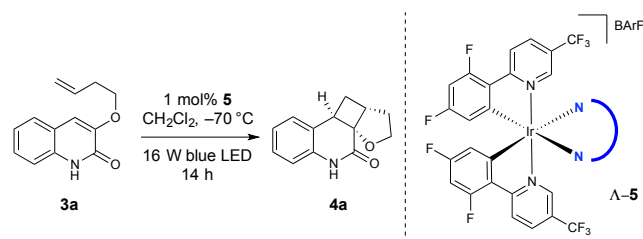
Herein, we describe the identification of a novel enantiopure iridium complex functionalized with a hydrogen-bonding domain that can serve as a highly enantioselective triplet sensitizer. The development of the optimal catalyst was guided not only by photophysical considerations but also by a rational study of substrate binding. The catalyst that emerged from these investigations exploits a unique dual hydrogen bonding interaction to organize a quinolone substrate and is capable of providing high enantioselectivities at loadings as low as 0.1 mol%, significantly lower than the most effective chiral triplet sensitizers described to date.

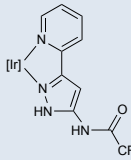
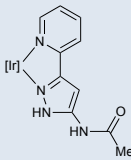
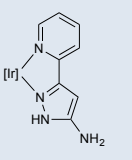
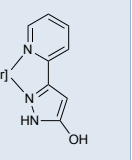
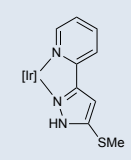
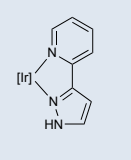
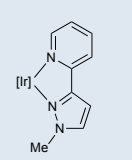
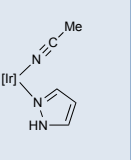
RESULTS AND DISCUSSION

Optimization and scope studies. Our preliminary investigations (Table 1) were based on three central premises. First, we elected to study 3-alkoxyquinolone **3** as a model substrate because its triplet energy is computationally estimated to be ~55 kcal/mol, easily within a range accessible using common iridium(III) complexes previously studied in our laboratory.^{11a,c,12} It is also similar in structure to the quinolones and coumarins that are the optimal substrates for previously reported chiral organic photosensitizers, which provides an opportunity to directly compare the effectiveness of these photoacatalysts. Second, iridium(III) photocatalysts bearing electron-deficient cyclometalated phenylpyridine ligands can possess quite high-energy triplet excited states. Thus, we adapted the synthetic route developed by Meggers to prepare enantiopure complexes of general structure **5** that we hoped would have a triplet energy sufficient to sensitize **3**. Finally, Meggers has reported a range of chiral-at-metal complexes bearing L₂ ligands functionalized with Brønsted acidic moieties that serve as highly effective hydrogen-bonding asymmetric catalysts in non-photochemical applications. We hoped that a heterocyclic ligand previously utilized to activate nitroalkenes^{19a,b} might similarly be capable of binding **3** within the stereoinducing environment defined by the octahedral Ir stereocenter. In

our initial experiments, irradiation of **3** with blue LEDs in the presence of 1 mol% of Ir catalyst **5a** at -70 °C resulted in the formation of **4** in 49% ee (Table 1), confirming the validity of our design plan.

Table 1. Effects of Modified Hydrogen-Bonding Ligands



 5a 98% yield 49% ee	 5b 93% yield 47% ee^a	 5c 24% yield 58% ee	 5d 73% yield 28% ee^a
 5e 82% yield 69% ee^a	 5f 91% yield 69% ee	 5g 78% yield 1% ee	 5h 42% yield 68% ee

^a Conducted with Δ-**5**. The sign of the ee value is corrected for the absolute stereochemistry of the catalyst.

Next, we interrogated the role the acidic trifluoroacetamide N-H bond plays as a H-bond donor (Table 1). We replaced the trifluoroacetamide moiety with a variety of other groups bearing hydrogen bond donors (**5b-d**), but surprisingly, there was no clear correlation between pK_a and the ee of the cycloadduct. This suggests that the presence of this hydrogen bond-donating substituent on the pyrazole ring is likely not critical for binding the substrate. Consistent with this hypothesis, an analogue bearing a thioether substituent (**5e**) incapable of donating a hydrogen bond provided improved ee. Moreover, a complex featuring an unsubstituted pyridylpyrazole ligand and provided both faster rate and high ee (**5f**). We found that the pyrazole moiety is necessary and sufficient for this level of enantiocontrol. A complex in which the critical N-H of the pyridylpyrazole ligand is blocked with a methyl group (**5g**) provided no enantioinduction. In contrast, the use of a complex bearing a monodentate pyrazole ligand and an acetonitrile ligand (**5h**) afforded almost the same ee as the optimal catalyst with a bidentate pyridylpyrazole ligand, albeit with diminished reactivity.

