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Enantioselective photochemistry via Lewis acid catalyzed triplet energy transfer

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Abstract

Relatively few catalytic systems are able to control the stereochemistry of electronically excited organic intermediates. Here we report the discovery that a chiral Lewis acid complex can catalyze triplet energy transfer from an electronically excited photosensitizer. This strategy is applied to asymmetric [2+2] photocycloadditions of 2'-hydroxychalcones using tris(bipyridyl) ruthenium(II) as a sensitizer. A variety of electrochemical, computational, and spectroscopic data rule out substrate activation via photoinduced electron transfer and instead support a mechanism in which Lewis acid coordination dramatically lowers the triplet energy of the chalcone substrate. We expect that this approach will enable chemists to more broadly apply their detailed understanding of chiral Lewis acid catalysis to stereocontrol in reactions of electronically excited states.

The ability to control the stereochemistry of organic reactions is a defining characteristic of contemporary synthetic chemistry. Because access to structurally well-defined organic molecules is important for progress in fields of research ranging from drug discovery to materials science, numerous chiral catalysts have been developed to control the enantioselectivity of a wide range of mechanistically diverse organic transformations. Photochemical reactions, however, have long proven to be challenging to conduct in an enantioselective fashion, particularly using substoichiometric stereocontrolling catalysts. (1,2) This represents a fundamental gap in synthetic methodology because the reactivity of electronically excited organic molecules is distinctive and often impossible to replicate using non-photochemical techniques.(3,4)

Recently, a renewed interest in synthetic applications of photoinduced electron transfer(5) has resulted in the development of several strategies for performing highly enantioselective photocatalytic reactions. In general, these protocols have involved the photochemical generation of reactive intermediates using an organic or transition metal photoredox catalyst; subsequently, a second chiral Lewis acid,(6) Brønsted acid,(7,8) or organic catalyst(9,10)

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All authors contributed to the writing and editing of the manuscript.

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then influences the stereochemistry of ensuing reactions and affords highly enantioenriched products. The key bond-forming events in all of these photoredox reactions necessarily occur via photogenerated reactive intermediates in their electronic ground-state configurations. Although photoactivation provides a particularly convenient strategy for the generation of the open-shell radical and radical ion intermediates involved in these reactions, similar reactive intermediates can be generated via a variety of non-photochemical means. (11) Stereochemical control over the distinctive reactivity of excited-state organic intermediates remains a largely unsolved challenge.

The difficulty of controlling electronically excited organic molecules using exogenous chiral catalysts is commonly attributed to their characteristically short lifetimes, which arise from fast unimolecular vibrational and emissive deactivation pathways that are not available to ground-state reactive intermediates. Highly enantioselective catalytic reactions of photoexcited organic substrates have only recently been reported, using either chiral hydrogen-bonding organic sensitizers(12–16) or, more recently, chiral Lewis acid catalysts. (17–20)

We were particularly intrigued by this latter advance because Lewis acid catalysis offers a mature, well-understood platform for asymmetric synthesis. The ability to generalize a chiral Lewis acid strategy for excited state photoreactions would offer a powerful tool for organic photochemistry. Bach's seminal results in this area have demonstrated that chiral oxazaborolidines can be used to mediate asymmetric [2+2] photocycloadditions of enones (17–20) (Figure 1A). These impressive proof-of-principle studies nevertheless rely upon subtle changes in the absorption properties of the substrate that arise upon coordination to a Lewis acid.(21) High levels of enantiomeric excess (ee) are only feasible if the catalyst–substrate complex can be photoexcited preferentially over the unbound, achiral substrate in order to minimize the participation of racemic background reactions. Because this approach requires a delicate balancing of the singlet excited state properties of both the free substrate and the chiral Lewis acid-substrate complex,(22) the range of substrates that have been shown to provide high enantioselectivities to date using Bach's chiral oxazaborolidine strategy has proven to be somewhat narrowly constrained to cyclic enones.

We envisioned an alternative approach in which a chiral Lewis acid would serve as a catalyst for triplet energy transfer from a racemic triplet sensitizer. The coordination of Lewis acids to enones can significantly perturb the energy of their singlet excited states, a phenomenon first documented by Frederick Lewis several decades ago.(23,24) The effect of Lewis acid coordination on triplet energies, to the best of our knowledge, has not been the subject of similarly detailed exploration. We hypothesized that if coordination of a Lewis acid to an enone could produce a bathochromic shift in the energy of its singlet excited state, the same interaction might exert an analogous effect on its triplet state energy as well. If so, it should be possible to design a system in which triplet energy transfer from an appropriate sensitizer would become thermodynamically feasible only when a substrate enone is bound to a chiral Lewis acid co-catalyst (Figure 1B).

