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Cooperative Stereoinduction in Asymmetric Photocatalysis

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Abstract

Stereoinduction in complex organic reactions often involves the influence of multiple stereocontrol elements. The interaction among these can often result in the observation of significant cooperative effects that afford different rates and selectivities between the matched and mismatched sets of stereodifferentiating chiral elements. The elucidation of matched/mismatched effects in ground-state chemical reactions was a critically important theme in the maturation of modern stereocontrolled synthesis. The development of robust methods for the control of photochemical reactions, however, is a relatively recent development, and similar cooperative stereocontrolling effects in excited-state enantioselective photoreactions have not previously been documented. Herein, we describe a tandem chiral photocatalyst/Brønsted acid strategy for highly enantioselective [2+2] photocycloadditions of vinyl pyridines. Importantly, the matched and mismatched chiral catalyst pairs exhibit different reaction rates and enantioselectivities across a range of coupling partners. We observe no evidence of ground-state interactions between the photocatalysts and conclude that these effects arise from their cooperative behavior in a transient excited-state assembly. These results suggest that similar matched/mismatched effects might be important in other classes of enantioselective dual-catalytic photochemical reactions.

Graphical Abstract

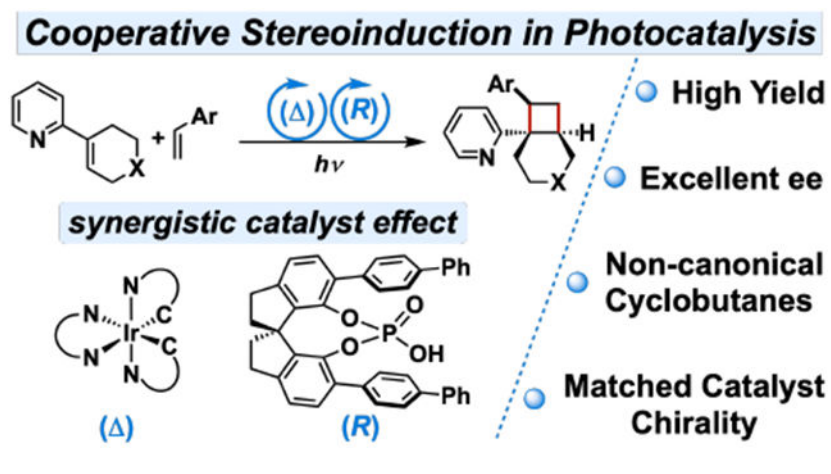[*]**Corresponding Author** tyoon@chem.wisc.edu.
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Cooperative Stereoinduction in Photocatalysis

synergistic catalyst effect

- High Yield
- Excellent ee
- Non-canonical Cyclobutanes
- Matched Catalyst Chirality

INTRODUCTION:

The ability to predict and control the stereochemical outcome of a chemical transformation is a defining characteristic of modern organic synthesis. A central concern in stereochemically complex reactions is the combined influence of multiple interacting stereochemical elements. When two chiral components interact in a reaction that forms a product with at least one new stereocenter, they can either reinforce each other's individual preferences in a "matched" case, or their intrinsic preferences can oppose one another in a "mismatched" case.[1] Large differences in the rate and selectivity of matched and mismatched sets of analogous reactions have been documented in classical, ground-state asymmetric synthesis and represent some of the canonical experiments in the field of asymmetric catalysis (Figure 1A).[2] Similar effects have rarely been observed in excited-state reactions, in part because general strategies for highly enantioselective photochemical reactions have only recently emerged.[3] Herein, we report the highly enantioselective excited-state [2+2] photocycloaddition reaction of vinyl pyridines using tandem chiral Brønsted acid and Ir(III) photocatalysis. Importantly, we observe a significant stereochemical matching effect between the chirality of the Brønsted acid and Ir(III) co-catalysts. This observation suggests that similar cooperative stereocontrolling effects could be relevant in other tandem asymmetric photocatalytic methods.