These studies suggested that the acidic N-H bond of the pyrazole provides a critical interaction with some Lewis basic functional group on the substrate, which we presumed was likely the quinolone carbonyl. In order to better understand the mode of substrate binding, we carried out an NMR titration experiment with **3** and (±)-**5f**. As expected, the chemical shift associated with the pyrazole N-H changes significantly as a function of added **3**. The response fits well

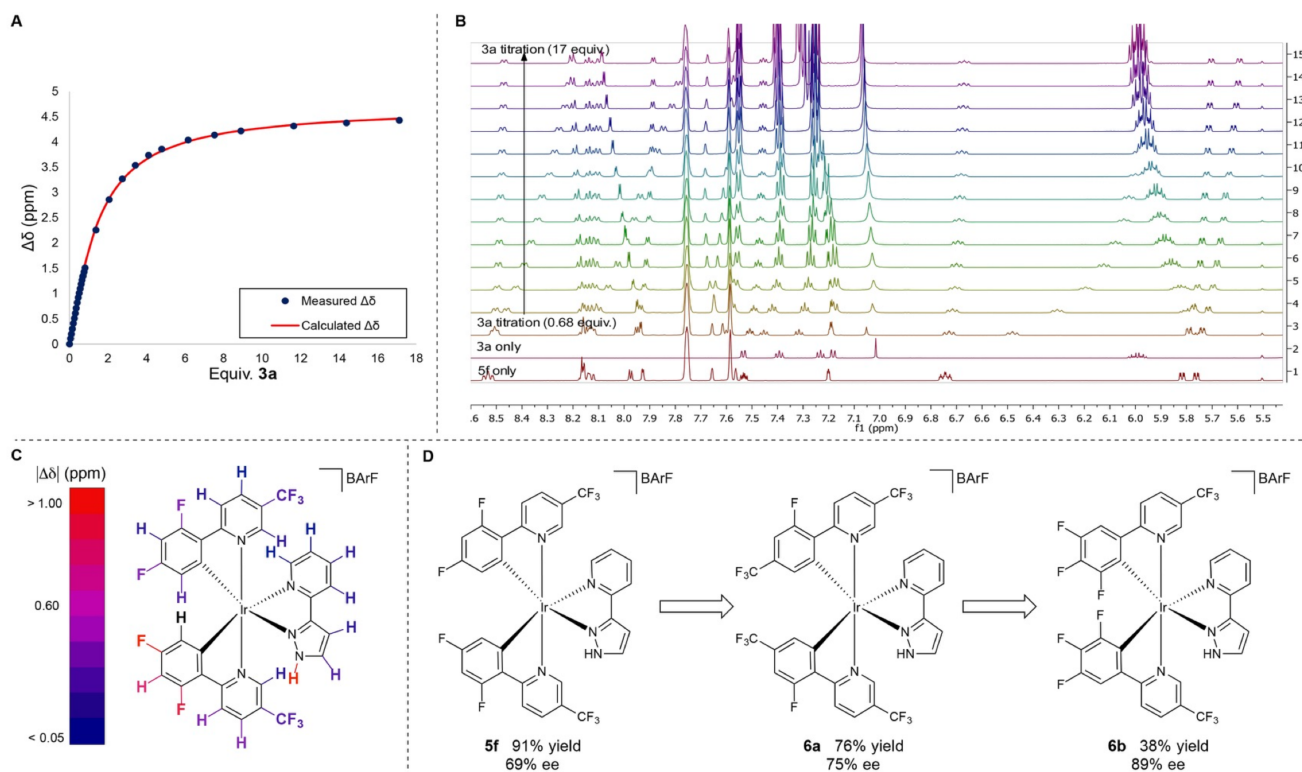


Figure 1. A. Binding isotherm obtained by monitoring the pyrazole N–H resonance of catalyst **5f** upon addition of varying concentrations of quinone **3a**. B. Stack plot of ^1H NMR spectra depicting changes in the aromatic region of catalyst **5f** upon titration with **3a**. C. Heat map showing where the largest changes in NMR chemical shifts are localized on catalyst **5f**. D. Optimization of the cyclometalating ligand of the photocatalyst.

to a 1:1 binding model, and from these data we calculated an association constant of $K_a = 560 \text{ M}^{-1}$ (Figure 1A).

