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Enantioselective [2+2] Cycloadditions of Cinnamate Esters: Generalizing Lewis Acid Catalysis of Triplet Energy Transfer

Mary Elisabeth Daub,[†] Hoimin Jung,[‡,§] Byung Joo Lee,[†] Joonghee Won,[‡,§] Mu-Hyun Baik,*[,§,‡] and Tehshik P. Yoon*[,†]

[†]Department of Chemistry, University of Wisconsin–Madison, Madison, Wisconsin 53706, United States

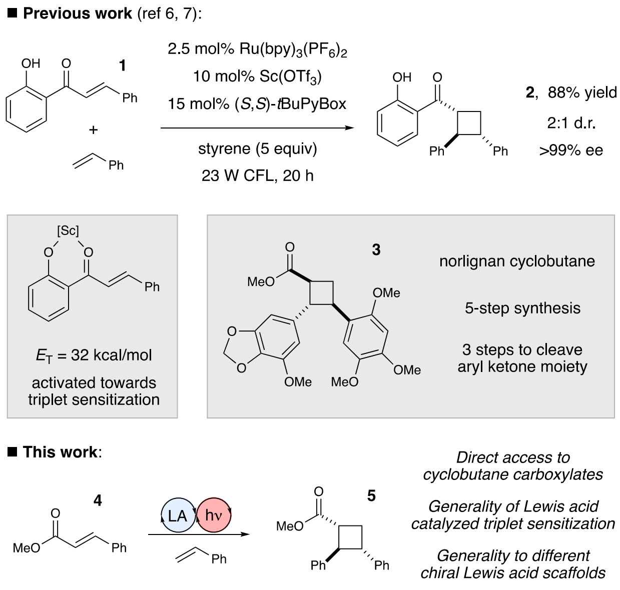
[‡]Department of Chemistry, Korea Advanced Institute of Science and Technology (KAIST), Daejeon 34141, South Korea

[§]Center for Catalytic Hydrocarbon Functionalizations, Institute for Basic Science (IBS), Daejeon 34141, Republic of Korea

ABSTRACT: We report the enantioselective [2+2] cycloaddition of simple cinnamate esters, the products of which are useful synthons for the controlled assembly of cyclobutane natural products. This method utilizes a co-catalytic system in which a chiral Lewis acid accelerates the transfer of triplet energy from an excited-state Ir(III) photocatalyst to the cinnamate ester. Computational evidence indicates that the principal role of the Lewis acid co-catalyst is to lower the absolute energies of the substrate frontier molecular orbitals, leading to greater electronic coupling between the sensitizer and substrate and increasing the rate of the energy transfer event. These results suggest Lewis acids can have multiple beneficial effects on triplet sensitization reactions, impacting both the thermodynamic driving force and kinetics of Dexter energy transfer.

Control over the stereochemistry of photochemical reactions remains a significant challenge in organic synthesis.[1] While the rational development of highly enantioselective thermal reactions benefits from well-understood design principles for the deployment of chiral Lewis acid catalysts,[2] a similarly comprehensive understanding of Lewis acid catalysis in asymmetric photoreactions has yet to be established. Bach has reported the most well-developed chiral Lewis acid strategy in asymmetric photoreactions to date, in which binding of α,β-unsaturated carbonyl compounds to chiral oxazaborolidine catalysts alters their ability to absorb light.[3] Meggers has recently described an analogous approach using a chiral-at-metal Rh Lewis acid catalyst binding to unsaturated *C*-acylimidazoles.[4] One central challenge in asymmetric photochemistry has been the difficulty of suppressing uncatalyzed background processes:[5] any direct photoexcitation of uncoordinated substrates can result in the competitive formation of racemic products. Moreover, all known highly enantioselective excited-state photocycloaddition reactions have involved either cyclic enones or acyclic substrates bearing chelating auxiliary groups. Asymmetric photocycloadditions of simple acyclic compounds such as α,β-unsaturated esters have yet to be achieved with useful selectivities.