Asymmetric dual photocatalysis—the combination of a photocatalyst with a second photoinactive chiral co-catalyst—is arguably among the most flexible methods for controlling stereochemistry in photochemical reactions.[3a] Notably, the photocatalysts used in these dual-catalytic reactions are often pseudo-octahedral Ru– and Ir–polypyridyl complexes that possess helical Δ- or Λ-chirality about the metal center.[4] Meggers exploited this metal-centered stereochemistry to design remarkably effective single-component organometallic photocatalysts for a range of useful, highly enantioselective organic photoreactions.[5] However, in dual-catalytic asymmetric photoreactions, the innate chirality of the photocatalysts is largely ignored, and they are used as a racemic mixture that masks any possible matched/mismatched effects between the catalysts. In many reactions, using racemic photocatalyst is sensible. These include, for example, MacMillan's seminal photoredox–organocatalytic alkylation of aldehydes[6] and our group's Lewis acid controlled

enantioselective excited-state [2+2] photocycloadditions of chalcones (Figure 1B).[7] The collisional photoactivation step in these reactions generates reactive intermediates that can dissociate and react outside the chiral influence of the photocatalyst. As a result, the enantiodetermining environment of the reaction is generally presumed to be determined solely by the stereochemistry of the chiral co-catalyst and not by the chirality of the photocatalyst. To the best of our knowledge, the effect of the photocatalyst chirality in dual catalytic photoreactions has only been investigated by Ooi, who developed a chiral borate anion that controlled the stereochemistry of an enantioselective photochemical [3+2] cycloaddition. In these studies, the individual enantiomers of the [Ir] photocatalyst cation showed no effect on the rate of reaction or degree of stereoinduction (Figure 1C).[8]

We report herein the first example of cooperative stereoinduction involving a chiral [Ir] photocatalyst for a dual-photocatalytic transformation (Figure 1D). This observation arose during the development of an asymmetric method for the [2+2] photocycloaddition of vinyl pyridines. We were attracted to this problem because nearly all catalytic enantioselective [2+2] photocycloadditions reported to date have involved carbonyl-based substrates,[9] which limits the structural variety of complex cyclobutanes synthetically accessible in enantiopure form.[10] Chiral Brønsted acids are often ideally suited for activating different classes of organic substrates than do Lewis acids,[11] and they have been used effectively in several asymmetric reactions of pyridines. We hypothesized, therefore, that a dual catalytic system comprising a chiral Brønsted acid and a triplet sensitizing photocatalyst[12] might enable the first highly enantioselective [2+2] photocycloaddition of vinyl pyridines. Concurrent with our investigation, Gschwind and Bach published the first chiral Brønsted acid catalyzed enantioselective [2+2] photocycloaddition using a photoactive acid catalyst.[13] Similarly, we recently published a chiral Brønsted acid catalyzed [2+2] photocycloaddition that relied on a chromophore activation mechanism.[14] However, these reactions require carbonyl-based substrates similar to previously reported methods. The dual-catalytic system we describe herein enables the synthesis of previously inaccessible enantioenriched pyridyl cyclobutanes and reveals excited-state matched/mismatched catalyst pairs that we believe have important implications in the emerging field of asymmetric photocatalysis.

RESULTS AND DISCUSSION:

Optimization and Scope Studies.

Figure 2A summarizes the optimization studies that resulted in this central observation. Irradiation of vinyl pyridine **1** and styrene in the presence of a BINOL-derived chiral phosphoric acid (CPA1) and rac[Ir(dtbppy)$_2$(dMeObpy)]PF$_6$ (rac-[Ir]) afforded the corresponding cycloadduct in low yield and selectivity (Figure 2A, entry 1). The reaction yield increased in less polar solvents (Figure 2A, entries 2–3), consistent with enhancement of Brønsted acid/base interactions in low-dielectric media (Figure 2B); the enantiomeric excess (ee), however, remained low. A screen of alternate chiral phosphoric acids revealed that 3,5-CF$_3$-SPINOL-derived CPA2 provided the cyclobutane product in a significantly higher 64% ee (Figure 2A, entry 4). Lowering the temperature to −40 °C improved cycloadduct d.r. with a modest effect on the ee (Figure 2A, entry 5). A 4-biphenyl-SPINOL (CPA3) proved optimal, affording the desired cycloadduct in high yields, excellent d.r., and

94% ee (Figure 2A, entry 6). Control reactions demonstrated the necessity of the CPA (Figure 2A, entry 7), the iridium photosensitizer (Figure 2A, entry 8), and light (Figure 2A, entry 9). Surprisingly, control experiments with an achiral photosensitizer (thioxanthone) resulted in decreased ee (Figure 2A, entry 10). Because we observed no background reaction using thioxanthone alone in the absence of CPA3, this result thus seemed to implicate a substrate–photocatalyst interaction in the stereochemistry-determining step of the transformation. As a test for this putative interaction, we first examined the effect of photocatalyst chirality on the enantioselectivity of the [2+2] photoreaction. Enantiopure [Ir] complexes were prepared using the method of Meggers,[15] and upon examining their performance in the model [2+2] photoreaction, we found that –[Ir] affords the cycloadduct in significantly higher yield and ee than Λ–[Ir] (Figure 2C). We further performed an experiment using enantiopure Λ–[υ] and racemic CPA3, which provided *ent*-**2** in 29% ee despite the lack of any obvious means for interaction between the photocatalyst and substrates (Figure 2D). Together, these results implicate an unprecedented co-operative influence of photocatalyst and co-catalyst stereochemistry on the outcome of an asymmetric photochemical transformation.