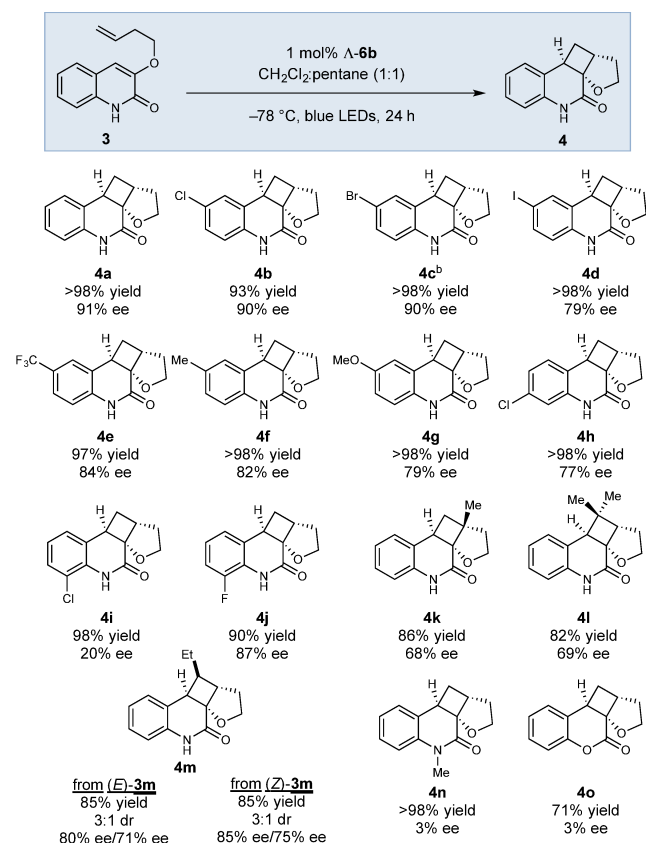
While performing this titration study, we observed that the chemical shifts of other protons also changed over the course of the titration (Figure 1B). As expected, the signal associated with the critical pyrazole N–H enjoyed the largest chemical shift change, but several other signals also shifted significantly. Moreover, the magnitude of $\Delta\delta$ varied over a wide range as a function of position. These observations suggested a strategy for further optimization of the chiral photocatalyst. We reasoned that large changes in chemical shift at various positions on the catalyst would likely correlate to close contacts with the substrate. Thus, modification at those positions associated with the largest chemical shift changes might be expected to have a substantial impact on the enantioselectivity of the catalyst.

These chemical shift changes are graphically summarized in Figure 1C. Several features of this heat map warrant comment. First, while the pyrazole moiety itself is strongly affected by association of the substrate, consistent with its critical role in binding, its pyridyl substituent is not strongly impacted. This is consistent with the empirical observation that a complex lacking the pyridyl group nevertheless provides high ee (Table 1, **5h**). Second, most of the significant changes in chemical shift are localized to one of the two cyclometalating phenylpyridine ligands; the other is comparatively unaffected. Moreover, the magnitude of the chemical shifts on the cyclometalating phenyl moiety are generally larger than on the pyridyl group. Thus, it seems reasonable to suppose that alteration of the cyclometalating ligands, and specifically the substituents about the phenyl ring, should have a large impact on the enantioselectivity of the photocycloaddition.

Optimization studies varying the structure of the cyclometalating ligands are in good agreement with this expectation (Figure 1D). Modest changes to the fluorination pattern on the phenyl group result in large increases in enantioselectivity, albeit at the cost of reaction rate. Catalyst **6b**, which provides 89% ee in the cycloaddition reaction, exhibits a substantially larger association constant of $K_a = 3000 \text{ M}^{-1}$, suggesting that the stronger interaction between the catalyst and substrate might be responsible for the heightened selectivity.