Figure 1. Strategies for Lewis acid catalyzed triplet activation

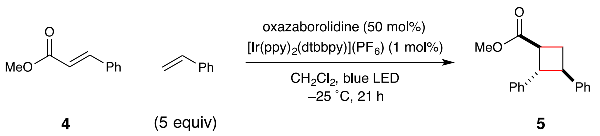


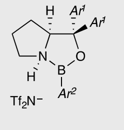
Our group recently described a novel dual-catalyst approach towards highly enantioselective Lewis acid catalyzed [2+2] photocycloadditions (Figure 1).[6,7] These studies showed that the triplet energy of 2′-hydroxychalcone (**1**, E_T = 54 kcal/mol) becomes dramatically lowered upon coordination to a chiral Sc(III) Lewis acid (32 kcal/mol). Racemic background cycloaddition can be avoided by utilizing a Ru(II) sensitizer whose triplet energy (45 kcal/mol) is sufficient to activate the Lewis acid complex but not the free chalcone. This enabled us to develop highly enantioselective Lewis acid catalyzed [2+2] photocycloadditions of 2′-hydroxychalcones with a variety of alkene reaction partners.[8] We highlighted the synthetic utility of this process by completing an enantioselective synthesis of a representative norlignan cyclobutane natural product (**3**).[9]

The use of chelating 2′-hydroxychalcones as substrates is a significant synthetic limitation, as the resulting 2′-phenoxyketones are not common functional groups in cyclobutane-containing natural products and are difficult to manipulate. The asymmetric synthesis of **3**, for example, required only five steps, but three were required to cleave the aryl ketone to the requisite methyl ester.[8] We wondered, therefore, if the concept of Lewis acid catalyzed triplet sensitization might be generalizable to other classes of enone substrates. Simple cinnamate esters would be particularly attractive substrates because their asymmetric intermolecular photocycloadditions would afford a direct route towards the class of chiral cyclobutane natural products that includes **3**.

It was not obvious, however, that Lewis acids would have the same effect on the triplet energies of cinnamate esters as they do on the more extended π system of 2′-hydroxychalcones. Moreover, cinnamate esters cannot participate in the bidentate chelating interactions that are critical for well-organized, highly enantiodifferentiating transition state assemblies with many common classes of chiral Lewis acids, including the transition metal bis(oxazoline) complexes[10] that have been optimal in many of our laboratory's most successful asymmetric photoreactions.[5] Thus, as a strategic consideration in our initial screening process, we focused upon chiral Lewis acids that are known to provide effective enantiocontrol with monodentate carbonyl substrates.

Table 1. Optimization of chiral Lewis acid structure.[a]





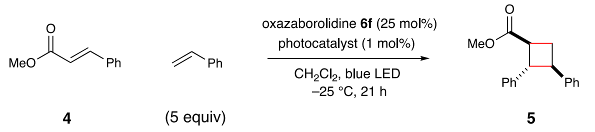
oxazaborolidine catalyst (**6**)

entry	catalyst	Ar^1	Ar^2	yield	d.r.	ee
1	**6a**	Ph	2-MeC_6H_4	82%	2:1	89%
2	**6b**	3,5-$(CF_3)_2C_6H_3$	2-MeC_6H_4	3%	1:1	ND
3	**6c**	3,5-$Me_2C_6H_3$	2-MeC_6H_4	27%	3:1	90%
4	**6d**	3,5-$Me_2C_6H_3$	2-FC_6H_4	75%	4:1	95%
5	**6e**	3,5-$Me_2C_6H_3$	2,4-$F_2C_6H_3$	84%	4:1	97%
6	**6f**	3,5-$Me_2C_6H_3$	2,4,6-$F_3C_6H_2$	92%	6:1	98%

[a] Yields and diastereomer ratios determined by ^{1}H NMR spectroscopy. Enantiomeric excess of the major diastereomer determined by chiral HPLC.

