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Enantioconvergent Radical−Radical Cross-Coupling via Magnesium-Mediated Charge-Transfer Photocatalysis

Lei Yan, Hui-Qing Yang, Wan-Lei Yu, Xu-Gang Zhang, and Peng-Fei Xu*

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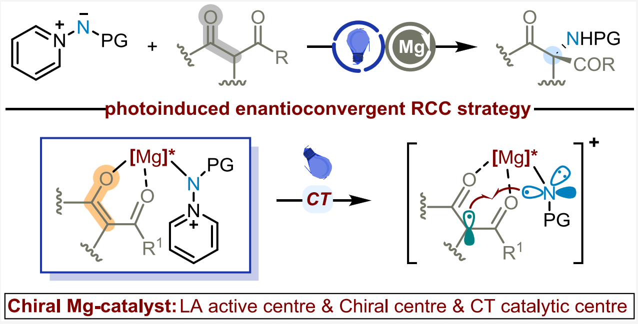

ABSTRACT: Radical asymmetric reactions represent a crucial strategy in asymmetric synthesis, which is characterized by their high reaction efficiency and unique reactivity profiles. Despite significant progress in radical-based asymmetric transformations, the formation of C−N bonds using nonredox metal complexes via the inner-sphere stereocontrol mechanism remains a formidable challenge in the development of novel asymmetric catalytic strategies. This study introduces an innovative and highly efficient asymmetric photochemical bifunctional catalysis that utilizes a combination of magnesium salts and chiral PyBOX-type (pyridine-bisoxazoline) C_2-symmetric ligands under visible light irradiation. This approach enables the selective α-amidation of β-keto esters via an *N*-centered radical mechanism, facilitating the synthesis of substituted β-keto amino acid derivatives with a fully substituted stereocenter. The reaction proceeds in good yields (up to 79%) and excellent enantioselectivity (up to 94%). The catalysis proceeds through the in situ formation of prochiral quaternary charge-transfer complexes, which promote the Lewis acid-supported generation of radicals, thereby mediating the subsequent enantioconvergent radical−radical cross-coupling. Notably, the β-keto ester serves a trifunctional role as a sensitizer, reductant, and radical precursor, while the *N*-protected iminopyridinium ylide functions as both the oxidant and *N*-centered radical precursor. Experimental and computational mechanistic studies corroborate the enantioconvergent radical−radical cross-coupling process.

■ INTRODUCTION

The exploration of novel asymmetric catalytic strategies will significantly contribute to the advancement of chiral pharmaceuticals, chiral agrochemicals, chiral functional materials, and their related applications.[1] Although photocatalysis[2] has garnered significant attention for its ability to form previously inaccessible chemical bonds under mild conditions, achieving asymmetric induction in highly reactive photoexcited species, such as radical ions or radicals, remains a significant challenge.[3] Asymmetric bifunctional catalysis provides an efficient, streamlined, and environmentally sustainable method for achieving high enantioselectivity in photochemical reactions, thereby obviating the need for supplementary photosensitizers.[4] Nonredox metal complexes have emerged as efficient asymmetric photochemical bifunctional catalysts, facilitating both electron transfer and chiral inducement.[5] In these reactions, radical species are typically generated through reactive intermediates formed by the coordination of radical acceptors to chiral metal catalysts. Upon photoexcitation, these intermediates undergo outer-sphere single-electron transfer (SET) with radical precursors (Figure 1A). However, radical−radical cross-coupling (RCC) is affected by the activity of the two different radicals, which makes both cross- and enantioselectivity of the reaction more challenging.

Two primary strategies have been developed to address this challenge in asymmetric photocatalysis using chiral metal catalysts: (a) nonredox metals mediate enantioselective coupling of prochiral radical intermediates with transient free radicals[5d] and (b) redox-active metals undergo sequential oxidative addition reactions with two different free radicals, forming high-valent organometallic complexes that achieve stereochemical control through inner-sphere process.[6] Although existing methods have demonstrated efficient enantiocontrol in RCC reactions, approaches that simultaneously meet the dual requirements of radical generation and asymmetry induction via Lewis acid-catalyzed inner-sphere mechanisms remain underdeveloped. To complement the inner-sphere mechanism of redox metal catalysis, we propose an enantioconvergent photocatalysis strategy. In this system, dual-coordination of reaction intermediates with a chiral Lewis acid catalyst leads to the formation of ordered charge-transfer

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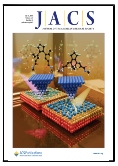