Given the sensitivity of hydrogen bonding interactions to solvent dielectric, we wondered if the substrate–catalyst interaction might be strengthened by reducing the solvent polarity. Indeed, conducting the reaction in 1:1 CH_2Cl_2 :pentane resulted in an increase in the measured binding constant to $K_a = 19000 \text{ M}^{-1}$ and the formation of cycloadduct **4** in quantitative yield and 91% ee. Complex **6b** is an exceptionally effective asymmetric photocatalyst; it provides high ee's at catalyst loadings considerably lower than the optimal conditions reported for chiral organic photosensitizers.^{9,10} As a demonstration of this point, we conducted a [2+2] cycloaddition using only 0.1 mol% of **6b**. Although this led to the formation of **4** at diminished rate (38% yield at 24 h), there was negligible effect on enantioselectivity (88% ee). These results underscore the remarkable photocatalytic properties of this family of Ir(III) photosensitizers, which generally provide superior reactivity compared to classical organic sensitizers.

Table 2. Scope and Limitations of Enantioselective [2+2] Photocycloaddition^a



^a Isolated yields on 0.25 mmol scale. ^b Reaction conducted for 48 h.

A brief examination of substrates (Table 2) demonstrates that structurally related quinolones can also provide excellent yield and high ee in this transformation. Chloro- and bromo-substituted quinolones behave comparably to the parent substrate (**4b** and **4c**), while an iodinated substrate exhibited diminished ee (**4d**) due to an uncatalyzed background reaction arising from direct excitation. However, only trace amounts of de-iodinated product were observed under our conditions, consistent with the low energy of the visible light utilized in this procedure. Electron-poor (**4e**) and electron-rich (**4f**, **4g**) quinolones also react in high yields and good enantioselectivities. Substitution of a chlorine at the 8-position of the quinolone (**4i**) results in a dramatic drop to 20% ee, presumably because this large substituent interferes with the critical hydrogen bonding contact necessary for catalyst binding. In contrast, the smaller 8-fluoroquinolone (**4j**) exhibits only a slight decrease in enantioselectivity compared to **4a**. The alkene tether can also be modified, though with somewhat diminished enantioselectivity. Finally, we also tested substrates in which the amidyl N–H moiety is either blocked with an alkyl substituent (**4n**) or replaced by an oxygen that is incapable of donating a hydrogen bond (**4o**). In both cases, these substrates give good yields but negligible ee. This suggests that the quinolone N–H bond plays a critical role in organizing the substrate relative to the stereodetermining Ir ligand sphere, but that it is not important for the success of the sensitized cycloaddition itself.

Mechanistic investigations. The design strategy for the development of Ir complex **6b** was premised upon the ability of similar octahedral Ir polypyridyl complexes to catalyze a wide variety of primary

photoreactions, including cycloadditions, via triplet energy transfer. However, we also considered several mechanistic alternatives for this reaction.

First, we examined the possibility that the [2+2] cycloaddition might be initiated by photoinduced electron transfer, rather than energy transfer. Electrochemical studies in CH₂Cl₂ indicate a substrate oxidation potential of +1.59 V and reduction potential of <−1.7 V vs. SCE, both of which lie well outside the potentials of the photoexcited catalyst (+1.27 V and −0.78 V, respectively). Thus, photoinduced electron transfer to or from the photocatalyst is not thermodynamically feasible. Second, control experiments indicate that no reaction occurs in the absence of photocatalyst or in the dark, ruling out alternative mechanisms involving either direct excitation of **3a** or a purely thermal process in which the iridium catalyst serves as a chiral Brønsted acid.

Finally, Meggers very recently reported that a chiral-at-metal Rh Lewis acid is capable of catalyzing the [2+2] photocycloadditions of enones with excellent enantioselectivity.²³ The optimal Rh catalyst for this reaction, however, was not proposed to behave as a triplet sensitizer. Instead, Meggers showed that the rhodium center forms an association complex with the substrate, in a manner analogous to the Lewis acid catalyzed photocycloaddition methods described by Bach.⁹ The key enabling feature of this reaction is the appearance of a strong, long-wavelength feature in the UV-vis spectrum of the Rh–substrate complex that is significantly enhanced relative to the sum of the individual spectra of the catalyst and substrate. We conducted an analogous UV-vis absorption experiment using Ir catalyst **6** and quinolone **3** (Figure 2). While there is a subtle bathochromic shift in the absorption spectrum of **6** upon addition of a 20-fold excess of **3**, the effect is comparatively modest. Moreover, the fact that **6** remains an effective photocatalyst for cycloaddition of substrates that cannot form the same hydrogen-bonded complex as **3a** (Table 2, **3n** and **3o**) indicates that pre-association is not critical for photoactivation to occur, and that a different mechanism is likely operative.