Oxazaborolidine catalysts (**6**) are among the most successful chiral Lewis acids in this class, [11] and Bach[3] and Brown[12] have both reported highly enantioselective cyclobutane syntheses that feature this class of privileged chiral Lewis acids. Indeed, oxazaborolidine **6a** immediately provided promising results; upon irradiation of cinnamate **4** with styrene in the presence of 1 mol% [Ir(ppy)$_2$(dtbbpy)](PF$_6$) and 50 mol% of chiral Lewis acid **6a**, cycloadduct **5** was produced in 89% ee, and 2:1 d.r. (Table 1, entry 1). Modification of the 3,3-aryl substituents had a negative impact on the yield of the cycloaddition, although the 3,5-dimethylphenyl-substituted catalyst appeared to provide a modest improvement in selectivity (entries 2 and 3). Modification of the 1-substituent, on the other hand, had a dramatically positive influence. Replacing the *o*-tolyl group with more electron-deficient *o*-fluorophenyl or 2,4-difluorophenyl substituents led to an increase in both the rate and selectivity of the cycloaddition (entries 4 and 5). The optimal 2,4,6-trifluorophenyl catalyst **6f** affords cycloadduct **5** in 6:1 d.r., and 98% ee under these conditions (entry 6).

Table 2. Optimization of photocatalyst identity.

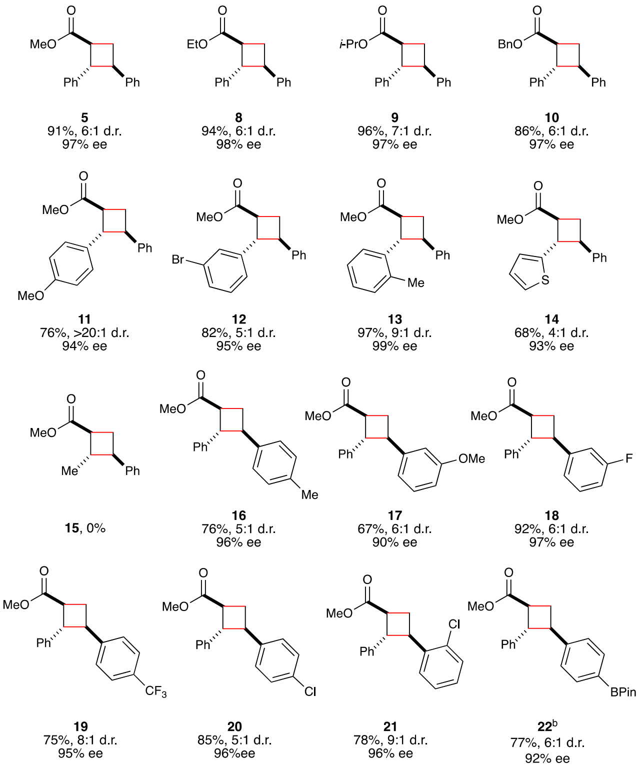


entry	photocatalyst	E_T (kcal/mol)[a]	yield[b]	d.r.[b]	ee
1	$[Ru(bpy)_3](PF_6)_2$ (**7a**)	46	0	–	–
2	$[Ir(dtbppy)_2(dMeObpy)](PF_6)$ (**7b**)	48.6	4	–	–
3	$[Ir(dtbppy)_2(dtbbpy)](PF_6)$ (**7c**)	49.4	7	–	–
4	$[Ir(ppy)_2(dMeObpy)](PF_6)$ (**7d**)	50.6	21	5:1	89%
5	$[Ir(ppy)_2(dtbbpy)](PF_6)$ (**7e**)	51.0	28	4:1	92%
6	$[Ir(Fppy)_2(dtbbpy)](PF_6)$ (**7f**)	53.3	82	6:1	96%
7	$[Ir(dFppy)_2(dtbbpy)](PF_6)$ (**7g**)	57.1	93	6:1	90%
8	$[Ir(dF(CF_3)ppy)_2(dtbbpy)](PF_6)$ (**7h**)	61.0	18	3:1	65%
9	none	–	0	–	–

[a] Values determined from the emission maxima of the photocatalysts (10 μM in CH_2Cl_2) with 410 nm excitation. [b] Yields and diastereomer ratios determined by ^1H NMR spectroscopy. Enantiomeric excess of the major diastereomer determined by chiral HPLC.