There are few methods for the asymmetric synthesis of heteroarene-substituted cyclobutanes and none involving an excited-state vinylheteroarene. Studies investigating the scope of this novel asymmetric cyclobutane synthesis were therefore conducted and are summarized in Figure 3. Notably, cooperative stereocontrol appears to be a general feature of this method. Higher yield, d.r., and ee are consistently obtained when –[Ir] is used as the photocatalyst compared to either Λ–[Ir] or rac–[Ir], although in many cases, rac-[Ir] still afforded the desired cycloadduct with high ee (**2**–**6** and SI). Electron-rich styrenes (**3**–**4**) afford increased rates of cycloaddition in slightly higher ee than electron-poor styrenes (**5**–**6**). *Meta*-substitution of the styrene (**7**) maintains excellent selectivity, but we observed a small decrease in ee with *ortho*-substituted styrenes (**8**–**9**). A reaction with α-methylstyrene (**10**) successfully sets two adjacent quaternary stereocenters, and the reaction with β-methylstyrene (**11**) controls the stereochemistry of all four atoms of the product cyclobutane. In contrast to the generality observed with the styrene coupling partner, we noticed that small structural perturbations to the vinyl pyridine would often cause a significant change in ee (**12**–**13**), consistent with its putative role in interacting with the chiral acid catalyst. Changes to the alkene moiety allowed for additional diversification; substituted rings (**14**), heterocycles (**15**), and smaller rings (**16**) were well tolerated. We observed a drop in diastereoselectivity when using *ortho*-substituted styrenes and structurally diverse vinyl pyridines; we attribute these observations to a steric effect and a perturbation of coordination with CPA3 respectively. The absolute configuration of the parent cycloadduct **2** was determined from the crystal structure of its HCl salt (Figure 2E).

Mechanistic Investigations.

The unexpected observation of co-operative stereoinduction between the chiral photocatalyst and Brønsted acid prompted us to interrogate the mechanism of this asymmetric cycloaddition in greater detail. First, we ruled out electron transfer as an activation mechanism by cyclic voltammetry; the relative reduction potentials of the photocatalyst and vinyl pyridine in the presence and absence of CPA3 indicate that excited-state electron

transfer is not thermodynamically feasible, and that this reaction most likely occurs through an energy transfer pathway. From the emission spectrum of the photocatalyst, we determined its triplet energy to be $E_T = 59$ kcal/mol (see SI). We estimated the triplet energy of vinyl pyridine **1** with density functional theory to be $E_T = 54$ kcal/mol (see SI). Stern–Volmer experiments demonstrated that neither styrene nor free vinyl pyridine substantially quench the emission of the [Ir] triplet state. However, in the presence of trifluoroacetic acid (TFA) as a surrogate for the CPA, protonated vinyl pyridine substantially quenches the [Ir] emission with a Stern–Volmer constant (K_{SV}) of 10.8 M^{-1} (Figure 4A). These experiments show that energy transfer to the vinyl pyridine is accelerated in the presence of Brønsted acids.

A conventional energy-transfer mechanism would involve a collisional interaction between the CPA3–vinyl pyridine salt and excited iridium; in this mechanism, the excited-state vinyl pyridine would be freely diffusing independent of the photosensitizing [Ir] complex. However, we can readily exclude this standard mechanism given the marked effect of photocatalyst stereochemistry on the enantioselectivity of this reaction. Even if the two enantiomers of [Ir] gave different rates for diffusional energy transfer, no effect on ee would be expected if the enantioselective cycloaddition would occur outside of the stereochemical influence of the photocatalyst. Therefore, we conclude that the [Ir] photocatalyst must be intimately involved in the enantiodetermining step of any proposed mechanism.