In previous work, we have shown that chiral Lewis acids are effective in controlling the stereochemical course of reactions initiated by photoinduced electron transfer from an

electronically excited $\text{Ru}^*(\text{bpy})_3^{2+}$ photocatalyst.(6) Among the most substantial benefits of this two-catalyst strategy is the ability to modify the structure of a chiral Lewis acid for optimal stereocontrol without deleteriously impacting the desirable photophysical properties of the sensitizer. This flexibility opens photochemical synthesis to the wide range of privileged Lewis acid scaffolds known to be highly effective in other enantioselective reactions, and we have subsequently shown that the same strategy can be applied to a number of other reactions exploiting chiral Lewis acid catalyzed photoredox activation. (25,26) We propose that this concept, when applied to the more difficult problem of catalytic energy transfer, can have similarly broad ramifications.

The feasibility of Lewis acid catalyzed triplet energy transfer was initially tested by examining the effect of exogenous Lewis acids on photocatalytic reactions of 2'-hydroxychalcone (**2**) (Table 1). This substrate provides an ideal model system because the 2'-hydroxyaryl ketone moiety is predisposed towards association with a variety of Lewis acidic metals and because the photochemical properties of **2** have been thoroughly characterized. In particular, **2** has been experimentally shown to possess a triplet state 54 kcal/mol higher in energy than its closed-shell singlet ground state.(27) This triplet energy (E_T) is well outside of the range that should be reasonably accessible using $\text{Ru}(\text{bpy})_3^{2+}$ as a triplet sensitizer ($E_T = 46$ kcal/mol).(28) Indeed, an experiment in which **2** and diene **3** were irradiated with visible light in the presence of $\text{Ru}(\text{bpy})_3(\text{PF}_6)_2$ showed minimal evidence of productive photoreaction (entry 1). On the other hand, when the same reaction was conducted in the presence of various oxophilic Lewis acid additives, we were delighted to observe the formation of [2+2] cycloadduct **4** in good to moderate yields (entries 2–5). Control experiments indicated that the cycloaddition occurs only in the presence of both the photocatalyst and Lewis acid co-catalyst, as no cycloadduct is observed when $\text{Ru}(\text{bpy})_3^{2+}$ is omitted or when the reaction is conducted in the dark (entries 6 and 7). Given the strict dependence on the presence of a Lewis acid, we speculated that a highly enantioselective reaction might result from the use of a chiral Lewis acid complex. After investigating several classes of chiral ligands, we were pleased to find that Sc(III) PyBox complexes generally worked well as chiral Lewis acid co-catalysts, and ^tBu-PyBox (**7**) in particular provided promising ee (entries 8–10). Subsequent optimization of standard reaction variables(29) afforded our optimized conditions (entry 11), which produced cyclobutane **4** in high yields and excellent enantioselectivity. Finally, we conducted an experiment using a 2:1 mixture of *E* and *Z* 2'-hydroxychalcone as the substrate and found that the geometry of the alkene had no discernable impact on the stereoselectivity of the reaction, consistent with a stepwise triplet cycloaddition (entry 12).

This reaction represents a rare example of an enantioselective catalytic intermolecular photocycloaddition(16) and, to the best of our knowledge, the only example of a highly enantioselective cycloaddition of an acyclic excited-state enone. Studies exploring the synthetic scope of this transformation are outlined in Figure 2.(30) Variation of the β -aryl moiety of the chalcone is well tolerated. Substrates with *ortho*, *meta*, and *para* substituents on this ring provide excellent ee and good yields (**9–11**). Chalcones with electron-rich β -aryl groups participate in an uncatalyzed background cycloaddition under CFL irradiation, and therefore require irradiation with a monochromatic blue LED ($\lambda_{\text{max}} = 450$ nm) light source

for optimal enantioselectivities (**12–14**).³¹ Heteroaryl groups are also easily accommodated using this method (**14**). Substitution of the hydroxyphenyl moiety is tolerated (**15–16**) so long as this substituent does not interfere with the putative binding site for the chiral Lewis acid. Finally, a range of substituted and unsubstituted dienes also provide high ee's and good yields (**17–19**), and unsymmetrical dienes offer good levels of regioselectivity (**18–19**).

