Strategies for radical-radical cross coupling

Literature seminar #1

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11/20/2025

Contents

Background of radical-radical cross coupling

Radical-radical coupling
poor chemoselectivity

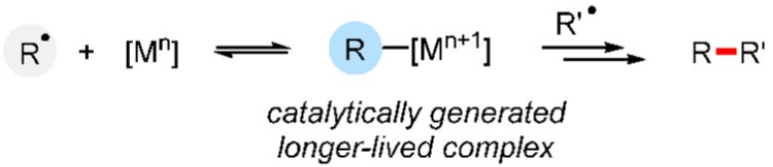
- Efficient and straightforward approach
- However, because the activation barrier for radical–radical coupling is very low, the reaction occurs extremely fast and is often diffusion-controlled.

— Once two radicals meet, they react almost instantaneously.

➢ Various strategies need to be considered to control cross radical–radical coupling reactions.

Conventional Strategies to control radical-radical cross coupling

(a) Trapping with a transition-metal and subsequent cross-coupling



1. Transition-Metal Catalysis

- Transient radicals form complexes with a transition metal, generating longer-lived organometallic intermediates.
- These intermediates then undergo C–C bond formation via reductive elimination in a radical/transition-metal crossover process.

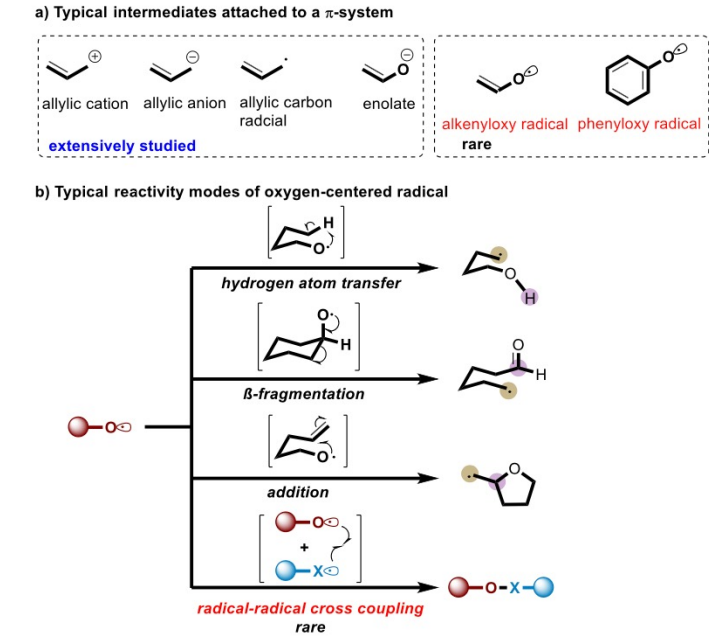
➢ These methods do not achieve genuine radical–radical coupling.

➢ Metal-free strategies for radical–radical cross-coupling are being explored.

Contents

Reactivity of Alkenyloxy Radicals and Challenges

Scheme 1. Oxygen-Centered Radicals and Enol Ester Synthesis



- Limited Use of Alkenyloxy Radicals due to:
  - High oxidation power
  - Strong electrophilicity
  - ➢ Most studies remain spectroscopic mechanistic, not synthetic.
- O-radicals generally undergo a few elementary reactions:
  - Hydrogen atom transfer (HAT) — dominant pathway
  - β-fragmentation
  - Addition to unsaturated bonds
  - Radical–radical coupling (mostly limited to N–O bond)
  - ➢ Cross-coupling involving O radicals (O–O or O–C/O–X) is extremely challenging.

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Strategies to control cross radical-radical coupling -PRE-

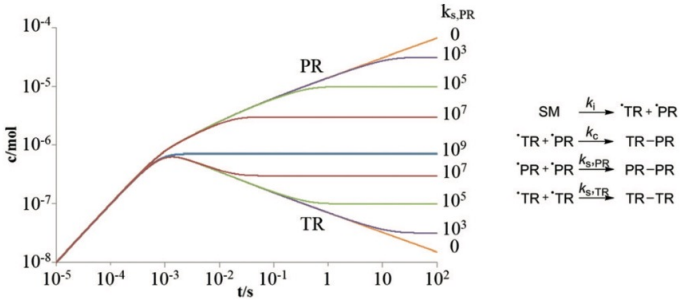

Figure 2. Simulation of dynamic systems obeying the principle of the PRE. Both radicals PR and TR are continuously generated at equal rates ($k_i = 10^{-3}\ s^{-1}$). The rate constant for the self-reaction of the persistent radical was varied ($2k_{s,PR} = 0$, 10^3, 10^5, 10^7, and $10^9\ M^{-1}\ s^{-1}$).

Angew. Chem. Int. Ed. **2020**, 59, 74-108

- Radicals are categorized by lifetime:

- Transient radicals (short-lived)
- Persistent radicals (long-lived)

- Selective Cross-Coupling is governed by the Persistent Radical Effect (PRE)

  - Persistent radical + transient radical
  - Both generated at similar rates

  → Lifetime differences lead to large concentration differences

  → high cross-selectivity

- Current Limitation
- Very few persistent radicals are known, while transient radicals are abundant.
- → This severely limits the synthetic scope of radical/radical cross-coupling.

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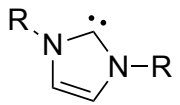
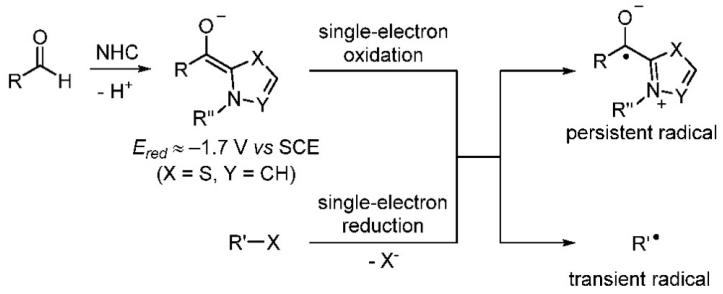
Strategies to generate ”Persistent Radical” –NHC Catalysis-



NHC (N-Heterocyclic Carbene)

Scheme 3. NHC-Derived Ketyl Radicals Generated via Single-Electron Oxidation of Breslow-Type Intermediates with Oxidizing C-Radical Precursors



J. Am. Chem. Soc. 2019, 141, 2, 1109–1117

- ❑ Redox Properties
  - Breslow intermediates and their enolates have relatively low oxidation potentials

→ Can be readily converted to Breslow Intermediate Radicals (BIRs) via easy SET process

→ They function as a new class of persistent radicals

  - Their persistence arises from the bulky NHC framework and stabilizing ketyl electronic structure.

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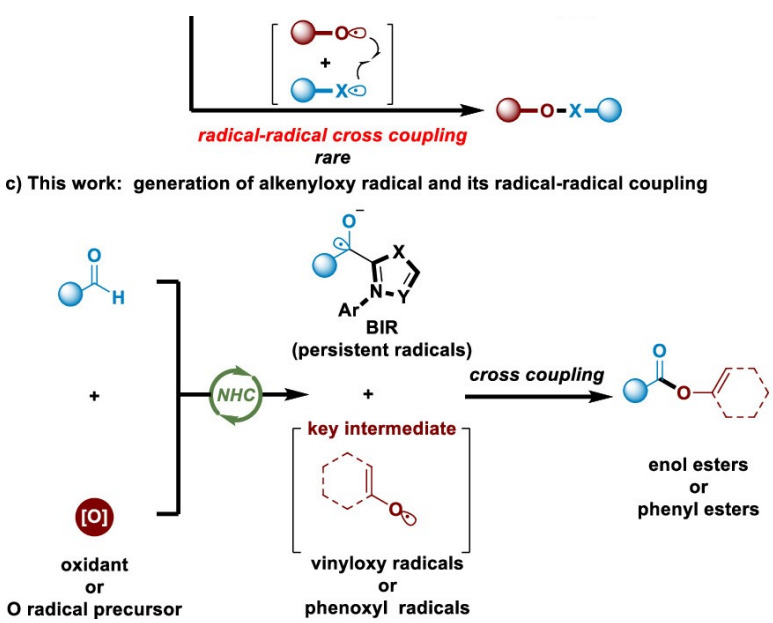
NHC & Breslow Intermediate: Gateway to Radical Reactions



- Breslow Intermediate Radicals (BIRs) readily couple with various radicals such as carbon- and sulfur-centered radicals.
- → If BIR can capture reactive oxygen radicals, then alkenyloxy radicals might also be engaged in controlled radical coupling.

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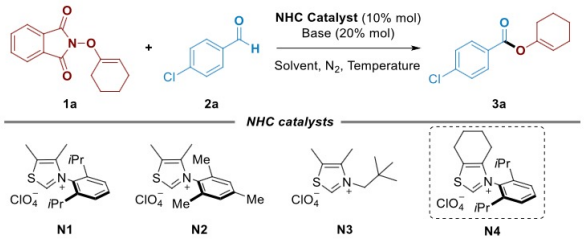
Screening of NHC catalysts

Table 1. Screening the Reaction Conditions[a]



entry	NHC catalyst	base	solvents	yield (3a)[b]
1	N1	Cs_2CO_3	DMF	6%[c]
2	N1	Cs_2CO_3	DMF	12%
3	N2, N3	Cs_2CO_3	DMF	NR
4	N4	Cs_2CO_3	DMF	26%
5	N4	Na_2CO_3	DMF	32%
6	N4	Li_2CO_3	DMF	52%[d]
7	N4	Li_2CO_3	DMSO	29%[d]
8	N4	Li_2CO_3	*N*-methyl-2-pyrrolidone	55%[d]
9	N4	Li_2CO_3	DMA	60%[d]
10	N4	Li_2CO_3	DMA	75%[d,e]

[a]Unless otherwise noted, the reaction was carried out with **1a** (0.2 mmol), **2a** (0.3 mmol), NHC catalyst (0.02 mmol), and base (0.04 mmol) in solvent (0.4 mL) at 60 °C for 8 h. [b]Isolated yields. [c]*N*-Oxysuccinimide was used. [d]A 1.0 mL amount of solvent (0.2 M) was used. [e]Temperature was 100 °C instead of 60 °C. For more details about the experimental procedures, see the Supporting Information.