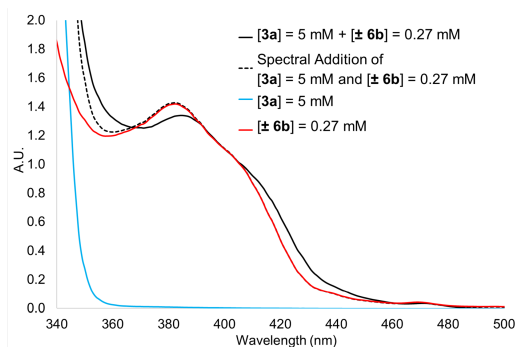


Figure 2. UV-vis absorption spectra for association of quinolone **3a** to catalyst **6b**.

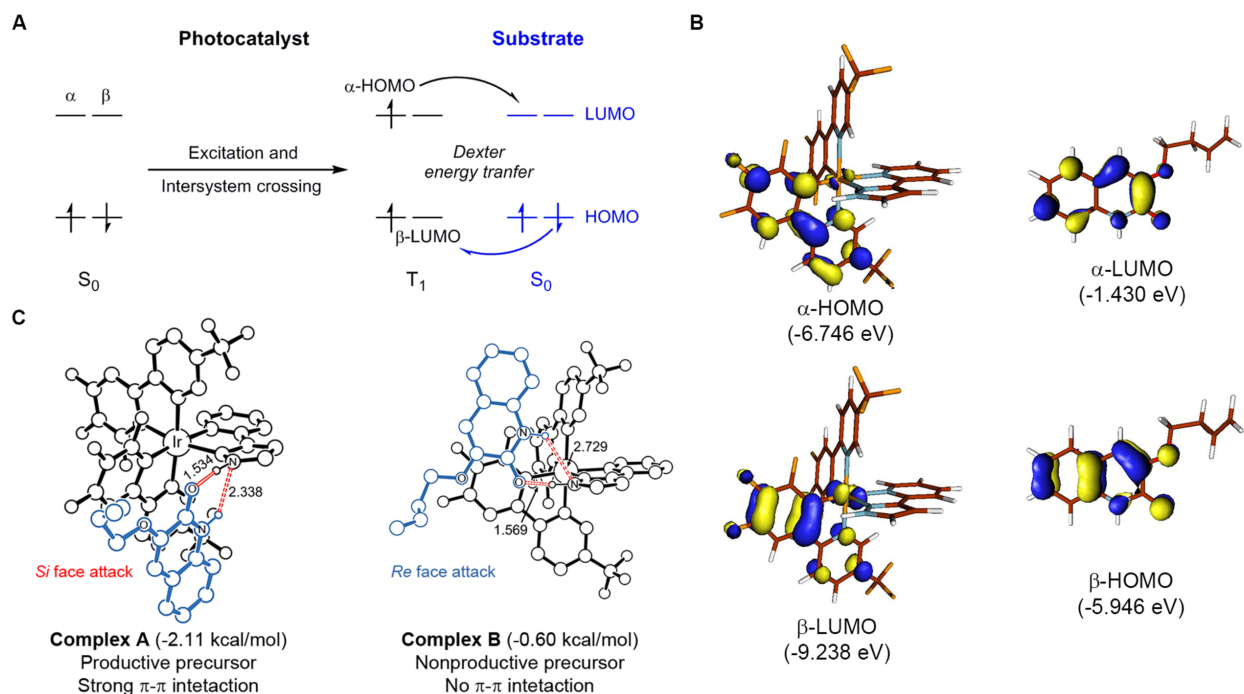


Figure 3. **A.** Conceptual illustration of Dexter energy transfer. **B.** Frontier molecular orbital plots of the triplet excited state Ir-photocatalyst and the singlet ground state quinolone. (isodensity value: 0.05 au) **C.** Computationally optimized structures for hydrogen bonding complexes.