A relatively high loading of oxazaborolidine (50 mol%) was required for this optimal enantioselectivity, however; lowering the catalyst loading to 25 mol% resulted in a diminution of selectivity to 4:1 d.r. and 92% ee (Table 2, entry 5). This dependence of product ee upon catalyst loading suggested a competitive racemic background process. We hypothesized that tuning the photocatalyst to minimize direct, Lewis-acid-free sensitization might restore high ee at lower catalyst loading. Indeed, the rate and selectivity of the cycloaddition depend upon the triplet energy of the photocatalyst. $Ru(bpy)_3^{2+}$ (E_T = 46 kcal mol^{-1}) is an ineffective photocatalyst (entry 1). Using photocatalysts of increasing triplet energy, both yield and enantioselectivity increase, reaching optimal enantioselectivity with $[Ir(Fppy)_2(dtbbpy)](PF_6)$ (E_T = 53.3 kcal mol^{-1}) (entry 6). Beyond this point, the yield of cycloadduct continues to increase, but the ee diminishes, suggesting that the rate of formation of racemic cycloadduct by direct sensitization of unbound cinnamate becomes competitive (entry 7). The highest triplet energy photocatalyst investigated, however, afforded lower yield and ee (entry 8). At this point the triplet energy of this photocatalyst surpasses that of styrene (E_T = 60 kcal mol^{-1}), enabling competitive quenching of the photocatalyst and a loss in overall efficiency.

Figure 2. Scope studies for enantioselective [2+2] photocycloadditions of cinnamate esters.[a]



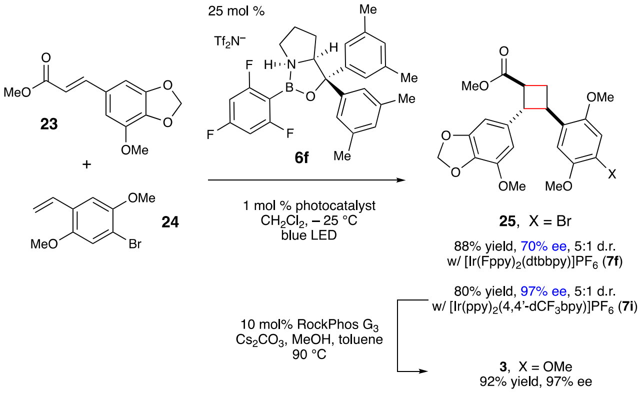
5 91%, 6:1 d.r. 97% ee
8 94%, 6:1 d.r. 98% ee
9 96%, 7:1 d.r. 97% ee
10 86%, 6:1 d.r. 97% ee
11 76%, >20:1 d.r. 94% ee
12 82%, 5:1 d.r. 95% ee
13 97%, 9:1 d.r. 99% ee
14 68%, 4:1 d.r. 93% ee
15, 0%
16 76%, 5:1 d.r. 96% ee
17 67%, 6:1 d.r. 90% ee
18 92%, 6:1 d.r. 97% ee
19 75%, 8:1 d.r. 95% ee
20 85%, 5:1 d.r. 96%ee
21 78%, 9:1 d.r. 96% ee
22[b] 77%, 6:1 d.r. 92% ee

[a] All reactions conducted using 1 equiv of cinnamate ester, 5 equiv of styrene, 25 mol% oxazaborolidine **6f**, 1 mol% photocatalyst **7f**, and irradiating for 24 h unless otherwise noted. Yield values represent the isolated yield of both diastereomers. Diastereomer ratios determined by ^1H NMR. Enantiomeric excess of the major diastereomer determined by chiral HPLC. [b] Reaction irradiated for 76 h.