- Background: Previous study confirmed sulfur radical generation under NHC catalysis → used as basis for reaction optimization
- Substrate: N-(cyclohexoxy)succinimide (1a)
- Initial conditions (entry1) → enol ester 3a obtained in 6% yield
  - Issue: Low substrate oxidation potential, significant unreacted starting material

➢ The steric and electronic properties of the NHC catalyst had a significant influence on the reactivity,

Optimal reaction conditions:
Substrate: N-(cyclohexoxy)succinimide
Catalyst: NHC precursor N4
Base: Li_2CO_3
Solvent: DMA, 0.2 M
Temperature: 100 °C

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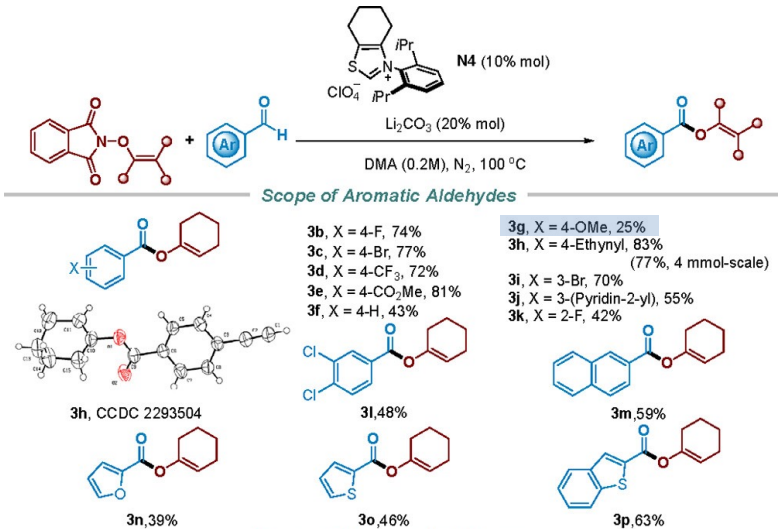
Substrate scope of enol ester synthesizing –Aldehyde –



- Para-EWGs: moderate to high yield (3b–3f)
- Para-EDGs: lower yield (3g)
  - Electron-rich aldehydes form Breslow intermediates less efficiently
- Compatible with sensitive unsaturated groups (alkynyl) (3h)
  - Product structures confirmed by X-ray crystallography
- Meta/ortho-substituted: moderate to high yields (3i-3k)
- Polysubstituted and naphthalene product: moderate (3l–3m)
- Heteroaromatic systems (furan, thiophene, benzothiophene): well tolerated (3n-3p)
- α,β-unsaturated and alkyl aldehydes: unsuccessful
  - → Due to inefficient Breslow intermediate formation

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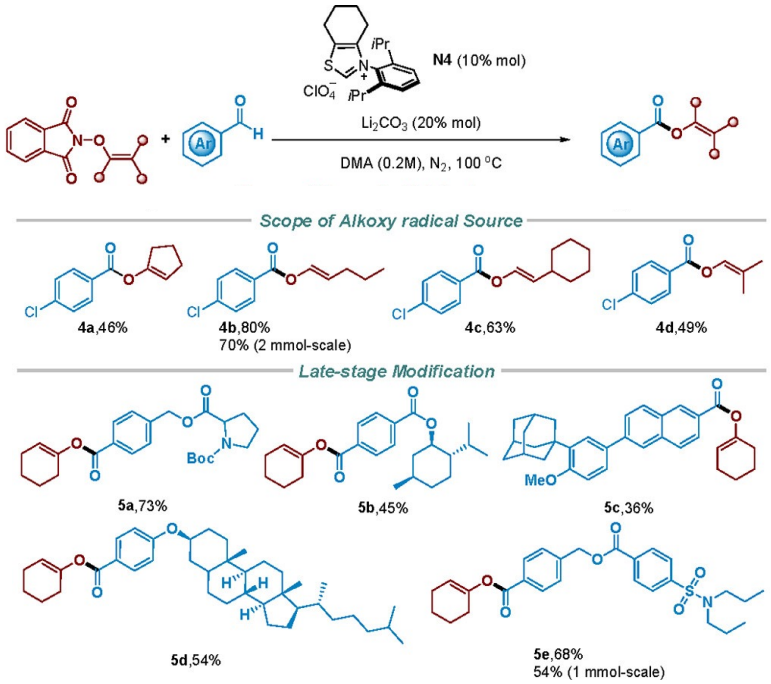
Substrate scope of enol ester synthesizing – Alkoxy radical –



- ✓ High functional group tolerance
  - Cyclopentenoxy, linear, terminal, and branched olefins reacted smoothly (4a–4d)
- ✓ Allowing the late-stage functionalization of natural products or small molecule drugs.
  - Natural product or drug-derived aldehydes compatible (L-proline, L-menthol, adapalene, dehydrocholesterol, probenecid) (5a–5e)
- ✓ Scalable to gram amounts (1–4 mmol) (3h, 4d, 5e)

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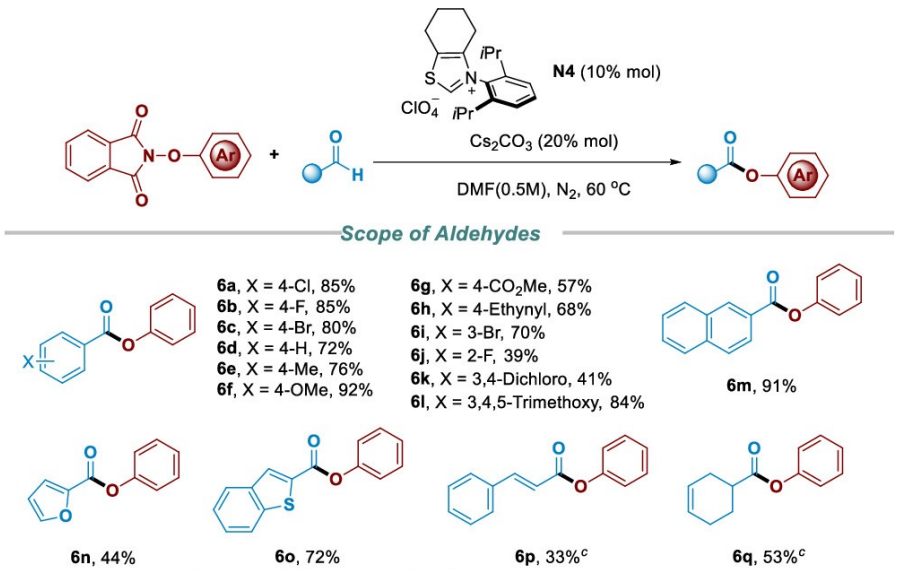
Substrate scope of phenyl ester synthesizing. – Aldehyde –



- ✓ Broad compatibility with aromatic aldehydes
  - (para-, meta-, and ortho-substituted: good to high yields)
  - ✓ In contrast to the enol ester synthesis, electron-rich aryl aldehydes → high yield

→ Because the radical–radical coupling between the Breslow intermediate and the phenoxy radical is the rate-determining step

- ✓ Compatible with more complex aromatic systems
  - Polysubstituted benzaldehydes (6k-6l)
  - Heteroaromatic aldehydes (6m-6o)

- ✓ α,β-unsaturated and aliphatic aldehydes tolerated (6p, 6q)

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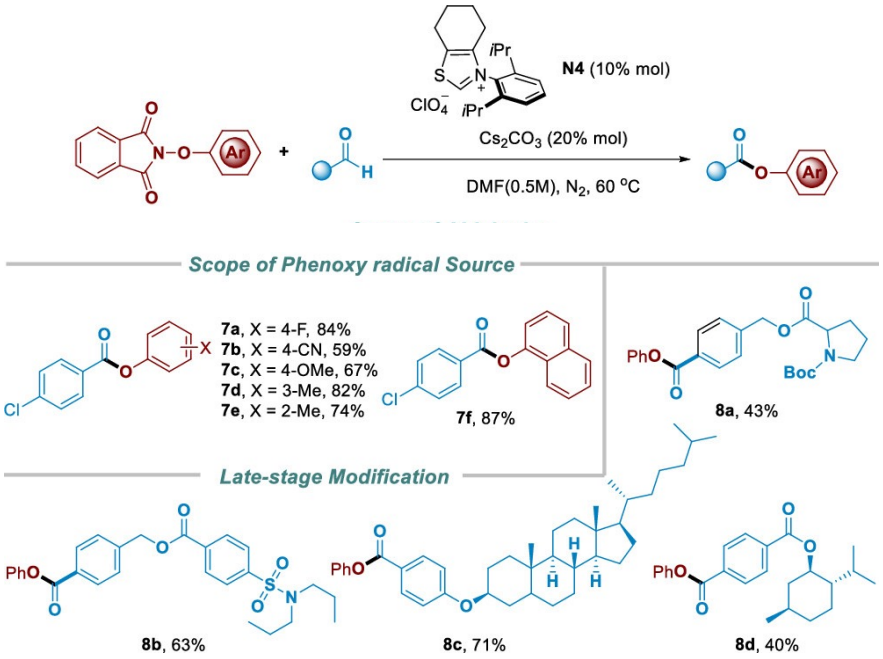
Substrate scope of phenyl ester synthesizing – Phenoxy radical –



✓ Broad compatibility of phenoxy radicals
With different steric and electronic properties

- All substrates provided the corresponding phenyl esters in moderate to high yields (7a–7f)

✓ Successful late-stage modification

- Aldehydes derived from L-proline, probenecid, dihydrocholesterol, and L-menthol were all tolerated (8a–8d)

➢ Limitation

- Introduction of alkoxy groups was unsuccessful

→ Likely due to the instability of the corresponding alkoxy radicals.