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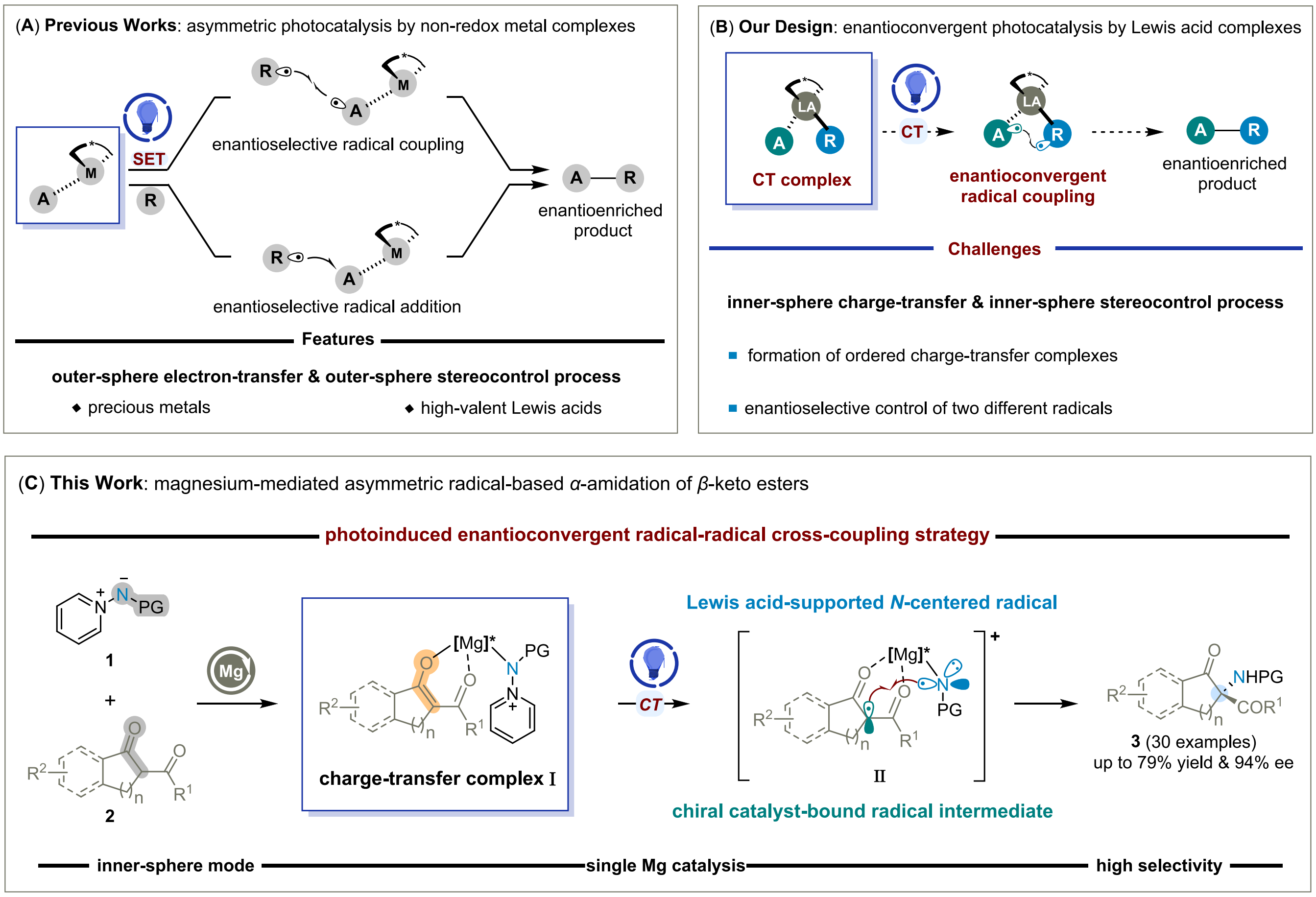
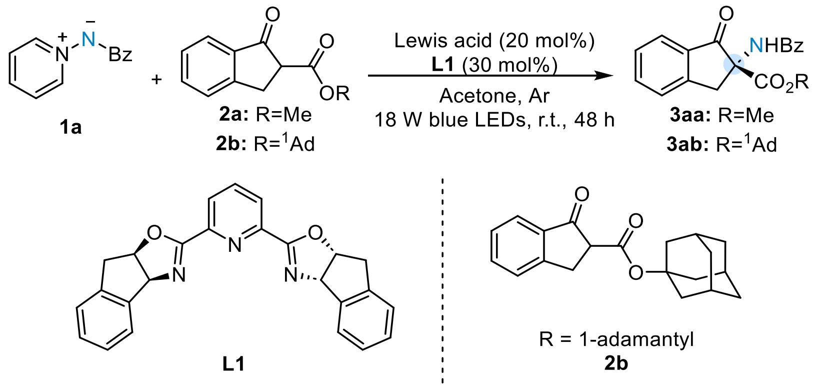


Figure 1. Background and project design. (A) Previous strategies to achieve stereocontrol of radical species in asymmetric photocatalysis by nonredox metal complexes. (B) Overview of our design for enantioconvergent photocatalysis by Lewis acid complexes. (C) Development of radical-based intermolecular amidation through magnesium-enabled enantioconvergent photocatalysis. A = radical acceptor; R = radical precursor; M = nonredox metal catalyst; LA = Lewis acid; CT = charge-transfer.

complexes. Upon photoexcitation, the complexes facilitate charge-transfer, generating metal−supported radical species that can participate in enantioconvergent RCC reactions, provided they remain bound to the chiral catalyst (Figure 1B).