We considered two ways in which the chiral co-catalysts ([Ir] and CPA3) might interact to provide cooperative stereoinduction. First, a ground-state interaction would preorganize the chiral photocatalyst and Brønsted acid adduct into the diastereomeric complexes { –[Ir] —[(*R*)-CPA3–**1**]} and {Λ–[Ir]—[(*R*)-CPA3–**1**]}, each of which could operate as a single diastereomerically pure unit. Knowles and Alexanian recently reported a reaction involving an iridium photocatalyst associated with an anionic phosphate co-catalyst via Coulombic and hydrogen-bonding interactions.[16] Unlike this prior report, however, NMR titrations performed with –[Ir] and (*R*)-CPA3 provided no evidence for a ground-state interaction with or without pyridine present to act as a surrogate for **1**. Similarly, we observed no significant changes in the absorption profile of the photocatalyst upon the addition of either (*R*)-CPA3 or (*R*)-CPA3-**1** (see SI). Together, these experiments rule out the formation of ground-state diastereomeric complexes as a mechanism for cooperative stereoinduction.

In the absence of any ground-state interaction between the catalysts, we concluded that photoexcited –[Ir]³ and Λ–[Ir]³ must associate with [(*R*)-CPA3–**1**] into transient diastereomeric excited-state complexes. These diastereomeric complexes would be expected to show distinct photochemical properties and different reactivity towards styrene, consistent with the observed matched/mismatched effect. To interrogate this possibility, we studied the photoluminescence spectra of the iridium photocatalysts. Surprisingly, excitation of [Ir] in the presence of (*R*)-CPA3 resulted in an increase in the emission intensity; both –[Ir] and Λ–[Ir] gave similar increases. A substantially larger increase in emission was observed upon the addition of 10 equiv. of vinyl pyridine to a solution containing (*R*)-CPA3 and -[Ir] (*matched conditions*), along with an apparent hypsochromic shift in the emission signal (Figure 4B). This feature is not observed upon direct irradiation of CPA3–**1** in the absence of -[Ir] (see SI). Under otherwise identical conditions, excitation of Λ–[Ir] resulted in a much smaller increase in emission intensity (*mismatched conditions*). Stern–Volmer analysis of

this interaction could not be conducted due to the presence of this new overlapping emission feature and the relatively short lifetime of the free Ir photocatalyst. However, the distinct difference in emission intensity confirms a diastereomeric difference in the interaction of (*R*)-CPA3 with Δ–[Ir] and Λ–[Ir] in the excited state.

We were intrigued by the possibility that the matched/mismatched effect might arise from the differential reactivity of the two transient diastereomeric [Ir—CPA3–**1**] excited-state complexes. If so, we would expect the diasteromeric complexes to react with styrene at different rates. The addition of styrene to the combination of Δ–[Ir] and CPA3–**1** quenched the photoluminescence intensity (Figure 4C). Notably, the quenching was strongest at shorter wavelengths, corresponding to the emission from the proposed excited-state complexes. A Stern–Volmer analysis of the quenching between 440–490 nm provided a linear correlation with styrene concentration and a Stern–Volmer constant (K_{SV}) of 5.6 M^{-1}. The corresponding analysis of the quenching of the diastereomeric Λ–[Ir]—CPA3–**1** combination, on the other hand, resulted in 39% less efficient luminescence quenching (K_{SV} = 3.4 M^{-1}). Thus, as anticipated, the two diastereomeric catalyst complexes react with styrene with different efficiencies, consistent with the observed matched/mismatched effects.

Based on these combined observations, we propose the mechanism outlined in Figure 4D. The photocatalytic Δ-[Ir] chromophore is excited to afford a triplet state (Δ-[Ir]^3) that forms a transient excited-state complex with the preassociated CPA3–**1** complex, {Δ–[Ir]—[(*R*)-CPA3–**1**]}^{3}. Intracomplex energy transfer to [(*R*)-CPA3–**1**] followed by reaction with styrene results in the formation of highly enantioenriched cycloadduct **2**. The mismatched pathway follows a similar mechanism. However, the diastereomeric {Λ–[Ir]—[(*R*)-CPA3–**1**]}^{3} complex reacts with styrene less efficiently and produces **2** with lower ee. When the [Ir] photocatalyst is used as a racemate, both reaction pathways are operative, but the matched case can outcompete the mismatched case as evidenced by the high yield and ee obtained.