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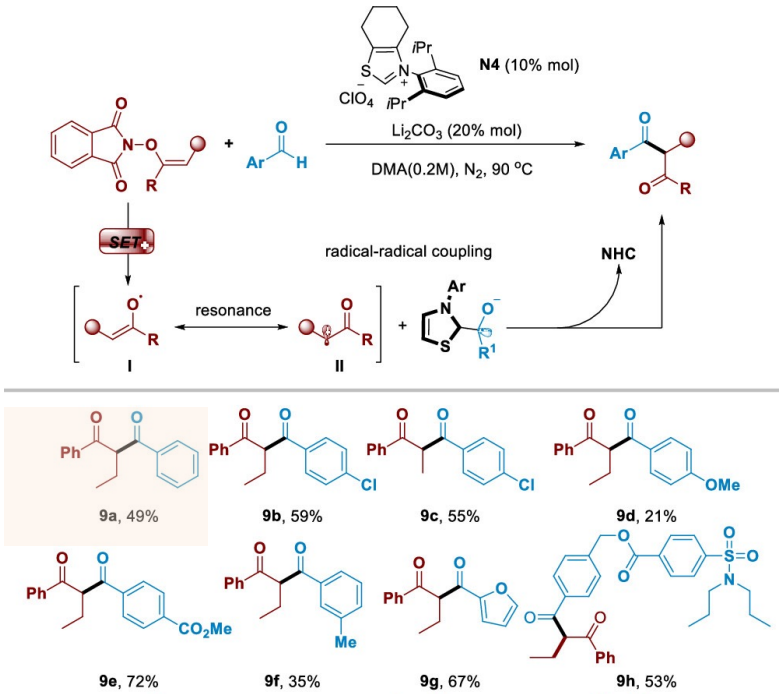
1,3- Diketone synthesis



- Investigation of alkoxy radical properties
  - Carbon-centered radicals are more stable than alkoxy radicals
  → Subsequent reactions more favorable
  - By tuning substituents on the radicals, the electron density can be controlled to selectively capture C-centered (II) or O-centered radicals (I).
  - Higher conjugation at the α-carbon increases electron density on carbon.
- 1,3-Diketone synthesis
  - Introduction of highly conjugated groups (e.g., phenyl) on olefins promotes carbon radical coupling with aldehydes (9a, 49%).

✓ High chemoselectivity: no side reaction with O radicals

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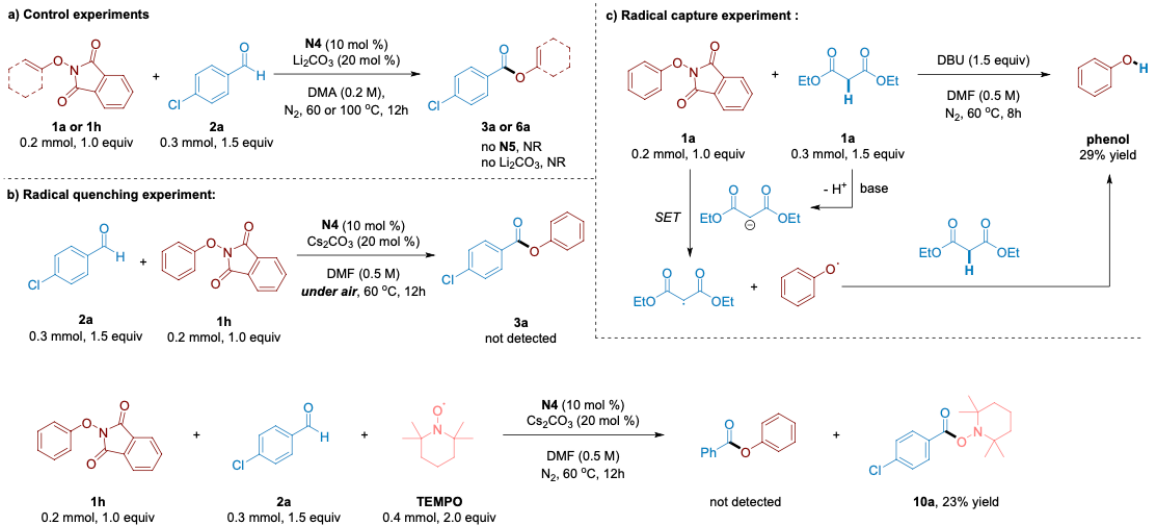
Mechanism studies



- Control experiment (a)
  - No NHC or no base → No product

  → Indicates the NHC catalyst played a key role
- Radical quenching experiment (b)
  - No product was observed when TEMPO or O_2 was added
  - Adduct of the benzoyl radical with TEMPO was detected

  → Suggest a radical pathway
- Radical capture experiment (c)
  - malonate anion reduces 1a → phenoxy radical → HAT → phenol

  → Direct Evidence for O-Radical Formation

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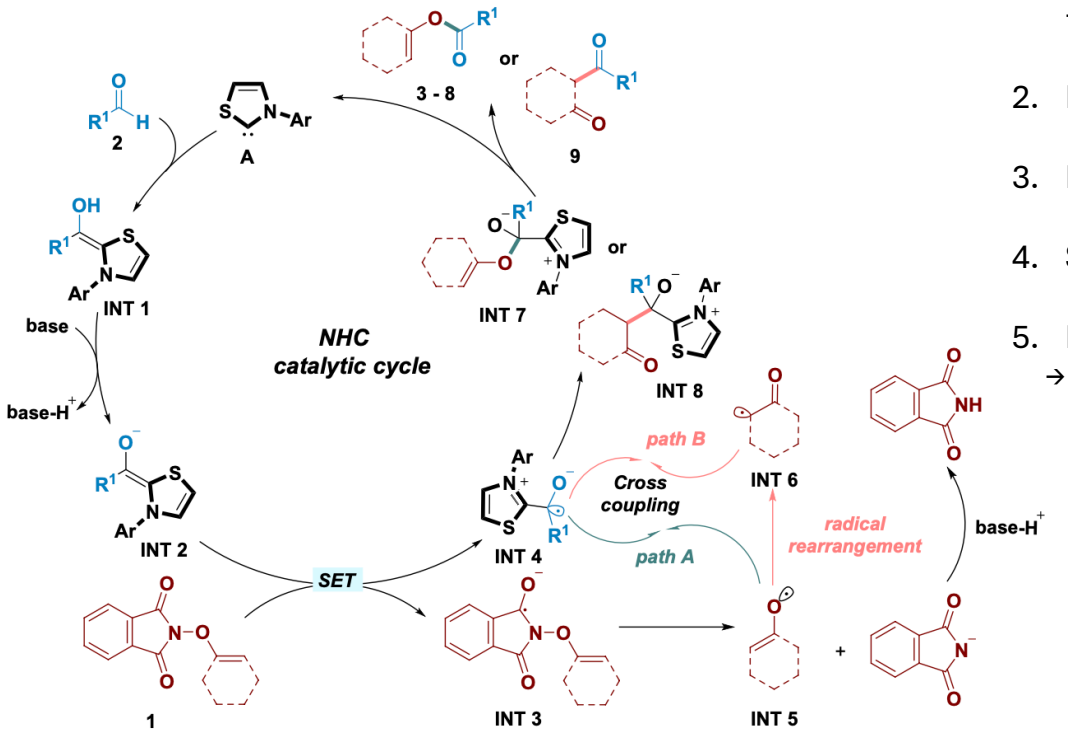
Proposed mechanism



1. Aldehyde 2 + NHC → Breslow intermediate INT1 → (base) → INT2
2. INT2 → SET → INT3 + INT4
3. INT3 → fragmentation → INT5 + phthalimide anion
4. Substituent effects: INT5 (C-radical) ↔ INT6 (O-radical)
5. INT4 + INT5/INT6 → coupling
   → ester / 1,3-diketone + NHC regeneration

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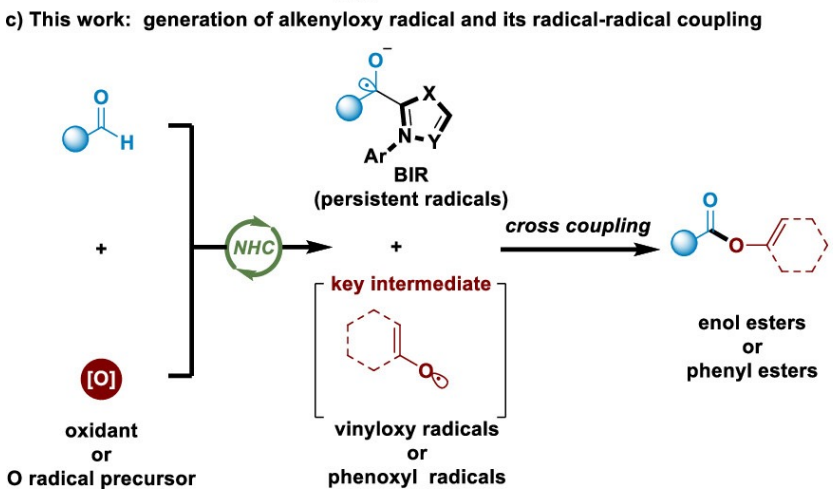
Short summary

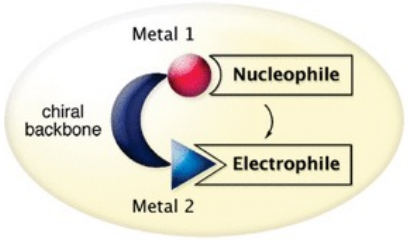


- ❑ First NHC-catalyzed C–O radical–radical coupling developed
- ❑ Applicable to enol/phenol esters and 1,3-diketones
- ❑ High functional group tolerance; late-stage functionalization feasible
- ❑ Scalable and efficient synthesis
- ❑ Potential for complex molecule synthesis and drug modification