Optically active amino acids, which are prevalent in natural products and pharmaceuticals, exhibit significant biological and medicinal activity.[7] The asymmetric α-amination[8] of β-keto esters provides an efficient and straightforward approach for synthesizing optically active β-keto amino acid derivatives with fully substituted stereocenters, a subject of considerable interest in both synthetic and medicinal chemistry. However, the electronic mismatch between the α-carbonyl carbon of β-keto esters and the amine reactants[9] presents significant challenges in achieving asymmetric α-amination. This process primarily depends on nucleophilic enolate formation of β-keto esters using various chiral catalysts, followed by an enol π-bond attack on *N*-electrophiles (e.g., azodicarboxylates[10] and organonitroso compounds[11]). *N*-protected iminopyridinium ylides have been successfully utilized in heterocyclic synthesis[12] and α-C−H bond activation of pyridines.[13] They have also demonstrated potential as multifunctional substrates in dearomatization of pyridines[14] and bifunctionalization reactions in photochemistry.[15] However, their application in photocatalytic systems for highly stereocontrolled formation of C−N bond[16] has yet to be investigated. Inspired by previous studies on the asymmetric photocatalytic reaction of β-keto esters[17] and the generation of *N*-centered radicals from *N*-protected iminopyridinium ylides,[18] we establish an inner-sphere mechanism for RCC reactions by integrating two coordination modes—carbonyl-directed chiral induction and ylide-enabled *N*-radical stabilization. Due to keto−enol tautomerism, β-keto esters exist in equilibrium with a fraction of enolate species, which can be oxidized through SET.[19] In our design, ylide-Lewis acid adducts,[20] formed from ylides and chiral magnesium/ligand complexes, coordinate with enolates to generate the prochiral quaternary charge-transfer complexes **I**. Upon visible light irradiation, this complex subsequently facilitates charge separation. This process generates Lewis acid-supported *N*-centered radicals and chiral catalyst-bound radical intermediates, which undergo enantioconvergent radical−radical cross-coupling to form chiral α-tertiary amines.[21] This approach effectively suppresses major challenges, such as competitive side reactions of substrate **2** catalyzed by Lewis acid and racemic background reactions. Based on these principles, we have developed a novel asymmetric photocatalysis system, combining the formation of a charge-transfer complex and a dual-coordination strategy, which provides the inner-sphere mode for radical generation and asymmetric induction, thus solving the stereocontrol challenge in the radical-based asymmetric α-amidation of β-keto esters (Figure 1C).

Table 1. Optimization of Reaction Conditions[a]



entry	2	Lewis acid	yield (%)[b]	ee (%)[c]
1	**2a**	$Sc(OTf)_3$	55	5
2	**2a**	$La(OTf)_3$	53	−15
3	**2a**	$Nd(OTf)_3$	56	−17
4	**2a**	$Mg(OTf)_2$	45	52
5[d]	**2a**	$Mg(OTf)_2$	60	58
6[d,e]	**2a**	$Mg(OTf)_2$	76	70
7[d,e]	**2a**	$Mg(acac)_2$	71	1
8[d,e]	**2a**	$Mg(ClO_4)_2\cdot 6H_2O$	79	70
9[d,e]	**2b**	$Mg(ClO_4)_2\cdot 6H_2O$	70	88
10[d,e,f]	**2b**	$Mg(ClO_4)_2\cdot 6H_2O$	70	90
11[d,e,g]	**2b**	$Mg(ClO_4)_2\cdot 6H_2O$	0	--

[a] Unless otherwise noted, all reactions were carried out with **1a** (0.15 mmol), **2** (0.1 mmol), Lewis acid (20 mol %), **L1** (30 mol %) in acetone (2.0 mL) at room temperature (around 25 °C) under Ar atmosphere and 18 W blue LEDs for 48 h. "-" = *ent*-**3aa**. [b] Yield of the isolated products. [c] ee values were determined by chiral HPLC analysis. [d] **1a** (0.1 mmol), **2** (0.15 mmol). [e] Acetone (4.0 mL). [f] 40 °C. [g] Without irradiation at 40 °C.