We next evaluated the scope of the reaction using these optimized reaction conditions (Figure 2). The yield and ee of the cycloaddition are insensitive to the identity of the ester moiety. (**8**–**10**), and cinnamate esters with electronically varied β-aryl substituents are competent substrates (**11**–**13**). Methyl (*E*)-3-(thiophen-2-yl)acrylate was readily transformed to cyclobutane **14**, indicating that heterocycles are tolerated. Methyl crotonate, however, failed to produce any cycloadduct (**15**), consistent with its higher triplet energy.[13] Various electronic substitution patterns on the styrene afforded cycloadducts with similar results (**16**–**21**). As we had observed in the asymmetric [2+2] cycloaddition of 2′-hydroxychalcones, electron-rich *p*-alkoxy-substituted styrenes undergo acid-promoted polymerization faster than the desired cycloaddition. Electron-donating groups at other positions (**17**) and electron-withdrawing substituents at all positions (**18**–**21**), on the other hand, were readily tolerated. The presence of a boronate ester slows the rate of cycloaddition (**22**), but the resulting enantioenriched cycloadduct bears a versatile synthetic handle.[14]

The absolute configuration of the cycloadducts was confirmed through a concise, two-step synthesis of norlignan **3** (Scheme 1). Because 4-alkoxy-substituted styrenes polymerize under the reaction conditions, the cycloaddition was conducted using 4-brominated styrene **23**. Interestingly, the ee of this cycloaddition under standard conditions gave good yields of **25** but disappointingly low stereocontrol (70% ee). We speculated that this might again be a consequence of direct, Lewis-acid-free sensitization; indeed, when the Lewis acid is omitted from this reaction, the racemic cycloadduct is formed in 82% yield. This background process can be minimized by further tuning the photocatalyst. $[Ir(ppy)_2(4,4'\text{-}dCF_3bpy)]PF_6$ (E_T = 39.2 kcal/mol) restores high enantioselectivity, affording cycloadduct **25** in 97% ee. Subsequent Buchwald aryl etherification[15] affords natural product **3** in two steps overall and confirms the absolute stereochemistry of the cycloaddition, which is consistent with standard models for stereoinduction using this class of oxazaborolidine Lewis acids.

Scheme 1. Streamlined synthesis of norlignan **3**.



Several lines of evidence support the formation of triplet-state cinnamate esters through energy transfer from the Ir photocatalyst. Wu and Reiser have independently reported the ability of Ir photocatalysts to sensitize [2+2] cycloadditions of cinnamates via energy transfer, and Wu showed that crossed cycloadditions between triplet-state cinnamates and styrenes are feasible.[16] In contrast, photoinduced electron transfer would generate enone radical anions that are reactive only towards electron-deficient alkenes and produce no product in reactions with simple styrenes.[17] The triplet nature of this reaction is also consistent with the dependence on photocatalyst structure (Table 2). While the yield of the reaction shows a clear relationship to the triplet energy of the photocatalyst used, there is no similar correlation to reduction potential. For instance, photocatalysts **7c** and **7d** have similar excited state reduction potentials but give very different yields, and **7f** provides faster rates than both despite its significantly more positive reduction potential.