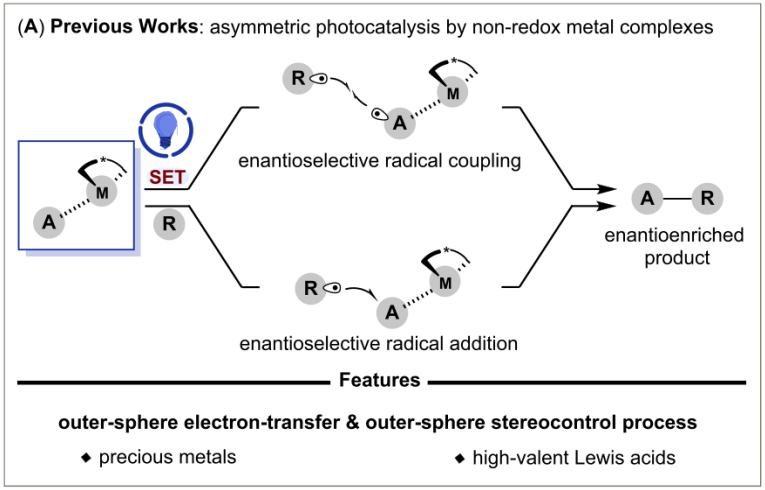
Org. Lett. **2024**, 26, 2456–2461

Contents

Asymmetric bifunctional catalyst



(a) bifunctional chiral catalyst

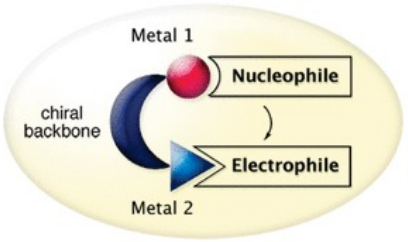


Asymmetric bifunctional catalysis

- A single catalyst simultaneously generates radicals and controls stereochemistry.
- Can be applied in photochemical reactions under mild, environmentally friendly conditions.
- No additional photosensitizers are required.

J. Am. Chem. Soc. **2025**, 147, 25264–25272

Two Conventional Strategies in Asymmetric Radical Reactions



(a) bifunctional chiral catalyst

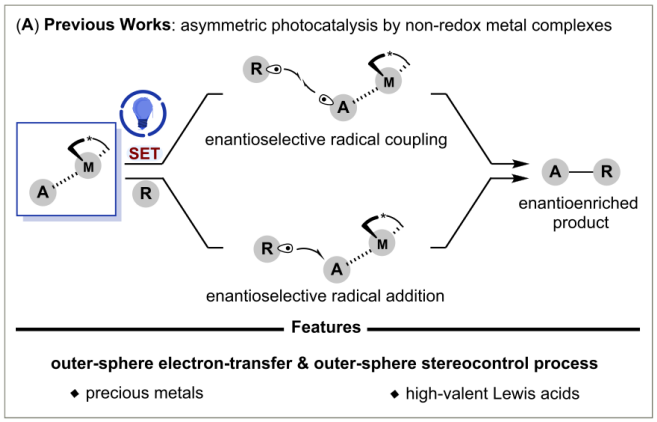
① **Redox-active metals (inner-sphere control)**

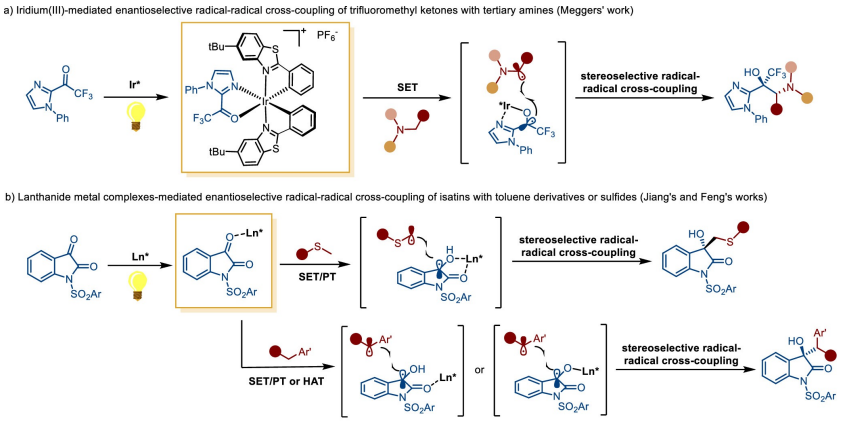
- Sequential oxidative addition with two different free radicals forms high-valent metal complexes.

- Radicals react while bound to the metal (**inner-sphere mechanism**), allowing better stereochemical control.

- **Challenges**
  - **Need redox-active metals**

Two Conventional Strategies in Asymmetric Radical Reactions





② Non-redox metals (outer-sphere control)

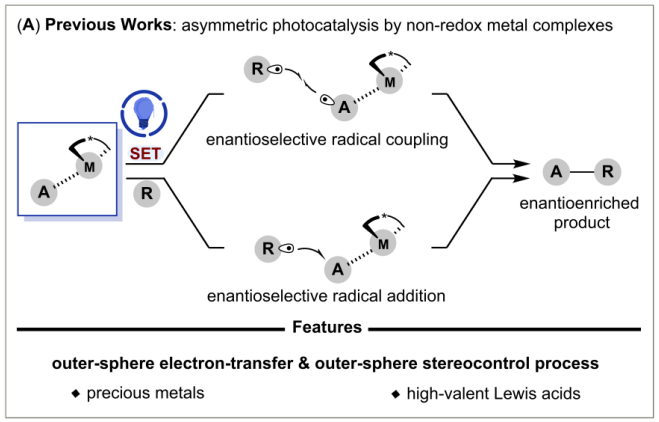
1. The radical acceptor coordinates to the chiral non-redox metal, forming a reactive intermediate.

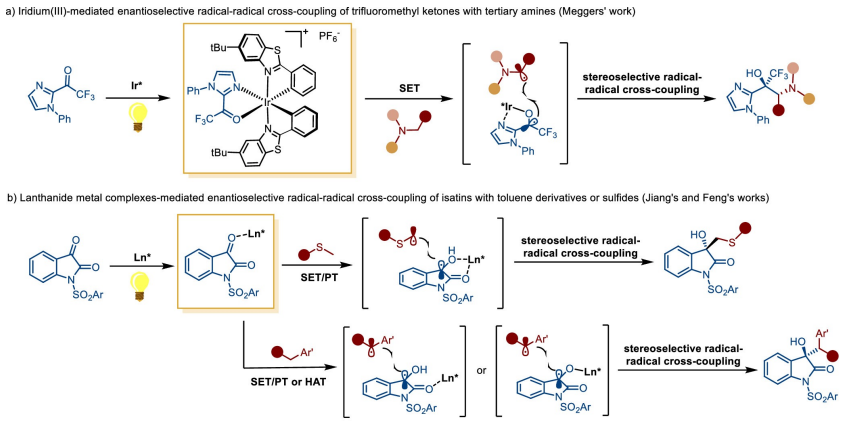
2. Photoexcitation promotes the complex to an electronically excited state and undergoes **outer-sphere SET** with the radical precursor, generating the radical species.
   - Radical generation doesn't rely on oxidative addition

3. Prochiral radical intermediates and transient radicals then participate in enantioselective radical–radical cross-coupling.

J. Am. Chem. Soc. **2025**, 147, 25264–25272

Two Conventional Strategies in Asymmetric Radical Reactions





② Non-redox metals (outer-sphere control)

- **Challenges**

- **Cross-selectivity and enantioselectivity is hard to maintain** because one radical is free in solution and not metal-bound.
  - Reactivity imbalance between the two radicals often leads to **side reactions** and diminished selectivity.

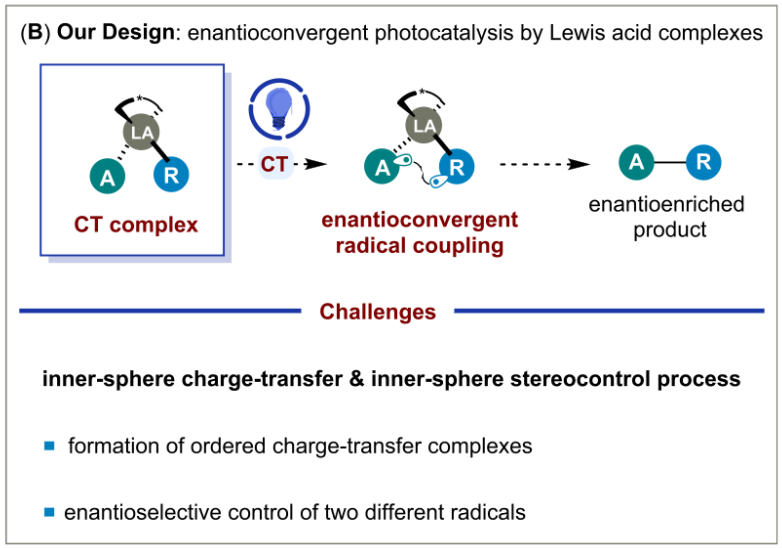
J. Am. Chem. Soc. **2025**, 147, 25264–25272

Two Conventional Strategies in Asymmetric Radical Reactions

	① Inner-sphere control	② Outer-sphere control
Metal	Redox-active metal	Non-redox metal
Radical generation	At metal center Oxidative addition	SET promoted by photoexcitation
Challenges	Need redox-active metal	Not excellent cross- and enantio-selectivity

- Approaches that simultaneously achieve radical generation and asymmetric induction through a Lewis acid–mediated inner-sphere mechanism remain underdeveloped.