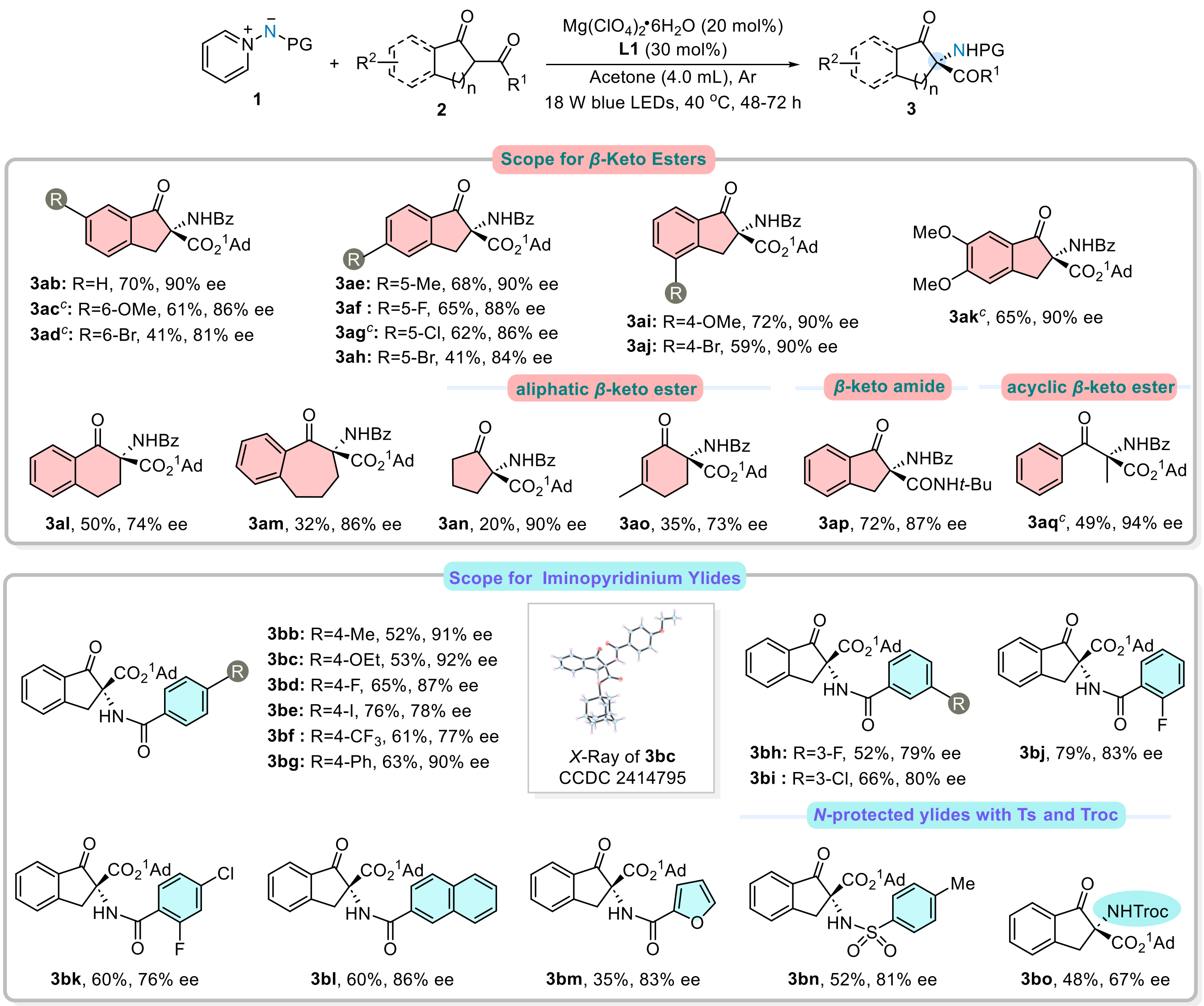
RESULTS AND DISCUSSION

Development of Reaction Conditions. We initially investigated the enantioconvergent RCC reactions between ylide **1a** and *β*-keto ester **2a** using Lewis acid $Sc(OTf)_3$ (20 mol %) in combination with chiral ligand **L1** (30 mol %). Under 18 W blue LEDs (λ_{max} = 460 nm) irradiation in acetone at room temperature, the desired product, **3aa**, was afforded in 55% yield, but with a low enantiomeric excess (ee) 5% (Table 1, entry 1). To improve the enantioselectivity, we explored alternatives to high-valent Lewis acids and found that $Mg(OTf)_2$ gave **3aa** in 45% yield with a more favorable 52% ee, which was considered satisfactory. (Table 1, entries 2−4; see the Supporting Information for details). Attempts to improve enantioselectivity with sterically differentiated chiral ligands and $Mg(OTf)_2$ were unsuccessful (Table S3, see the Supporting Information for details). However, optimizing the substrate ratio and reaction concentration led to significant improvements in both the yield and enantioselectivity (Table 1, entries 5−6). We then examined several other Mg-based Lewis acids to evaluate the anion effect, finding that the anion of Mg-based Lewis acids significantly influenced the enantioselectivity (Table 1, entries 7−8). Substituting the methyl ester (**2a**) with a 1-adamantyl group (**2b**) resulted in a notable increase in enantioselectivity (Table 1, entry 9, 88% ee). Further optimization at 40 °C improved the ee to 90%, with **3ab** isolated in a 70% yield (Table 1, entry 10). Control experiments with model substrates **1a** and **2b** confirmed that the photoreactivity was related to the Lewis acid. No product was formed in the dark (Table 1, entry 11). Additionally, when either $Mg(ClO_4)_2\cdot 6H_2O$ or the $Mg(ClO_4)_2\cdot 6H_2O$/**L1** complex was omitted, the reaction proceeded slowly, yielding racemic **3ab** in 9 and 35% yield, respectively. In the absence of **L1** but with $Mg(ClO_4)_2\cdot 6H_2O$, **3ab** was obtained in 59% yield (Table S8; see the Supporting Information for details). These results, combined with the anion effect studies, confirm that the asymmetric transformation proceeds via a photochemical mechanism facilitated by the chiral magnesium(II) complex.