Several lines of evidence support the hypothesis that this transformation involves substrate activation via energy transfer rather than photoredox catalysis. First, Porco has reported that redox activation of 2'-hydroxychalcones affords [4+2] cycloadducts upon reaction with dienes,^(32,33) rather than the [2+2] cycloadducts produced in the photocatalytic protocol we have developed. No traces of similar [4+2] Diels–Alder products were observed under our optimized photocatalytic conditions. We also independently investigated the possibility that this reactivity was the result of redox activation. Electrochemical characterization rules out photocatalytic one-electron oxidation as a mechanism of activation: no oxidation features below +1.60 V vs saturated calomel electrode (SCE) are observable in the cyclic voltammogram of **2**, either in the presence or absence of Sc(OTf)₃, indicating that Ru*(bpy)₃²⁺ is too weak an oxidant (*E_{ox} = +0.77 V) to activate the chalcone substrate this way. We did, however, observe a reduction feature with a half-wave potential of –1.2 V (vs. SCE) in the cyclic voltammogram of **2** that shifts to –0.47 V in the presence of Sc(OTf)₃. Although photoreduction of the Sc•**2** complex by Ru*(bpy)₃²⁺ (*E_{red} = –0.81 V vs. SCE) cannot be ruled out on the basis of these electrochemical data, we found that a variety of substantially less reducing Ru photocatalysts also successfully mediate this cycloaddition. For example, in an experiment replacing Ru(bpy)₃(PF₆)₂ with its much more electron-deficient analogue Ru(deeb)₃(PF₆)₂ (**20**), from which photoreduction of the Sc•**2** complex would be endergonic (*E_{red} = –0.42 V),⁽³⁴⁾ we nevertheless observed formation of cycloadduct **2** in 67% yield and similar enantioselectivity (Figure 3A).

Consistent with these results, attempts to replicate the [2+2] reaction using Sc(OTf)₃ in combination with a range of standard chemical one-electron reductants failed to produce any [2+2] products (Figure 3B). Similar experiments using chemical one-electron oxidants also did not afford any photocycloadducts. On the other hand, if an energy transfer process is indeed relevant to this Lewis acid catalyzed cycloaddition, it should be feasible to promote the reaction using alternative triplet sensitizers. Indeed, when the cycloaddition of 2'-hydroxychalcone **2** and diene **3** was performed under 350 nm irradiation in the presence of benzil (**21**, E_T = ~54 kcal/mol),⁽³⁵⁾ we observed modest yields of the desired [2+2] cycloaddition product but comparable enantioselectivity to the Ru(bpy)₃(PF₆)₂ catalyzed reaction (Figure 3C). Because of the high sensitivity of asymmetric catalysis to changes in mechanism,⁽³⁶⁾ we interpret this result as strong corroborating evidence for Lewis acid catalyzed triplet sensitization as the operative pathway.

Finally, we investigated the hypothesis that the Lewis acid co-catalyst in this energy transfer process serves to lower the triplet energy of the hydroxychalcone substrate. The S₀–T₁ gap for free **2** was computationally investigated (B3LYP/6-311+G(2d,p)). These calculations gave a triplet energy of 51 kcal/mol (Figure 4A), in reasonably good agreement with the reported experimental value of 54 kcal/mol.⁽²⁷⁾ The analogous computation on the Sc(III) complex of **2**, however, suggested that the energy of the lowest optimized triplet state would

be dramatically lowered to 32 kcal/mol.⁽³⁷⁾ This 20 kcal/mol bathochromic shift in triplet energy upon coordination to a Lewis acid would lie easily within a range where triplet energy transfer from Ru*(bpy)₃²⁺ would be exergonic, in good accord with our design plan. The magnitude of the effect suggested by calculation, however, was surprisingly large. To validate these computational results, we next investigated the emissive properties of **2** at near-IR wavelengths corresponding to the predicted triplet energy. In the absence of Sc(OTf)₃, there was no observable emission signal at wavelengths longer than 800 nm. However, when the emission study was conducted in the presence of added Sc(OTf)₃, we observed a feature at 876 nm, corresponding to an excited state energy of 33 kcal/mol, in excellent agreement with the computational prediction (Figure 4B). Moreover, the emission is partially quenched in the presence of oxygen, consistent with emission from a triplet state.