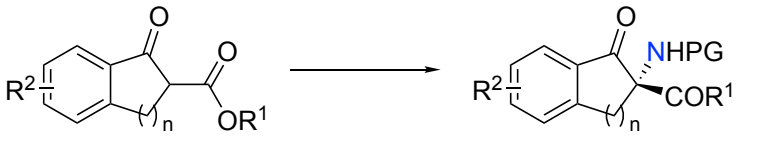
New enantioconvergent photocatalysis strategy



- Dual coordination of intermediates to a chiral Lewis acid forms ordered charge-transfer (CT) complexes.
- Upon photoexcitation, these CT complexes undergo charge transfer, generating Lewis acid–supported radical species.
- As long as these radicals remain bound to the chiral catalyst, they can participate in enantioconvergent radical–radical cross-coupling (RCC)

J. Am. Chem. Soc. **2025**, 147, 25264–25272

Enantioconvergent α-Amination of β-Keto esters



α-Amination of β-Keto esters

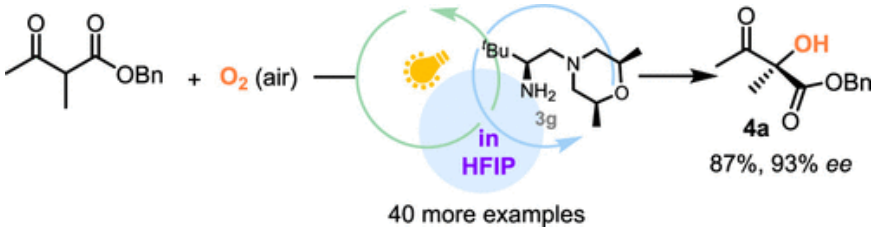
- Optically active amino acids are widespread in natural products and pharmaceuticals.
- → Exhibit important biological and medicinal activity

- Enantioselective α-amination of β-ketoesters provides efficient access to fully substituted, optically active β-keto amino acids.

- **Challenge**: Electronic mismatch between α-carbonyl and amine makes stereocontrol difficult.

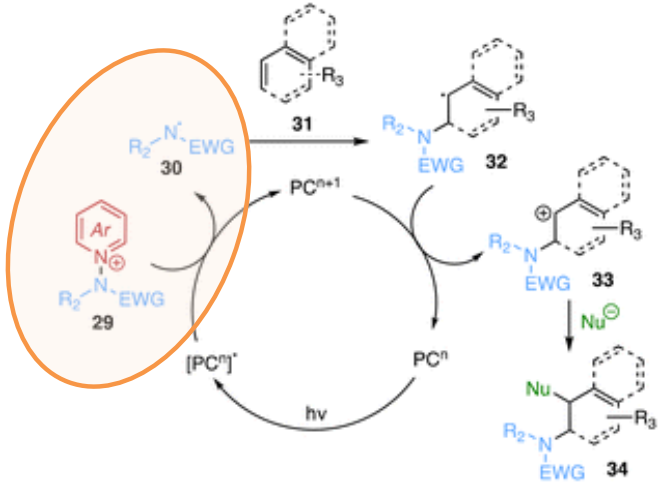
J. Am. Chem. Soc. **2025**, 147, 25264–25272

Inspiration for the new strategy



ACS Catal. **2023**, 13, 11, 7538–7543

Visible Light-Promoted Enantioselective Aerobic Hydroxylation of β-Ketocarbonyls by Chiral Primary Amine Catalysis



Org. Chem. Front. **2023**, 10, 2563–2580.

Generic catalytic cycle for photoredox activation of *N*-aminopyridinium salts proceeds through the generation and reaction chemistry of *N*-centered radicals

The new strategy was inspired by:

1. enantioselective photocatalysis of β-ketoesters
2. N-centered radical generation from N-protected iminopyridinium ylides.

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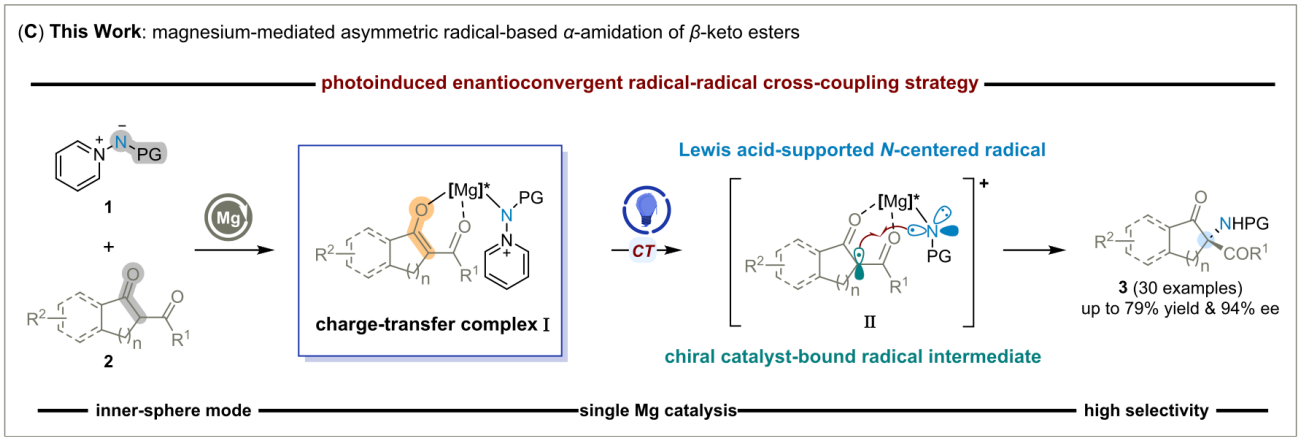
New enantioconvergent photocatalysis strategy



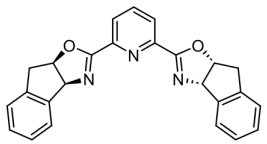
1. Dual coordination via inner-sphere mechanism
   - β-ketoester enolate and ylides coordinate to chiral Mg/ligand complex
   - Form a prochiral quaternary charge-transfer complex (CT complex I)
2. Photoexcitation for radical generation
   - CT complex undergoes charge separation
   - Produces Lewis acid–supported N-centered radicals and catalyst-bound radical intermediates

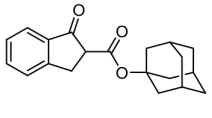
✓ Radical–radical cross-coupling forms chiral α-tertiary amines efficiently
✓ Minimizes side reactions and racemization

J. Am. Chem. Soc. **2025**, 147, 25264–25272

Optimization of Reaction Conditions

Table 1. Optimization of Reaction Conditions[a]


L1


R = 1-adamantyl
2b

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	--

- Initial conditions ($Sc(OTf)_3$ + L1): 55% yield, 5% ee
- Using $Mg(OTf)_2$ improved to 45% yield, 52% ee (entry 4)
- The nature of the anion had a significant impact on the enantioselectivity (entry 6,7)
- Optimization of substrate ratio, concentration, and temperature: 3ab 70% yield, 90% (entry 10)

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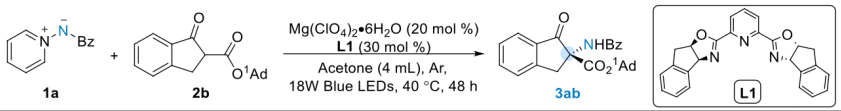
Control experiment

***Table S8*. Control experiments**



Entry	Light Source	$Mg(ClO_4)_2$• $6H_2O$	L1	Light	Yield (%)[a,b]	ee (%)[c]
1	18 W blue LEDs	√	√	√	70	90
2	18 W blue LEDs	√	×	√	59	N.A.
3	18 W blue LEDs	×	√	√	9	N.A.
4	18 W blue LEDs	×	×	√	35	N.A.
5	18 W blue LEDs	√	√	×	**0**	**N.A.**
6	370 nm	√	√	√	0	N.A.
7	390 nm	√	√	√	0	N.A.

[a]Reaction condition: **1a** (19.8 mg, 0.1 mmol), **2b** (46.6 mg, 0.15 mmol), $Mg(ClO_4)_2$• $6H_2O$ (6.6 mg, 20 mol%), **L1** (11.8 mg, 30 mol%) in acetone (4 mL) at 40 ℃ under irradiation of 18 W blue LEDs for 48 h. [b]Isolated yield. [c]ee was determined by chiral HPLC analysis. N.A. = not available.

As shown in ***Table S8***, **light** and **chiral magnesium (II) complex** were necessary.

- Confirmed reaction is light- and Lewis acid-dependent
  - No product in dark
  - Omission of either Lewis acid or L1 resulted in a sluggish reaction with no enantioinduction.

→ Indicate that the asymmetric transformation proceeds via a photochemical mechanism facilitated by the chiral magnesium(II) complex.