Substrate Scope. With the optimized conditions established, we next explored the substrate scope of the enantioconvergent RCC reactions, as shown in Scheme 1. A variety of *β*-keto esters **2** with different substituents and steric hindrance successfully reacted with ylide **1a**. For *β*-keto esters derived from 1-indanone, a substrate without substituents at C6 positions of the aryl ring had less impact on the reaction compared to those with substituents (**3ab-3ad**). Both electron-donating and electron-withdrawing groups at the C5 positions were well tolerated, producing products **3ae-3ah** with enantioselectivity ranging from 84 to 90% ee. Modifying the electronic properties of the aryl ring did not hinder the reaction, and enantioselectivities were generally higher at the C4 position than at C6. Products **3ai** and **3aj** achieved 90% ee. Substituents at both the C5 and C6 positions resulted in product **3ak** with 90% ee. The reaction also proceeded efficiently with six- and seven-membered bicyclic *β*-keto esters and aliphatic cyclic *β*-keto ester (**2l-2o**), yielding products **3al-3ao** in 20−50% yields with ee values ranging from 73 to 90%. Notably, a substrate containing an amide group was converted to product **3ap** with 72% yield and 87% ee. The reaction was also effective with acyclic *β*-keto esters, yielding product **3aq** with an impressive 94% ee. These results demonstrate broad substrate compatibility and excellent stereoselectivity.

Next, we examined the effect of different *N*-protected iminopyridinium ylides **1** with various substituents. Ylides **1b**

Scheme 1. Substrate Scope of the Enantioconvergent RCC Reactions[a,b]



[a]Unless otherwise noted, all reactions are conducted with **1** (0.1 mmol), **2** (0.15 mmol), $Mg(ClO_4)_2·6H_2O$ (20 mol %), **L1** (30 mol %), Acetone (4.0 mL), and 18 W blue LEDs at 40 °C under Ar atmosphere for 48 h. [b]Yield of isolated product; ee values were determined by chiral HPLC analysis. [c]72 h.

and **1c**, bearing electron-donating groups (methyl and ethoxy) at the *para*-position, were well tolerated, yielding products **3bb** and **3bc** in good yields (52 and 53%) with excellent enantioselectivities (91 and 92% ee). Ylides **1d**−**1g**, containing electron-withdrawing groups (e.g., F, I, and CF_3) and a phenyl substituent, also exhibited good enantioselectivities (77−90% ee), though yield was slightly reduced. Adjusting substitution at the *meta*-positions affected both reaction efficiency and enantioselectivity, with products **3bh** and **3bi** obtained in good yields (52 and 66%) and enantioselectivities of 79 and 80% ee, respectively. Enantioselectivity was most sensitive to the substituents near the carbonyl group. Nevertheless, the fluorine-substituted substrate **1j** reacted smoothly, yielding product **3bj** with 83% ee. A dihalogenated benzene ring also provided product **3bk** in 60% yield with 76% ee. Additionally, ylides **1l** (2-naphthalene) and **1m** (furan) gave products with good enantioselectivities (86 and 83% ee, respectively). Other protecting groups, such as sulfonamide and carbamate, were successfully incorporated, yielding products **3bn** and **3bo** with enantioselectivities of 81 and 67% ee. The absolute configuration of compound **3bc** was confirmed by X-ray crystallography.

Mechanistic Studies. To investigate the reaction mechanism, we conducted a series of experiments (Figure 2). First, the formation of **3ab** was completely inhibited in the presence of 3.0 equiv of the radical inhibitor 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), and the TEMPO-adduct was detected by HRMS, confirming the involvement of *α*-carbonyl radical intermediates (Figure 2A). Further, radical trapping experiments with highly reactive *N*-containing intermediates showed that the addition of 1,1-diphenylethylene to the model reaction decreased the yield of **3ab**, isolating product **4** in 19%. This result suggests the formation of an *N*-centered radical species rather than a nitrene radical anion (Figure 2B).[22] When compound **5** was used instead of **1a**, only trace amounts of **3ab** were produced. However, the enantioselectivity (59% ee) observed with the photocatalyst *fac*-$Ir(ppy)_3$ suggests competitive pathways: (i) outer-sphere stereocontrolled trapping[23]