Thus, the available experimental evidence suggests that a Dexter energy transfer mechanism is operative. The emission maximum of our catalyst is 480 nm, corresponding to a triplet energy of 59.6 kcal/mol. We computationally estimated the substrate triplet energy as 55.0 kcal/mol, which indicates that the state change associated with triplet energy transfer from the photocatalyst to **3** would be exergonic. Xanthone-sensitized [2+2] cycloadditions of quinolones have been studied extensively by Bach, who proposed an analogous mechanism.²⁴ Finally, independent experiments with stereochemically defined (*E*)-**3m** and (*Z*)-**3m** converge to the same diastereomeric ratio, consistent with a stepwise triplet cycloaddition in which bond rotation occurs faster than radical recombination, rather than a concerted singlet process.

Dexter energy transfer is an electron exchange process between a triplet-excited donor and a singlet acceptor molecule, as illustrated in Figure 3A, that can be conceptualized as a combination of two concerted events: (i) The movement of an electron in the α -HOMO of the excited donor to the α -LUMO of the acceptor and (ii) the transfer of an electron from acceptor to the β -LUMO of the donor. Here, the triplet energy donor is the excited state of the Ir-catalyst, and the acceptor is the quinolone substrate. For the Dexter energy transfer to occur effectively, the donor and acceptor orbitals must show proper overlap, as the double electron-transfer requires reasonably strong electronic coupling.

Examining the shapes of the orbitals that will engage in the exchange process is helpful for obtaining a rough idea of which portions of the catalyst and substrate must be arranged in close proximity. The orbital plots in Figure 3B show that both the α -HOMO and β -LUMO of the excited state of the Ir-catalyst are localized on the phenylpyridine (ppy) ligand that is cyclometalated to the Ir center. Since the α -LUMO and β -HOMO of the substrate are also found in the π -space, a catalyst-substrate geometry that enables the π -orbitals

of the quinolone to sufficiently overlap with the π -orbitals of the ppy-ligand is most appropriate. This arrangement requires a coplanar alignment of the substrate with the ppy-ligand, posing a stringent limitation on which of the many possible adducts will be competent in carrying out the Dexter energy transfer, which is proposed to ultimately determine the enantioselectivity.

The computationally derived encounter complex **A** (Figure 3C) successfully predicts the absolute sense of stereoinduction in the cycloaddition and exhibits structural features consistent with the experimental observations outlined above. A strong H-bonding interaction between the pyrazole and the quinolone carbonyl establishes the main contact, but an important π - π interaction between the substrate and cyclometalating ligand is also formed. This interaction may not only explain the large changes in chemical shift observed in the NMR titration experiments but may also be required for efficient coupling between the triplet excited state of the Ir sensitizer and the π orbital fragment of the substrate, as described above. Interestingly, there is an unusual N-H- π interaction between the quinolone amide and the pyrazole group that stabilizes this conformation and is consistent with the observation that the N-H of the quinolone is necessary to achieve enantioselectivity (cf. **4n**, **4o**). In contrast, complex **B**, which features an analogous hydrogen-bonding pattern but with the opposite *Si* face blocked, cannot establish the π - π interaction. Both complexes are calculated to be more stable than their two non-interacting components; **A** is located at -2.1 kcal/mol and **B** is located at -0.6 kcal/mol, respectively.

CONCLUSION

In conclusion, we have developed a highly effective chiral triplet sensitizer that combines the exceptional photochemical properties of transition metal coordination complexes with a hydrogen bond-

ing domain to orient the organic substrate. Notably, the robust photophysical properties of iridium(III) polypyridyl complexes enabled considerable optimization of both the cyclometalating and L_2 ligands. The flexibility of this strategy led us to discover an enantioselective catalyst that exploits an unexpected π - π interaction and unusual N-H to π hydrogen bond, rather than any direct inner-sphere substrate-catalyst association. The optimal complex can be utilized at catalyst loadings two orders of magnitude lower than current state of the art chiral organic photosensitizers. We believe this constitutes an attractive new approach to stereocontrol in excited state photoreactions, which have historically proven to be a formidable synthetic challenge. Further exploration of these design principles is a continuing theme of research in our laboratory.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, crystallographic data, Cartesian coordinates of all computed structures and energy components. The Supporting Information is available free of charge on the ACS Publications website.

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Notes

The authors declare no competing financial interests.

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