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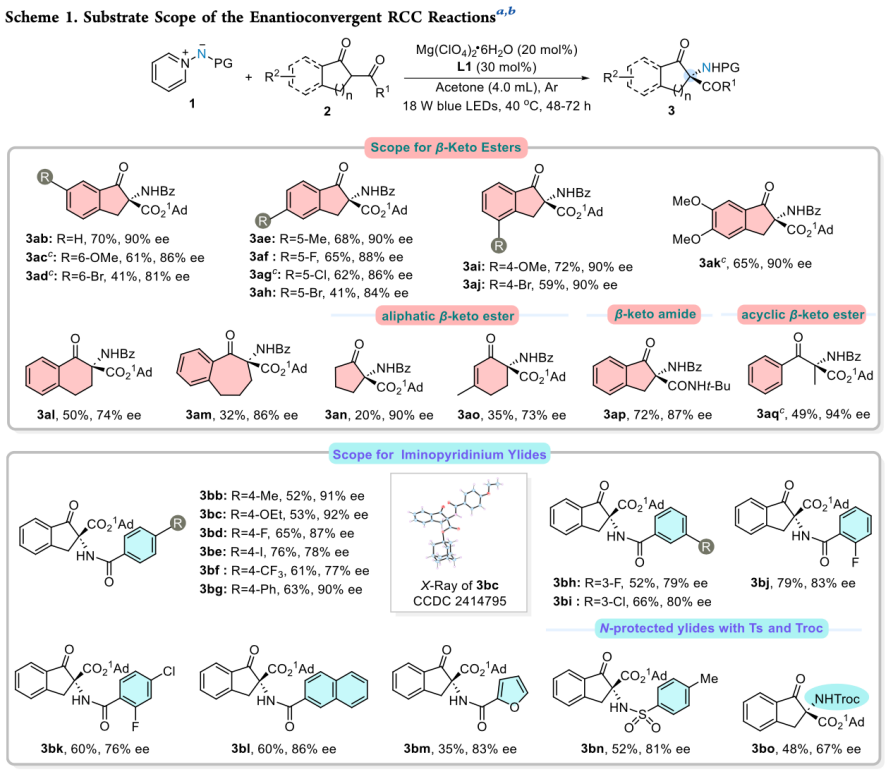
Substrate Scope



✓ Broad range of β-keto esters

- (aromatic, aliphatic, cyclic, acyclic) reacted smoothly, giving 73-94% ee
- Changes in the electronic properties of the aryl ring did not hinder the reaction

✓ Various iminopyridinium ylides tolerated (EDGs and EWGs)

- With EDGs (F, I, CF_3) or phenyl (1d–1g)

→ Good enantioselectivity (77–90% ee) with slightly reduced yields

- Compatible with other protecting groups (sulfonamide, carbamate)
- Absolute configuration confirmed by X-ray crystallography (3bc)

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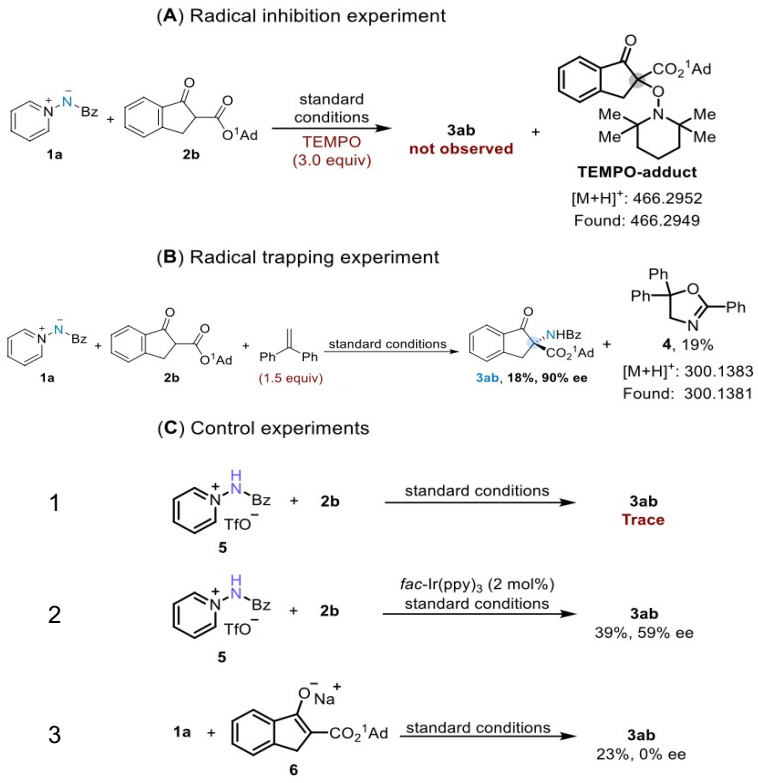
Mechanism Studies



✓ **Involvement of α-carbonyl radicals**

- Confirmed by TEMPO inhibition and detection of the TEMPO adduct (A)

✓ **Formation of N-centered radicals**, not nitrene anions

- Supported by radical trapping with 1,1-diphenylethylene (B)

- Experiments using compound 5 show competitive pathways (C, 1-2):
  - Outer-sphere stereocontrol by chiral Mg–enolate complexes
  - Nonselective background reactions

→ **Highlights the necessity of an inner-sphere mechanism,** which stabilizes two different radicals simultaneously within the chiral Mg coordination sphere

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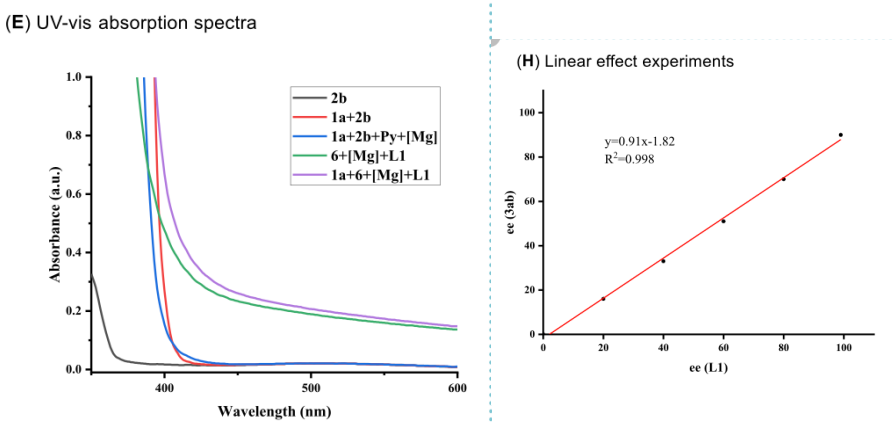
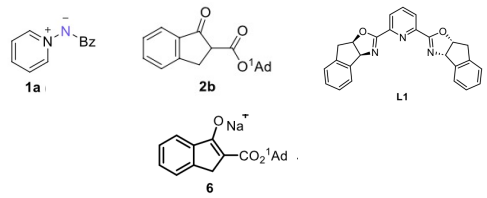
Mechanism Studies





- Bathochromic shifts (E) (β-keto ester (1a) + iminopyridinium ylides (2b) + Mg salt + Ligand L1)

→ Support the prochiral quaternary CT complexes

- Linear effect experiments show involvement of one molecule of chiral Mg catalyst in stereocontrol. (H)

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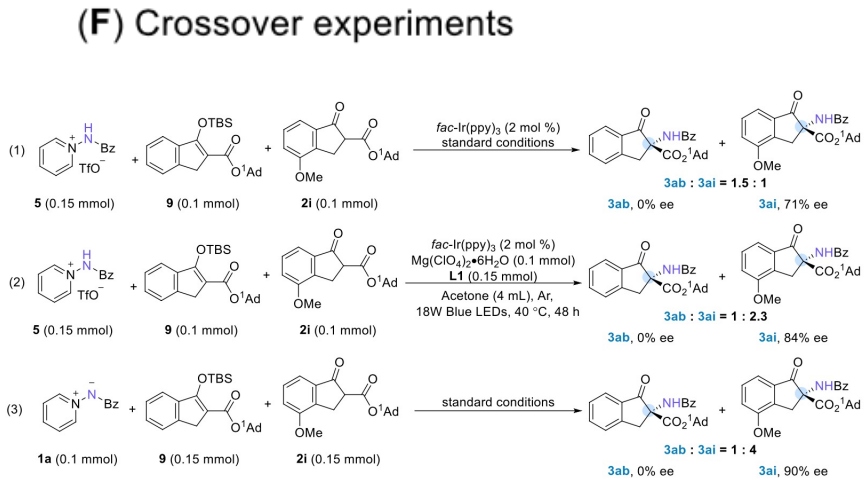
Mechanism Studies Crossover experiments: inner-sphere vs outer-sphere



1) Conditions: Standard + $Ir(ppy)_3$

- Outer-sphere pathway gives ee = 0%
- High ee of 3ai arises from inner-sphere mechanism.

2) Conditions: Increased catalyst ($Mg(ClO_4)_2$ and L1):

- More Mg–L1 favors inner-sphere pathway, increasing ee.
- Outer-sphere still ee = 0%.

3) Conditions: Substrate variation: 1a + excess 2i & 9

- Coordinating 2i reacts via inner-sphere; non-coordinating 9 triggers only background reaction (+ still ee = 0%).

▪Objective

- ▪Test if dual coordination of enolate and ylide (Mg–L1) is essential for high enantioselectivity.
- ▪Confirm that outer-sphere pathway (free radical trapping) provides no stereocontrol.

▪Conclusion

High enantioselectivity requires inner-sphere (dual coordination). Catalyst amount and substrate choice control inner-/outer-sphere contributions.