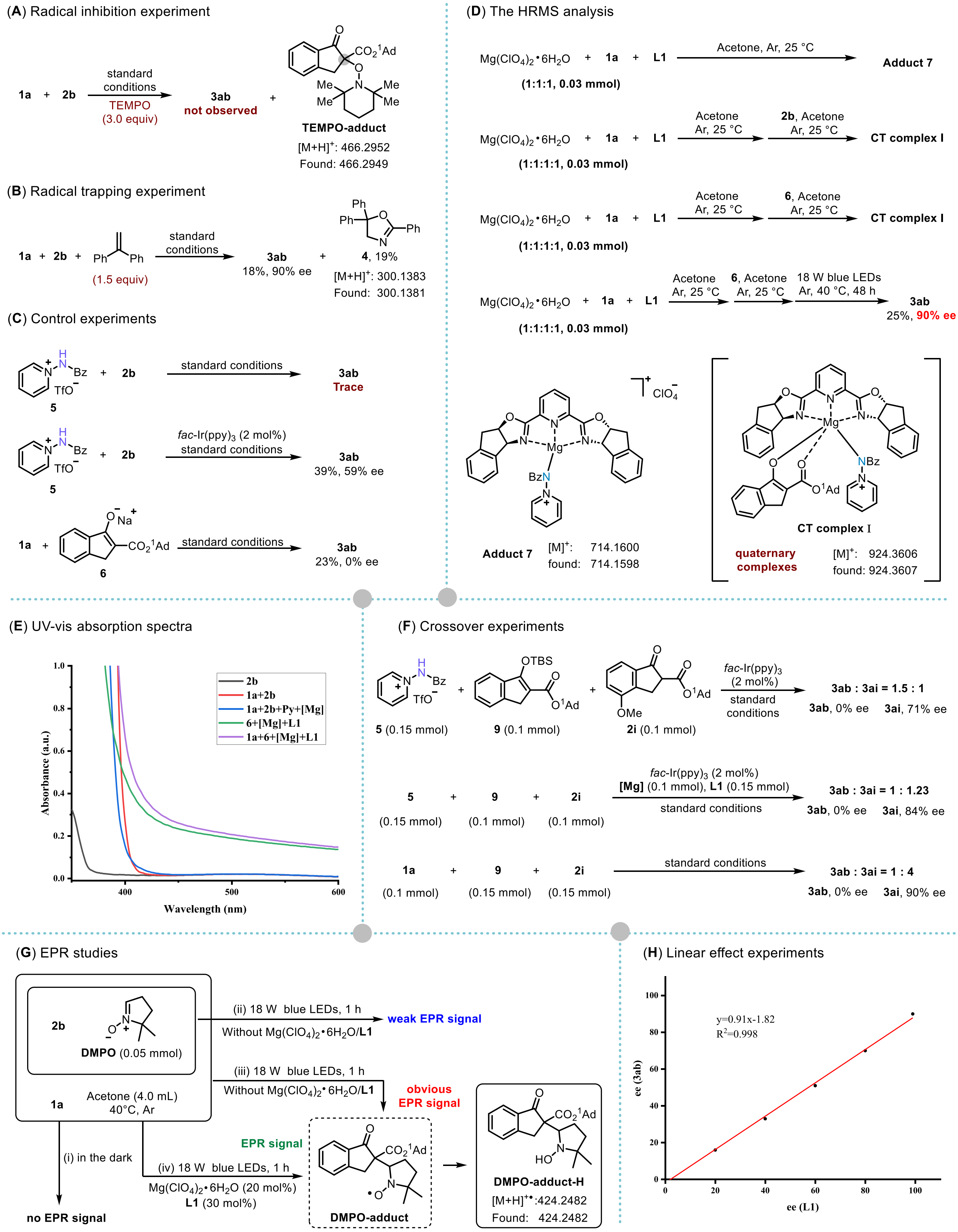
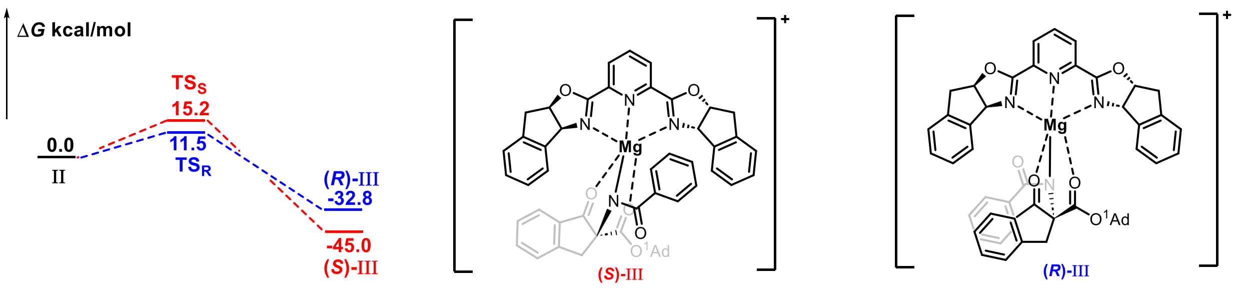


Figure 2. Mechanistic studies.

(**A**) Energy profiles calculated for the enantioselectivity-determining process.