CONCLUSION:

In conclusion, we report the first example of co-operative stereoinduction in a photocatalytic reaction, where the most selective conditions necessitate a stereochemical match between a chiral [Ir] photocatalyst and chiral Brønsted acid catalyst. Synthetically, this is the first method capable of controlling an excited-state vinylheteroarene to afford enantioenriched pyridine-substituted cyclobutane products. The observed matched/mismatched effects originate from the generation of diastereomeric excited-state cocatalyst pairs that have different photophysical dynamics and afford differing rates of reaction with styrene. To our knowledge, this coorperative stereoinduction involving excited-state catalyst pairs is unprecedented in dual catalysis, but it indicates that similar effects may be present across a range of tandem asymmetric photocatalytic methods.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENT

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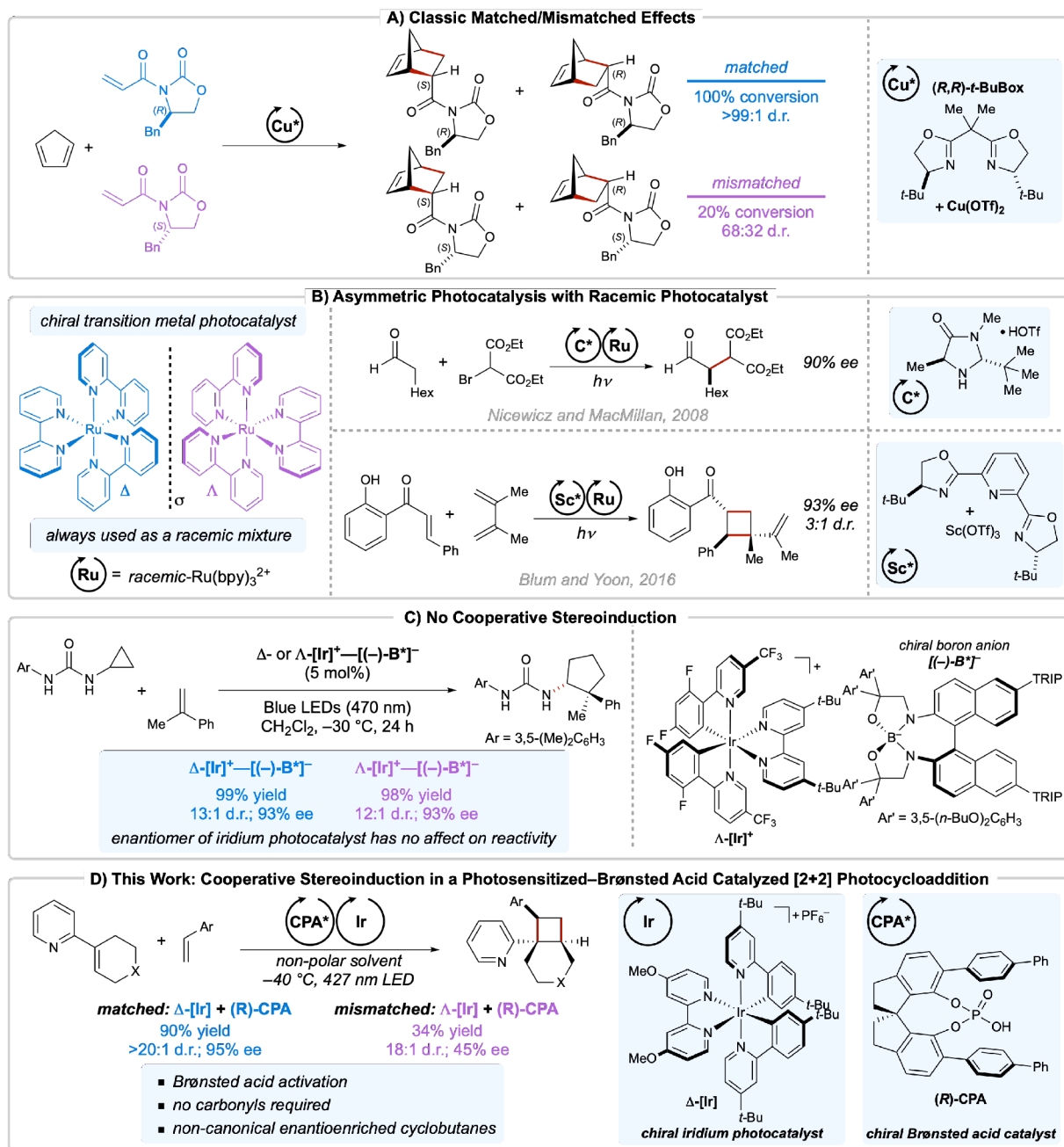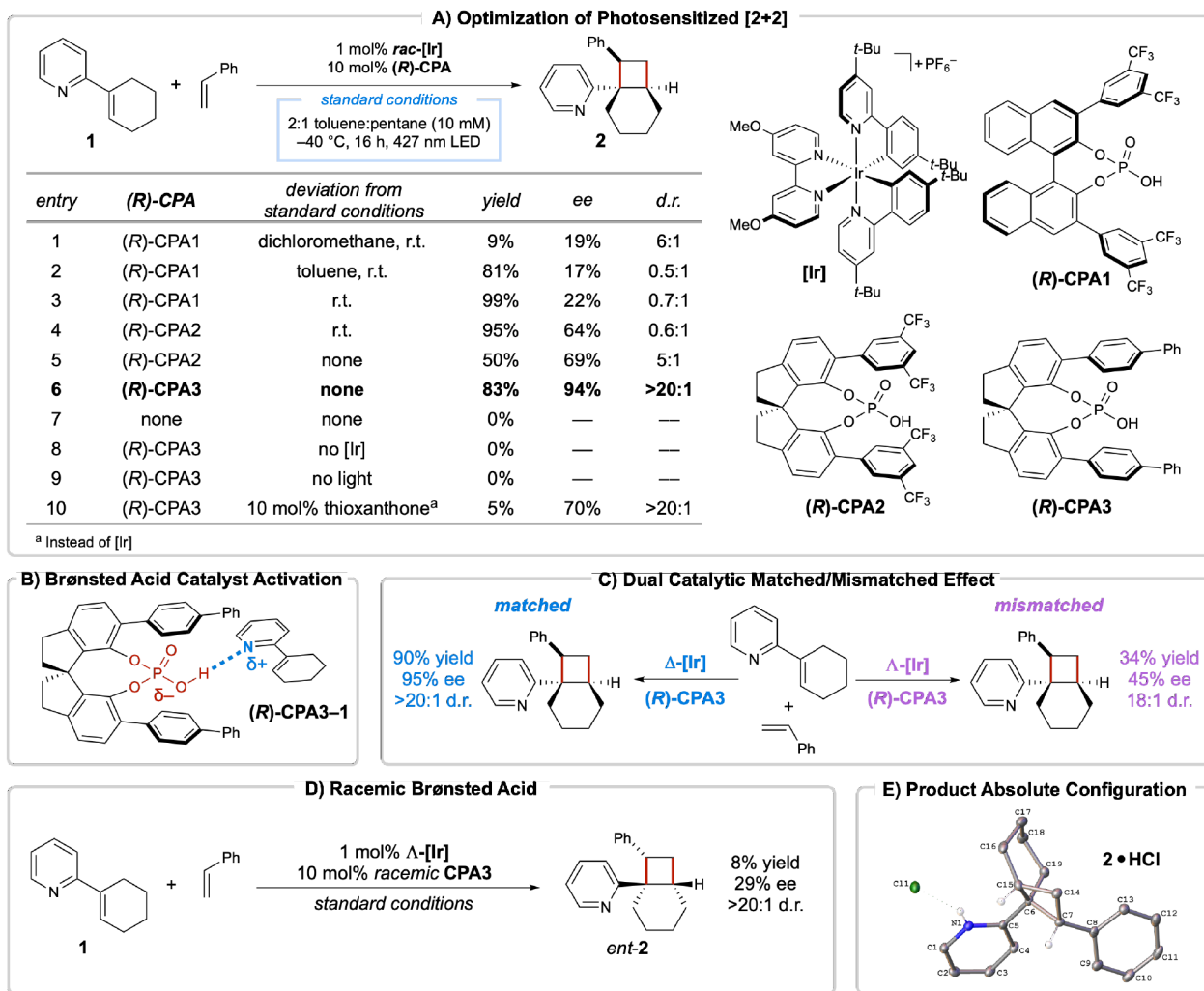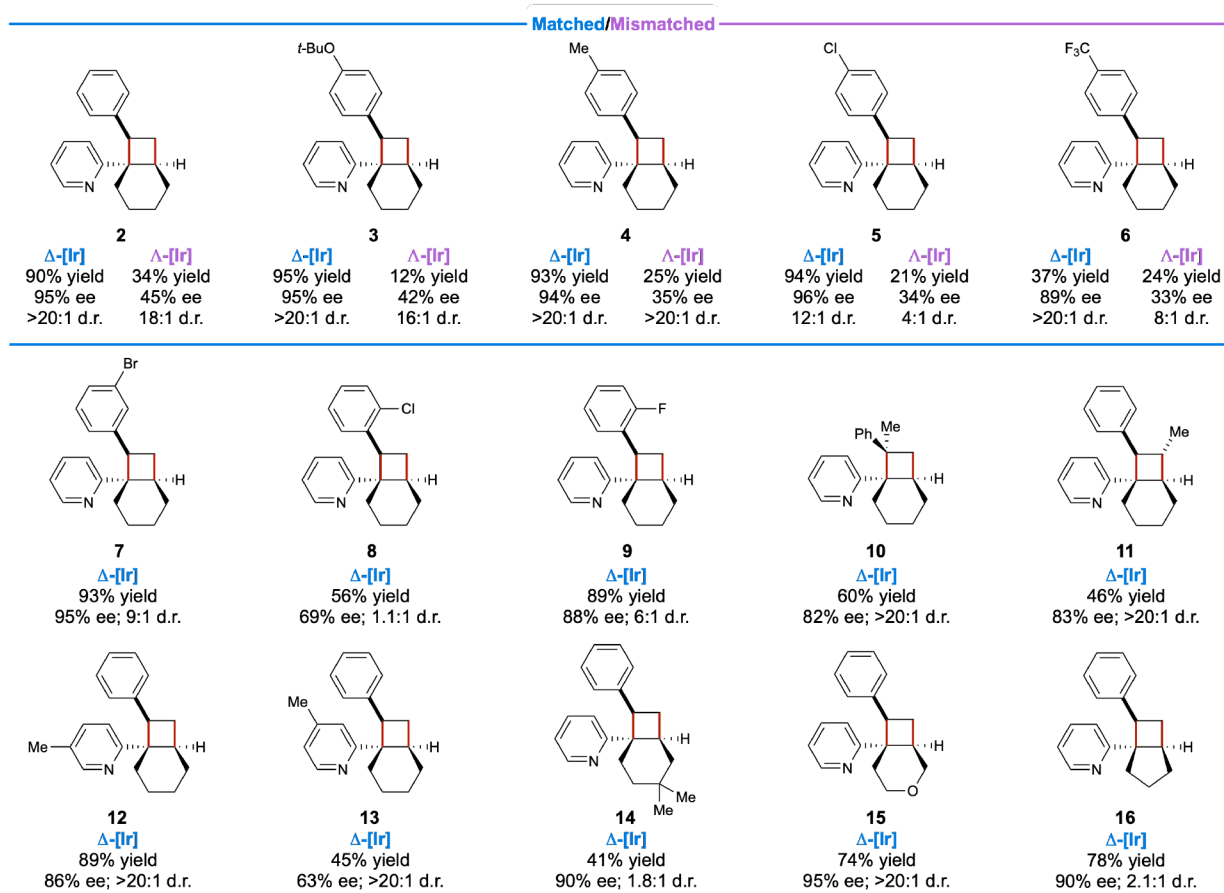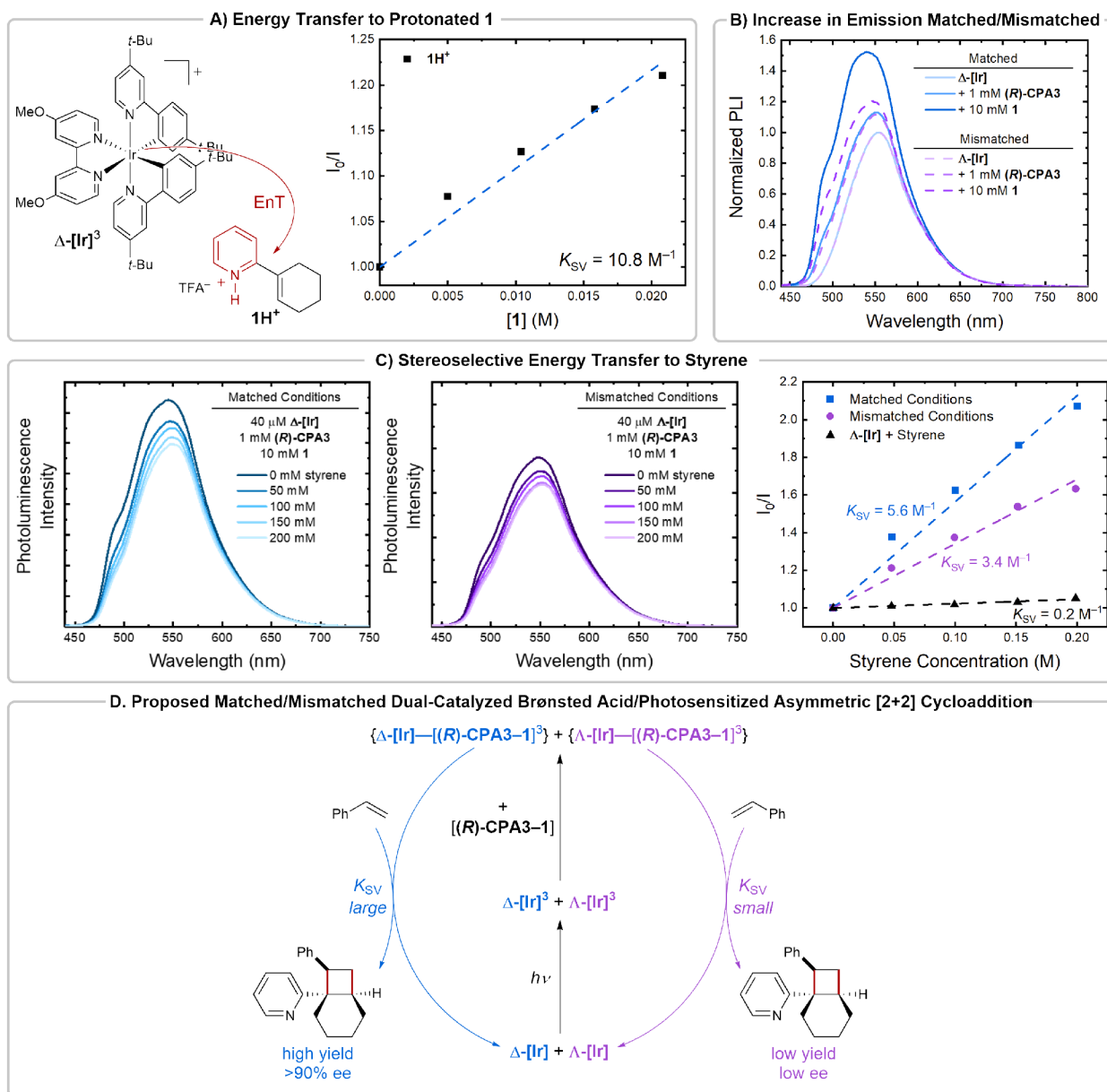
Figure 1.