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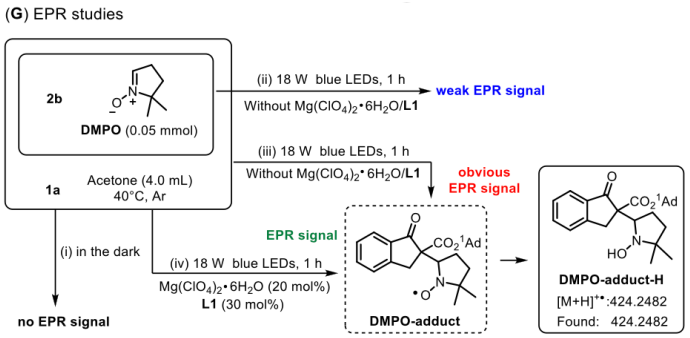
Mechanism Studies from EPR studies



Condition	Radical Generation	EPR Signal	Stereocontrol	Comments
(i) Dark (no light)	None	None	None	No reaction occurs → confirms photochemical nature of the reaction
(ii) 2b only (light)	Trace	Nearly none	None	Light-induced SET of enol tautomer generates a small amount of α-carbonyl radicals
(iii) 2b + 1a (light)	Increased	Strong sextet	None	Free radicals increase due to background reaction; uncontrolled radical formation
(iv) 2b + 1a + Mg^{2+} + L1 (light)	Moderate	Weak sextet	Yes	Radicals are generated and preorganized within the chiral Mg coordination CT complex → enantioconvergent control (inner-sphere mechanism)

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DTF calculations

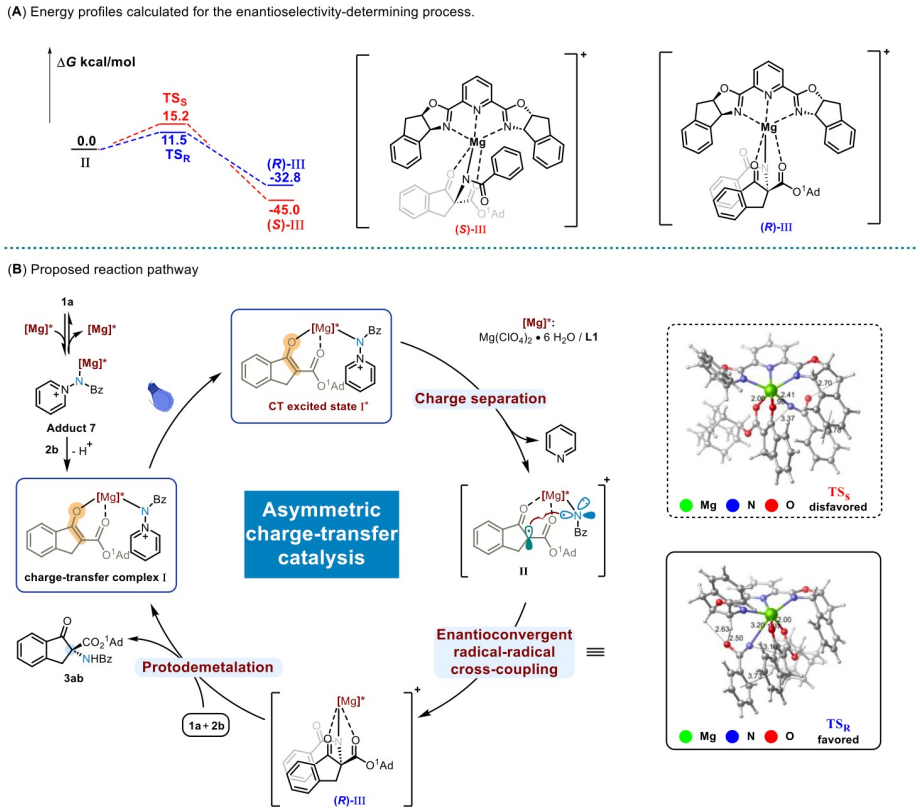

Figure 3. Mechanistic studies. (**A**) Energy profiles calculated for the enantioselectivity-determining process. (**B**) Proposed reaction pathway.

- DFT calculations show that intermediate II undergoes radical–radical cross-coupling via the TS_R transition state, which is the lowest-energy pathway ($\Delta G‡$ = 11.5 kcal/mol).
- The alternative TS_S pathway has a higher barrier ($\Delta G‡$ = 15.2 kcal/mol).
- The low-energy pathway is stabilized by π–π stacking, hydrogen bonding, and steric effects.
- The 3.7 kcal/mol energy difference explains the experimentally observed 90% ee.
- The absolute configuration of the product (R)-3ab aligns with DFT predictions.

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Mechanism Proposal

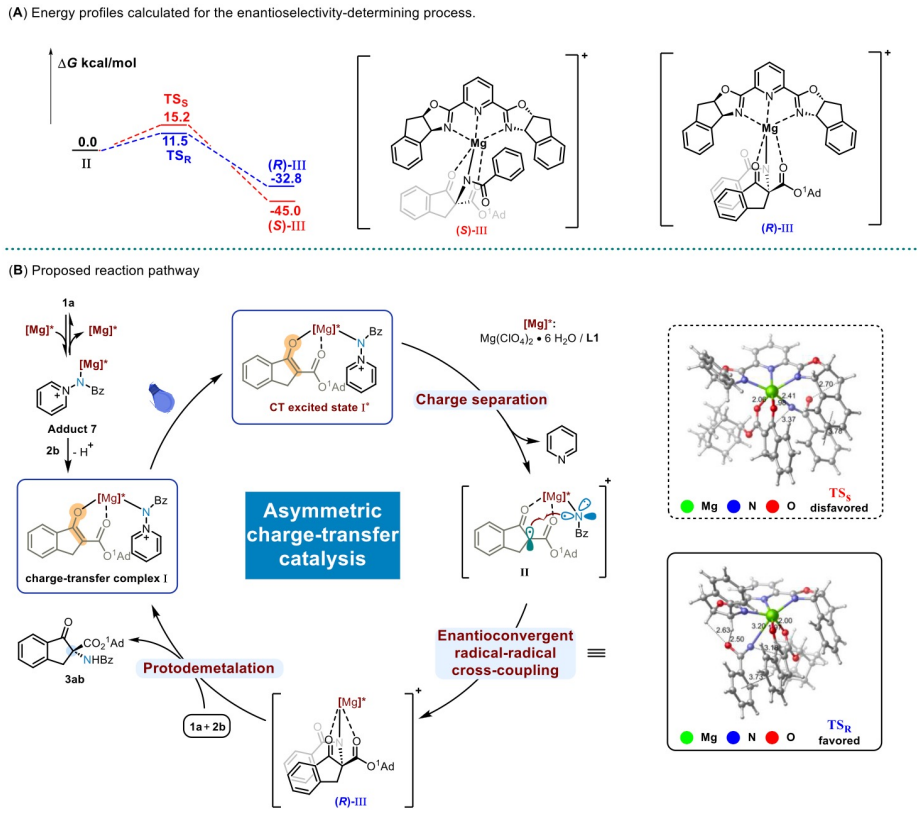

Figure 3. Mechanistic studies. (A) Energy profiles calculated for the enantioselectivity-determining process. (B) Proposed reaction pathway.

- Catalyst Activation:
  - N-protected iminopyridinium ylide 1a + Mg(ClO4)2·6H2O/L1 → ylide-Lewis acid adduct 7
- Prochiral Complex Formation:
  - Adduct 7 + β-keto ester 2b → prochiral quaternary CT complex I
- Photochemical Step:
  - Visible light irradiation → α-carbonyl radical + N-centered radical
- Enantioconvergent RCC:
  - Radical intermediate II → (R)-III → protodemetalation → 3ab
- Catalyst Regeneration:
  - Mg(ClO4)2·6H2O/L1 regenerated → new catalytic cycle

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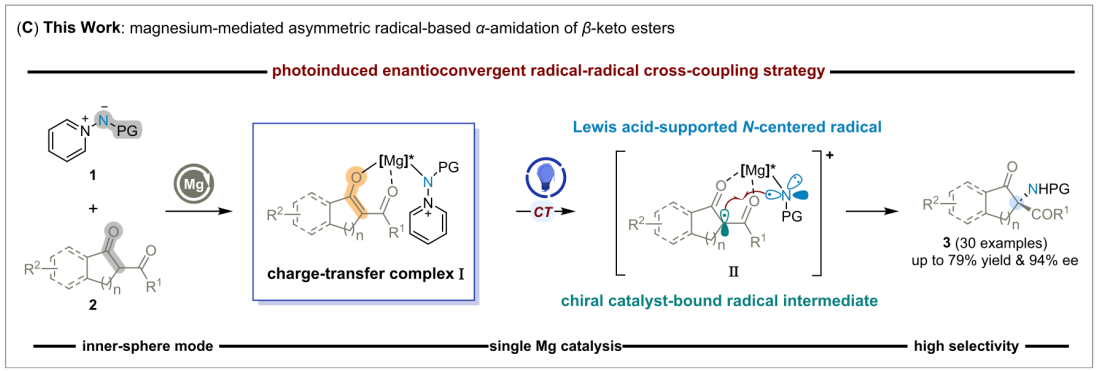
Short summary



- Dual-coordination strategy allows control of cross- and enantioselectivity in radical-radical coupling
- Broad substrate scope and good functional group tolerance
- Enables efficient synthesis of substituted quaternary β-keto amino acid derivatives
- Uses earth-abundant magnesium as an effective asymmetric photochemical catalyst

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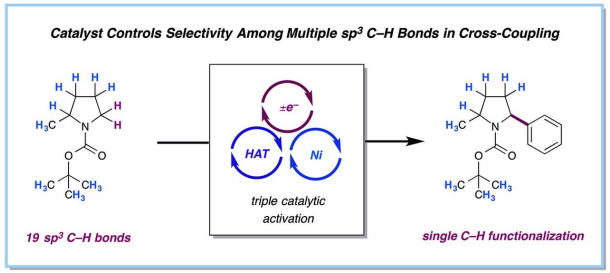
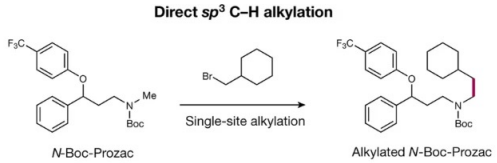
Contents

Advances in C–H Activation and Photoredox–Metal Dual Catalysis

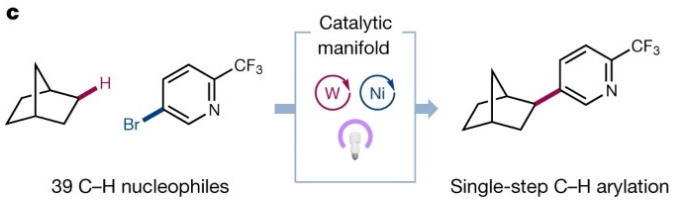


Science 352, 1304–1308 (2016)



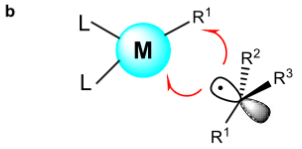
The matching of electronic polarity between the C–H bond and the HAT catalyst

Nature **volume 547**, pages 79–83 (2017)



Nature 560, 70–75 (2018).