(**B**) Proposed reaction pathway

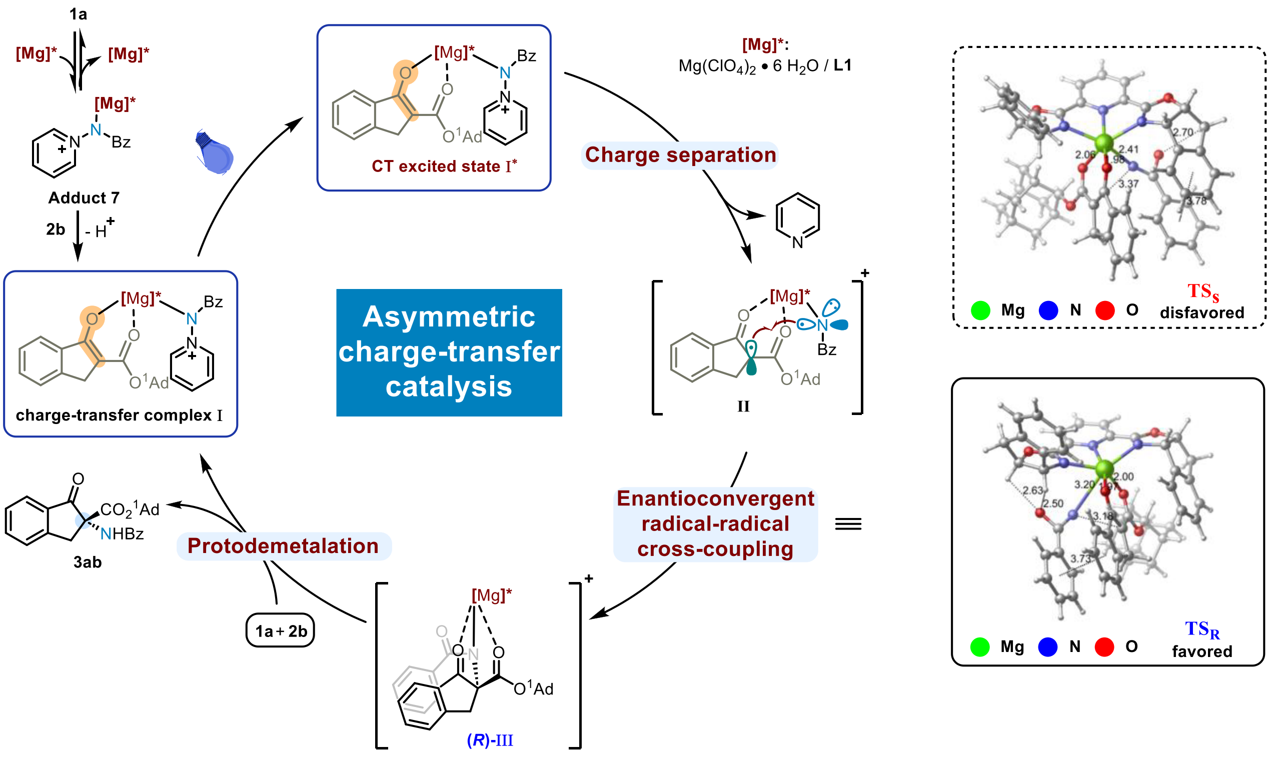


Figure 3. Mechanistic studies. (**A**) Energy profiles calculated for the enantioselectivity-determining process. (**B**) Proposed reaction pathway.

of free *N*-centered radicals by chiral Mg-enolate complexes and (ii) nonselective background reactions between free *N*-centered radicals and free enolates. This highlights the critical role of an inner-sphere mechanism, which stabilizes two different radicals within the chiral Mg coordination sphere, thereby suppressing nonselective background reactions (see the Supporting Information, Section 6.3). Substituting **6** for **2b** resulted in the formation of **3ab** without any enantioselectivity, and the coordination constraints caused by solubility make **6** preclude its participation in the inner-sphere catalytic cycle (Figure 2C). Further HRMS studies detected the ylide-Lewis acid adduct 7 in a mixture of $Mg(ClO_4)_2{\cdot}6H_2O$, **L1**, and **1a**, as well as the prochiral quaternary complexes in a mixture of $Mg(ClO_4)_2{\cdot}6H_2O$, **L1**, **1a**, and **2b**. Interestingly, an ordered charge-transfer complex, formed by further coordination of **6** with the ylide-Lewis acid adduct 7, was identified in a mixture of $Mg(ClO_4)_2{\cdot}6H_2O$, **L1**, **1a**, and **6**. This complex produced **3ab** with 90% ee upon 18 W blue LEDs irradiation (Figure 2D). These results suggest the formation of short-lived prochiral quaternary complexes during the reaction. When Mg-salt and ligand **L1** were added to a mixture of **1a** and **6**, we observed a bathochromic shift. This key finding confirms the formation of prochiral quaternary charge-transfer complexes (Figure 2E). The crossover experiments unequivocally demonstrate that simultaneous coordination of both the enolate and ylide to the chiral magnesium catalyst is essential for achieving high enantioselectivity (Figure 2F). The observed chemical shift perturbations in the NMR spectra provide robust evidence for the formation and structural evolution of the proposed Mg-coordinated quaternary complex (see the Supporting Information, Section 6.7). Cyclic voltammetry studies showed that $Mg(ClO_4)_2{\cdot}6H_2O$ enhances the oxidizing capacity of **1a**, while DBU increases the reducing capacity of **2b**, suggesting a Lewis acid-mediated charge-transfer photocatalysis between **1a** and enolate (see the Supporting Information, Section 6.5).

Electron paramagnetic resonance (EPR) studies were conducted using 5,5-dimethyl-1-pyrroline *N*-oxide (DMPO) as a radical spin-trapping agent. After adding 0.05 mmol of DMPO and irradiating with blue LEDs for 1 h, a sextet signal appeared, and no signal was observed in the absence of light, confirming that light is essential for the reaction (Figure 2G). The EPR signal (g = 2.0074, A_N = 14.01 G, and A_H = 24.14 G) indicated the formation of a *C*-centered radical, generated by photoinduced charge separation of the enolate, triggered by **1a**. This was further confirmed by the detection of the DMPO-adduct-H product via HRMS. The ligand exchange between **2b** and magnesium, conclusively demonstrated in the EPR experiments, is crucial for the formation of charge-transfer complexes as well as for the inner-sphere mechanism (see Supporting Information for details, Section 6.8).