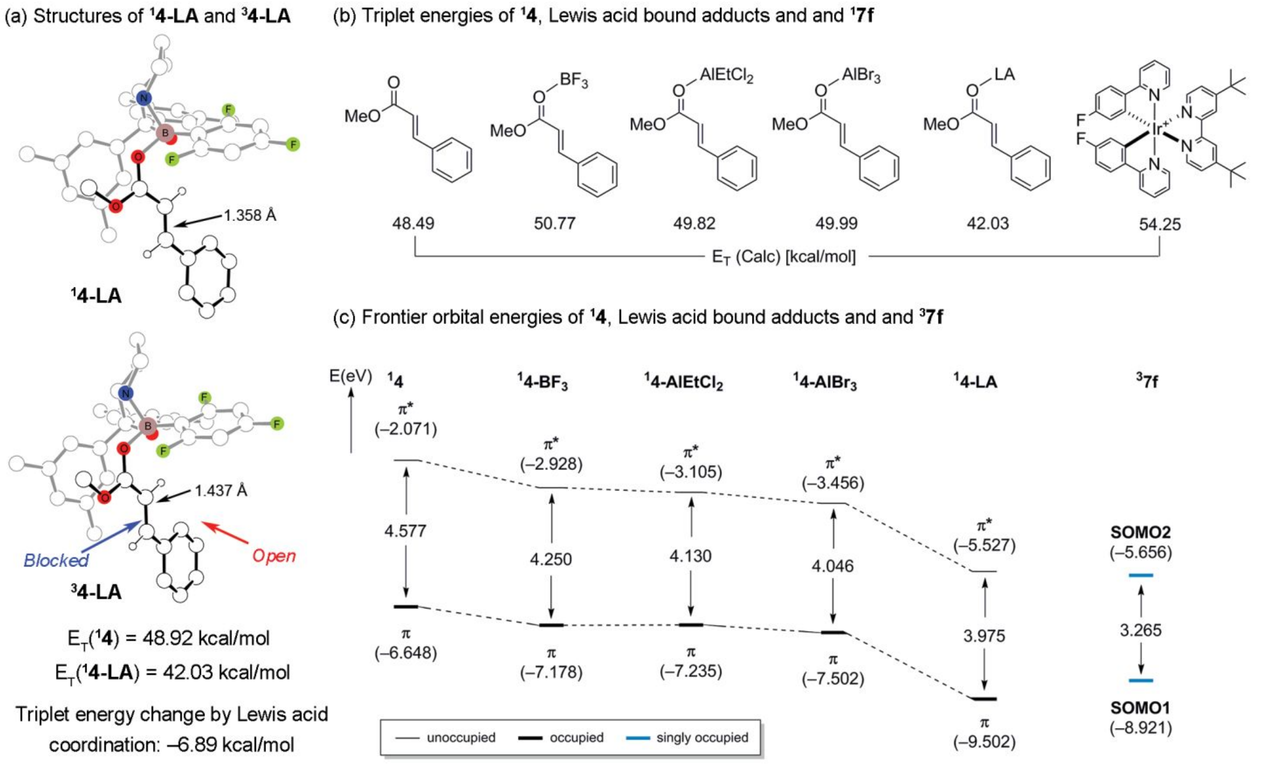


Figure 3. (a) DFT-optimized structures of Lewis acid(**6f**) bound methyl cinnamate **4-LA**. (Bond lengths in Å.) (b) Triplet energies, (c) frontier orbital energies for ^{1}**4**, Lewis acid bound adducts and photocatalyst **7f**. (B3LYP-D3/cc-pVTZ(-f)//B3LYP-D3/LACVP**(ε = 9.08 for CH_2Cl_2)

Density-functional theory (DFT) calculations were carried out to provide a better understanding of the role of the Lewis acid in photocycloaddition (Figure 3). We first evaluated the oxazaborolidine-coordinated methyl cinnamate complex **4-LA**. The optimized structures of its lowest-energy ground-state and triplet complexes (Figure 3a and 3b) are qualitatively similar; thus, facial selectivity in this process can be rationalized using the same empirical model that is generally applied to ground-state reactions using this class of chiral Lewis acids.[11]

We next examined the influence of Lewis on the singlet–triplet gap for **4**. The triplet energy for the methyl cinnamate **4** was calculated to be 48.9 kcal/mol, and this value decreased by 6.9 kcal/mol upon coordination to the oxazaborolidine. The magnitude of this decrease, however, was surprisingly small compared to the ~20 kcal/mol change in the triplet energy of 2′-hydroxycalcone upon activation by $Sc(OTf)_3$.[6] Moreover, triplet energy transfer to the activated cinnamate complex **4–LA** (42.0 kcal/mol) should be thermodynamically feasible from all of the photocatalysts tested, but we observe only trace reaction using Ir catalyst **7f** (53.3 kcal/mol). Finally, coordination of neutral Lewis acids such as $EtAlCl_2$ has negligible impact on the triplet energy of **4** but still catalyzes the racemic photosensitized cycloaddition (see Supporting Information). Thus, in this reaction, Lewis acid catalysis is not attributable primarily to a lowering of triplet energy.