Collectively, these studies reveal a previously unrecognized effect of Lewis acid coordination on the excited states of organic substrates. We have found that complexation of 2'-hydroxychalcones with Sc(III) results in a dramatic decrease in the energy of the triplet state. Current work in our laboratory is aimed at investigating the applicability of this strategy to other Lewis basic organic substrates and other transformations, which we hope will enable a flexible and robust strategy for catalytic enantiocontrol in a broad range of organic triplet-state reactions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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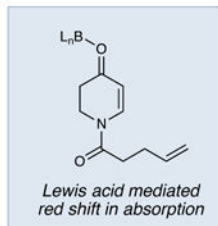
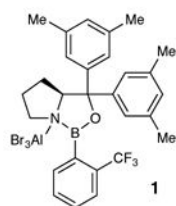
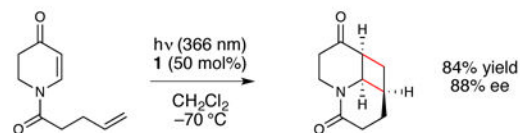
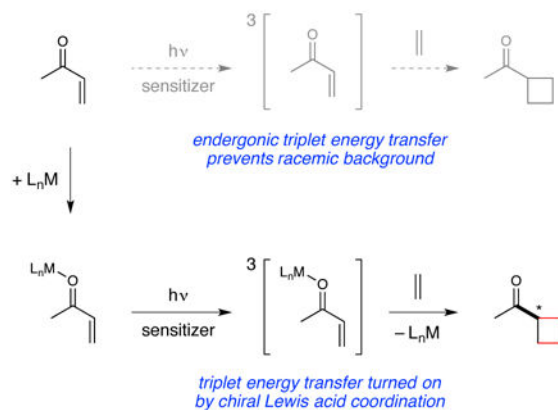
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A Previous work: (Bach, ref 20)**B This work:** Lewis acid catalyzed energy transfer**Figure 1. Enantioselective Catalysis Involving Excited State Organic Intermediates**

(A) Prior example of enantioselective Lewis acid catalyzed photoreaction involving direct photoexcitation of a chiral catalyst–substrate complex. (B) Design plan for Lewis acid catalysis of a triplet sensitization reaction.

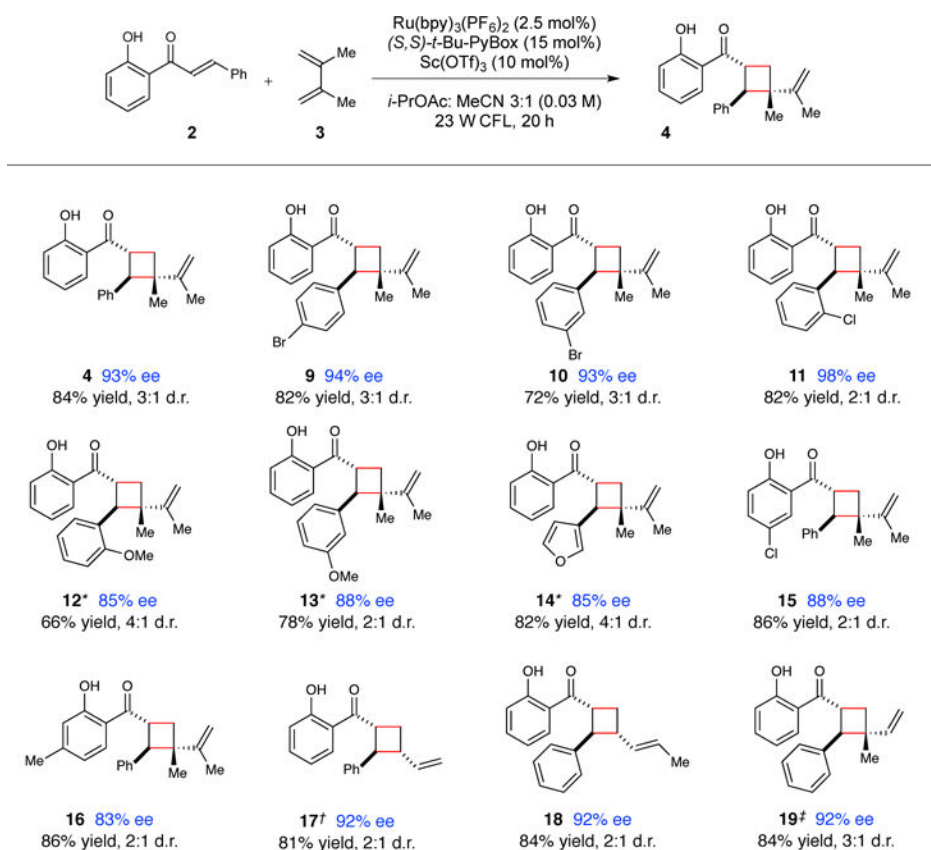


Figure 2. Scope of the enantioselective catalytic [2+2] cycloaddition of 2'-hydroxychalcones
 Data reflect the averaged isolated yields from two reproducible experiments. Diastereomer ratios were determined by ^1H NMR analysis of the unpurified reaction mixture. Enantiomer ratios were determined using chiral SFC or HPLC analysis. See supplementary material for details. *Irradiation was conducted using a blue LED lamp instead of a 23 W CFL bulb, 2 h irradiation time. †40 h irradiation time. ‡Isolated as a 6:1 mixture of regioisomers.