(A) Matched/mismatched effects observed in fundamental ground-state asymmetric catalysis. (B) Examples of asymmetric dual-catalytic photochemical reactions where chiral transition metal photocatalysts have been used as racemates. (C) Ooi's report showing no dependence of reaction selectivity on the chirality of the [Ir] photocatalyst (ref 8a). (D) This work highlighting cooperative stereoinduction between the [Ir] photocatalyst and the CPA.

Figure 2.
(A) Optimization of the enantioselective [2+2] photocycloaddition of vinyl pyridine **1** using racemic [Ir] as the photocatalyst. (B) Schematic depiction of Brønsted acid activation of **1**. (C) Empirical observation of dual-catalytic matched/mismatched effects in the photocycloaddition of **1**. (D) Highlighting the marked influence of the chiral [Ir] on the selectivity of the reaction. (E) X-ray crystal structure of **2**•HCl.

Figure 3.

Scope of the enantioselective [2+2] photocycloaddition. Conditions matched entry 6 in Figure 2A, 0.31 mmol. Diastereomer ratios (d.r.) were determined by proton nuclear magnetic resonance (^{1}H NMR) analysis of the unpurifed reaction mixture. Enantiomer ratios were determined using chiral supercritical fluid chromatography (SFC) analysis.

Figure 4.
(A) Stern–Volmer plot of the quenching of excited-state Δ-[Ir] with protonated **1** (**1H⁺**). Dashed line is a linear regression of the data. (B) Overlayed emission spectra of Δ-[Ir] (solid lines) and Λ-[Ir] (dashed lines) in the presence of (*R*)-CPA3 and (*R*)-CPA3 with 10 equiv. **1**. With only (*R*)-CPA3 the emission of Δ-[Ir] and Λ-[Ir] nearly overlay, while with both (*R*)-CPA3 and **1** a larger increase in emission is observed for Δ-[Ir]. (C) Quenching of emission of the mixture of Δ/Λ-[Ir], (*R*)-CPA3, and **1** by styrene along with Stern–Volmer plots. (D) Proposed mechanism.