Linear effects experiments revealed that only a single molecule of the chiral magnesium catalyst is involved in the stereocontrolled bond-forming step (Figure 2H). Density functional theory (DFT) calculations indicated the possibility that intermediate **II** undergoes enantioconvergent radical−radical cross-coupling via the $\mathbf{TS_R}$ transition state with a free energy barrier of 11.5 kcal/mol. In contrast, an alternative pathway via the $\mathbf{TS_S}$ transition state has a higher free energy barrier of 15.2 kcal/mol (Figure 3A, see the Supporting Information, Section 8). The lowest-energy pathway involves a combination of $\pi-\pi$ stacking, hydrogen bonding, and steric effects. This accounts for the observed 3.7 kcal/mol barrier difference and the experimentally observed enantioselectivity of 90% ee (Table 1, entry 10). The predicted configuration of (*R*)-**3ab** aligns with the experimental outcome.

Mechanism Proposal. Based on experimental results, computational evidence, and relevant literature,[24] we propose the following catalytic cycle for magnesium-mediated asymmetric charge-transfer photocatalysis (Figure 3B). The *N*-protected iminopyridinium ylide **1a** is activated by the $Mg(ClO_4)_2·6H_2O$/**L1** complex, leading to the formation of the ylide-Lewis acid adduct **7**. This adduct then coordinates with β-keto ester **2b**, forming the prochiral quaternary charge-transfer complex **I**. Upon visible light irradiation, this complex **I**, which was converted into the excited state **I***, enables efficient light absorption and subsequent charge separation to generate a chiral catalyst-bound α-carbonyl carbon radical and a Lewis acid-supported *N*-centered radical with pyridine. The resulting radical intermediates **II** undergo enantioconvergent radical−radical cross-coupling, forming intermediate **(*R*)-III**. This intermediate then undergoes protodemetalation to release the desired chiral product **3ab**, thereby regenerating the $Mg(ClO_4)_2·6H_2O$/**L1** complex, which can initiate a new catalytic cycle.

CONCLUSIONS

We have developed a novel magnesium-mediated charge-transfer photocatalysis that enables the previously inaccessible radical-based asymmetric α-amidation of β-keto esters. Through a combination of control experiments and computational studies, we demonstrated that the key to this strategy lies in the sequential coordination of the chiral Lewis acid magnesium catalyst with the iminopyridinium ylide and enolate. This coordination allows the magnesium complex to serve as both the exclusive source of chirality and as the charge-transfer catalytic and Lewis acid active center, providing a dual-coordination strategy to address the long-standing challenge of controlling cross- and enantioselectivity in nonredox metal-catalyzed RCC reactions. The protocol exhibits broad substrate applicability and good functional group tolerance, facilitating the synthesis of substituted quaternary β-keto amino acid derivatives. We believe that this pioneering asymmetric catalytic system combining magnesium, an earth-abundant metal, as an efficient asymmetric photochemical bifunctional catalyst with a multifunctional substrate-interacting framework will lay a strong foundation for future research in asymmetric photocatalysis involving magnesium, iminopyridinium ylides, and β-keto esters.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.5c03154.

> Experimental procedures, characterization data, NMR spectra for all compounds, and crystallographic data (PDF)

Accession Codes

Deposition Number 2414795 contains the supporting crystallographic data for this paper. These data can be obtained free of charge via the joint Cambridge Crystallographic Data Centre (CCDC) and Fachinformationszentrum Karlsruhe Access Structures service.

AUTHOR INFORMATION

Corresponding Author

Peng-Fei Xu − *State Key Laboratory of Applied Organic Chemistry, College of Chemistry and Chemical Engineering, Lanzhou University, Lanzhou 730000, China; State Key Laboratory for Animal Disease Control and Prevention, College of Veterinary Medicine, Lanzhou University, Lanzhou 730000, China*; orcid.org/0000-0002-5746-758X; Email: xupf@lzu.edu.cn

Authors

Lei Yan − *State Key Laboratory of Applied Organic Chemistry, College of Chemistry and Chemical Engineering, Lanzhou University, Lanzhou 730000, China*

Hui-Qing Yang − *School of Artificial Intelligence and Big Data, Henan University of Technology, Zhengzhou 450001, China*

Wan-Lei Yu − *State Key Laboratory of Applied Organic Chemistry, College of Chemistry and Chemical Engineering, Lanzhou University, Lanzhou 730000, China*

Xu-Gang Zhang − *State Key Laboratory for Animal Disease Control and Prevention, College of Veterinary Medicine, Lanzhou University, Lanzhou 730000, China*

Complete contact information is available at: https://pubs.acs.org/10.1021/jacs.5c03154

Notes

The authors declare no competing financial interest.

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