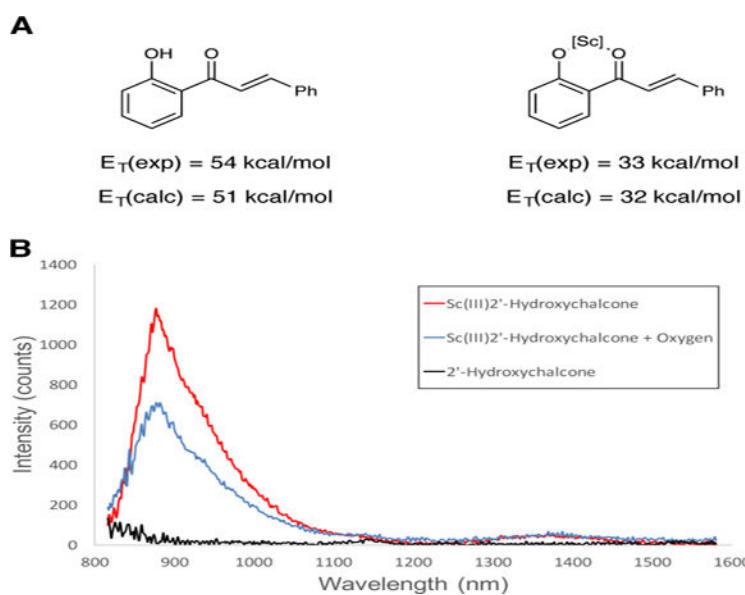
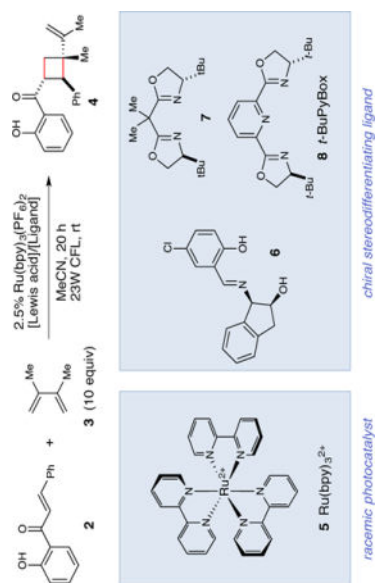


Figure 4. Computational and experimental evidence for a Lewis acid promoted decrease in triplet energy

(A) Experimental and calculated S_0 - T_1 gaps for 2'-hydroxychalcone **2** and its Sc(III) complex. (B) Experimental near-IR emission data for 2'-hydroxychalcone **2** in the absence (black) and presence (red) of Sc(OTf)₃. The emission is partially quenched in the presence of oxygen (blue).

Optimization and control studies for Lewis acid catalyzed enantioselective cycloadditions of 2'-hydroxychalcone.

Table 1



Entry	Lewis acid	Ligand	Note	Yield*	ee [†]
1	none	none	-	<5%	-
2	Al(OTf) ₃ (1 equiv)	none	-	70%	-
3	Ti(OEt) ₄ (1 equiv)	none	-	29%	-
4	Y(OTf) ₃ (1 equiv)	none	-	15%	-
5	Sc(OTf) ₃ (1 equiv)	none	-	88%	-
6	Sc(OTf) ₃ (1 equiv)	none	No Ru(bpy) ₃ (PF ₆) ₂	<5%	-
7	Sc(OTf) ₃ (1 equiv)	none	No light	<5%	-
8	Sc(OTf) ₃ (20 mol%)	6 (30 mol%)	-	52%	0%
9	Sc(OTf) ₃ (20 mol%)	7 (30 mol%)	-	64%	0%
10	Sc(OTf) ₃ (20 mol%)	8 (30 mol%)	-	75%	74%
11	Sc(OTf) ₃ (10 mol%)	8 (15 mol%)	3:1 <i>i</i> -PrOAc:MeCN	80%	93%
12 [‡]	Sc(OTf) ₃ (10 mol%)	8 (15 mol%)	3:1 <i>i</i> -PrOAc:MeCN	89%	93%

* Yields were determined by ¹H NMR using phenanthrene as a calibrated internal standard.

[†] Enantiomer ratios were determined by chiral SFC analysis. rt, room temperature.

[‡] Reaction conducted using a 2:1 ratio of *Z* and *E* 2'-hydroxychalcone as the starting substrate.