An analysis of the absolute energies of the relevant frontier molecular orbitals (FMOs) was more suggestive (Figure 3C). Dexter energy transfer formally involves the bidirectional exchange of electrons between the FMOs of the triplet donor and acceptor moieties, and thus the rate of energy transfer depends upon the degree of orbital overlap.[18] The π and π* orbital energies of the methyl cinnamate ^{1}**4** were calculated to be –6.65 and –2.07 eV, respectively, whereas the singly occupied molecular orbital (SOMO) energies of ^{3}**7f** were –5.66 and –8.92 eV. However, coordination of methyl cinnamate to a range of Lewis acids results in a significant lowering of its FMO energies, with stronger Lewis acids resulting in a more significant shift. Upon coordination of cationic oxazaborolidine **6f**, the FMOs on methyl cinnamate are nearly isoenergetic with the SOMOs of the triplet photocatalyst. Perturbation theory predicts that the interaction between these two species will increase as the gap between their FMO energies decrease;[19] thus, we expect an increase in the electronic coupling between the donor and acceptor and consequently more efficient triplet energy transfer. Thus, while coordination of the strongly Lewis acidic oxazaborolidine catalyst **6f** exerts a small effect on the stability of triplet cinnamate, we propose that the major effect responsible for the acceleration of the sensitized photoreaction is a Lewis acid mediated increase in electronic coupling between the triplet donor and acceptor. The concept of Lewis-acid-promoted FMO-lowering is well-appreciated in asymmetric catalysis of ground-state reactions.[19b] The insight that it is also relevant in excited-state photochemistry has potentially profound implications to the design of other enantioselective photoreactions.

To summarize, triplet-sensitized [2+2] photocycloadditions of simple cinnamate esters can be conducted in highly enantioselective fashion using chiral oxazaborolidine Lewis acids. Computational evidence suggests that the Lewis acids can accelerate Dexter energy transfer through two different functional roles. They can increase the thermodynamic driving force for energy transfer by stabilizing the triplet state of the organic substrate, and they can also increase the electronic coupling required for Dexter energy transfer by modulating the absolute position of the substrate frontier molecular orbitals. This analysis suggests that the impact of Lewis acids in triplet photoreactions might be quite general, and that chiral Lewis acids might be useful in the design of other photoreactions involving a wider array of simple Lewis basic organic substrates.

ASSOCIATED CONTENT

Supporting Information.

The Supporting Information is available free of charge on the ACS Publications website. Experimental procedures; characterization data; spectra for all new compounds; Cartesian coordinates of all computed structures (PDF)

AUTHOR INFORMATION

Corresponding Author

*Email: tyoon@chem.wisc.edu, mbaik2805@kaist.ac.kr

Notes

ORCID:
Mary Elisabeth Daub:
Hoimin Jung: 0000-0002-3026-6577
Joonghee Won: 0000-0002-2487-8788
Byung Joo Lee: 0000-0002-0078-7865
Mu-Hyun Baik: 0000-0002-8832-8187
Tehshik P. Yoon: 0000-0002-3934-4973

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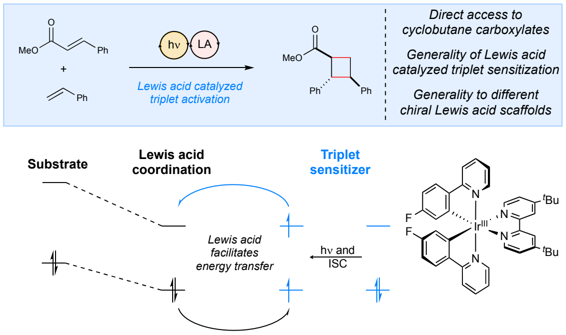
MeO
O
Ph
+
Ph
hν
LA
Lewis acid catalyzed triplet activation
MeO
O
Ph
Ph
Direct access to cyclobutane carboxylates
Generality of Lewis acid catalyzed triplet sensitization
Generality to different chiral Lewis acid scaffolds
Substrate
Lewis acid coordination
Triplet sensitizer
Lewis acid facilitates energy transfer
hν and ISC
F
F
N
N
N
N
Ir^III
ᵗBu
ᵗBu