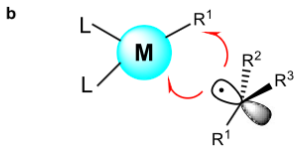
- Combining photoredox catalysis with transition metal catalysis has enabled reactions of non-directed substrates, expanding the scope of C–H functionalization.
- MacMillan reported numerous examples of $C(sp^3)$–$C(sp^2)$ and $C(sp^3)$–$C(sp^3)$ bond formations through HAT-mediated C–H cleavage followed by nickel-catalyzed cross-coupling.



Captured by transition metal
good chemoselectivity

Radical reactions to form $C(sp^3)$-$C(sp^3)$ bonds

Transition metal catalyzed cross coupling MacMillan and coworkers



Captured by transition metal
good chemoselectivity

Radical-radical cross coupling

Radical-radical coupling
poor chemoselectivity

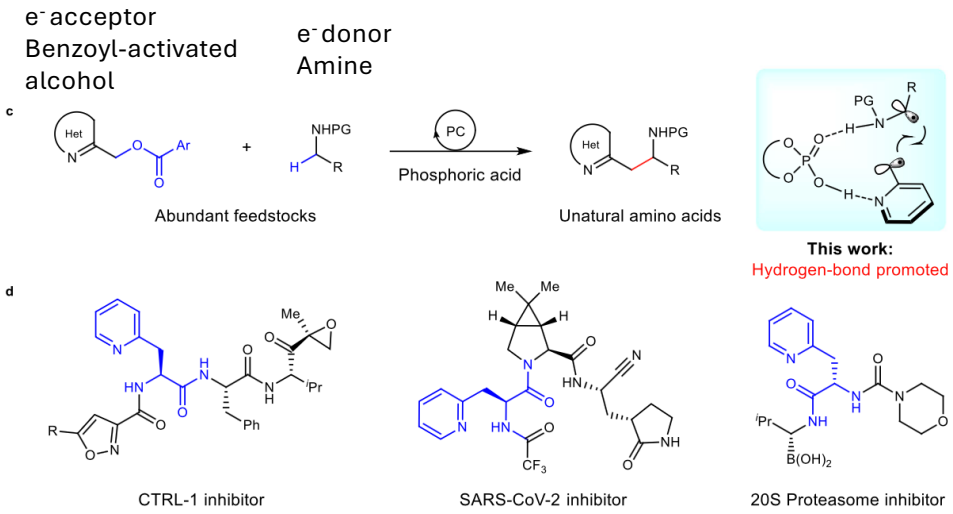
- Conventional radical–radical coupling suffers from **poor chemoselectivity** when the two radicals have similar electronic properties,

→ Lead to **complex mixtures and side products**

→ **Direcrt coupling to form $C(sp^3)$–$C(sp^3)$ bonds** has remained **highly challenging**

  - **Especially direct coupling between C-O and C-H is largely unexplored**.

Selective radical-radical cross-coupling promoted by hydrogen-bond



Unnatural amino acids and bioactive molecules

- This study introduces a SET strategy that cleaves amine α-C–H and heterobenzylic C–O bonds
- → Generating two radicals under photoredox conditions

- **Hydrogen-bond interactions with phosphoric acid** guide the selective radical–radical cross-coupling.

✓ The method is **redox-neutral, transition-metal-free**, and compatible with diverse aza-heterocycles.

✓ Enables efficient synthesis of **unnatural amino acids and bioactive molecules**.

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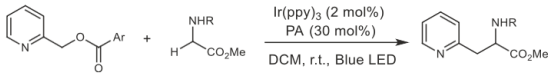
Optimization of Reaction Conditions



Entry	Derivation standard conditions	Yield (%)[b]
1	Ar = 3,5-di-CF_3-C_6H_3 (**1a**), R = Ph (**2a**)	49
2	Ar = **1a**, R = 4-CF_3-C_6H_4 (**2b**)	8
3	Ar = **1a**, R = 4-F-C_6H_4 (**2c**)	53
4	Ar = **1a**, R = 4-OMe-C_6H_4 (**2d**)	32
5	Ar = 2,4,6-trifluorobenzene (**1b**), R = **2a**	37
6	Ar = 2,4,6-trichlorobenzene (**1c**), R = **2a**	15
7	Ar = 4-CF_3-C_6H_4 (**1d**), R = **2a**	40
8	Ar = **1a**, R = **2a**, DME as solvent	33
9	Ar = **1a**, R = **2a**, MeCN as solvent	33
10	Ar = **1a**, R = **2a**, without PA	40
11	Ar = **1a**, R = **2c**, $NaHCO_3$ (2 eq)	64
12	Ar = **1a**, R = **2c**, $NaHCO_3$ (2 eq), 60 °C	72
13	the same conditions as entry 12, in DME	74
14	the same conditions as entry 12, without Ir	19
15	the same conditions as entry 12, in the dark	0

- 1a and 2a (N-phenylmethyl glycinate) underwent cross-coupling under $Ir(ppy)_3$ photocatalysis: 49% yield
- Substituents on glycinate (entry1-4):

  highest yield

  CF_3 < Fluoro < OMe

  EWG ↔ EDG
- Alcohol activating acyl group (entry 5-7):
  Benzoyl-activated alcohol = e^- acceptor
  - highly electrophilic one is most effective
    - 3,5-bis(CF_3)benzoate
- Solvent: CH_2Cl_2 optimal (entry 8-9)
- Yield improved with $NaHCO_3$, heating, and 1,2-DME: up to 74% (entry 11-13)

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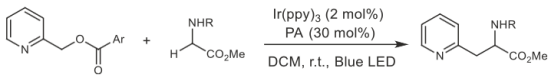
Optimization of Reaction Conditions



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5	Ar = 2,4,6-trifluorobenzene (**1b**), R = **2a**	37
6	Ar = 2,4,6-trichlorobenzene (**1c**), R = **2a**	15
7	Ar = 4-CF_3-C_6H_4 (**1d**), R = **2a**	40
8	Ar = **1a**, R = **2a**, DME as solvent	33
9	Ar = **1a**, R = **2a**, MeCN as solvent	33
10	Ar = **1a**, R = **2a**, without PA	40
11	Ar = **1a**, R = **2c**, $NaHCO_3$ (2 eq)	64
12	Ar = **1a**, R = **2c**, $NaHCO_3$ (2 eq), 60 °C	72
13	the same conditions as entry 12, in DME	74
14	the same conditions as entry 12, without Ir	19
15	the same conditions as entry 12, in the dark	0

- Control experiment
- No phosphoric acid → decreased yield (entry 10)
- No Ir catalyst → 19% yield, suggesting formation of a weak EDA complex (entry 14)
- Dark reaction
  → no product, light essential for SET process (entry 15)

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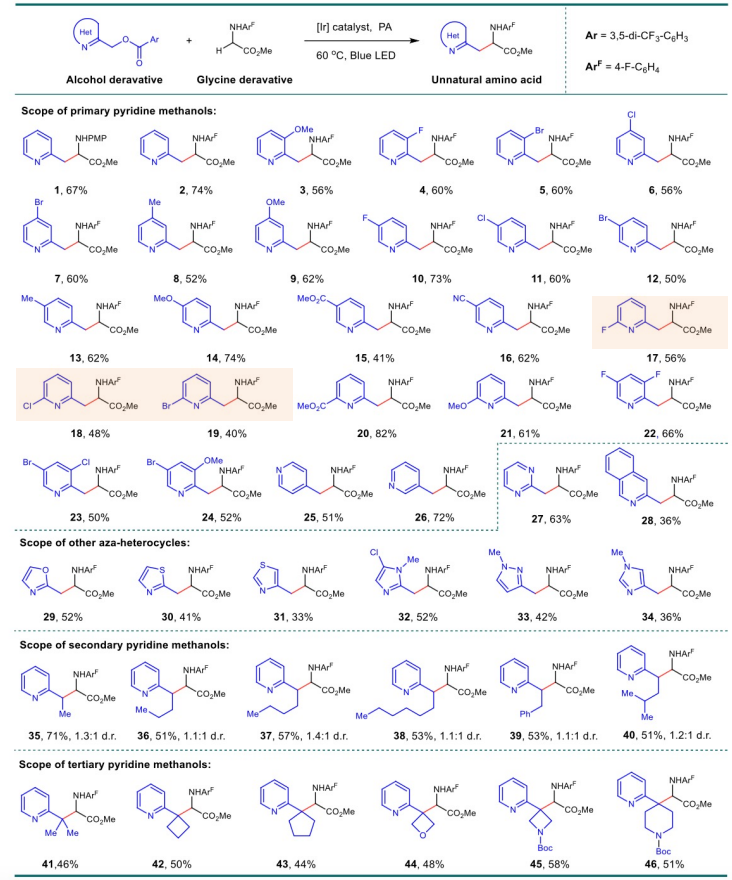
Substrate Scope – Alcohol derivative-



- Glycinate substrates: PMP (*p*-metoxy phenyl*)* substitution gave 67% yield, removable under oxidation

- Primary pyridine substitution:
  - 3,4,5-positions: moderate to good yields
  - 6-position: yield decreases as atomic radius increases (F → Cl → Br)

  → Affected by sterics

  → Suggests hydrogen-bond interactions are crucial for successful coupling
  - Multi-substituted pyridines and pyridinemethanol derivatives (3, 4-position): moderate to good yields

- Aza-heterocycles : moderate yields

→ Traditional methods struggle to synthesize nitrogen-containing unnatural amino acids, making this method a significant strength.

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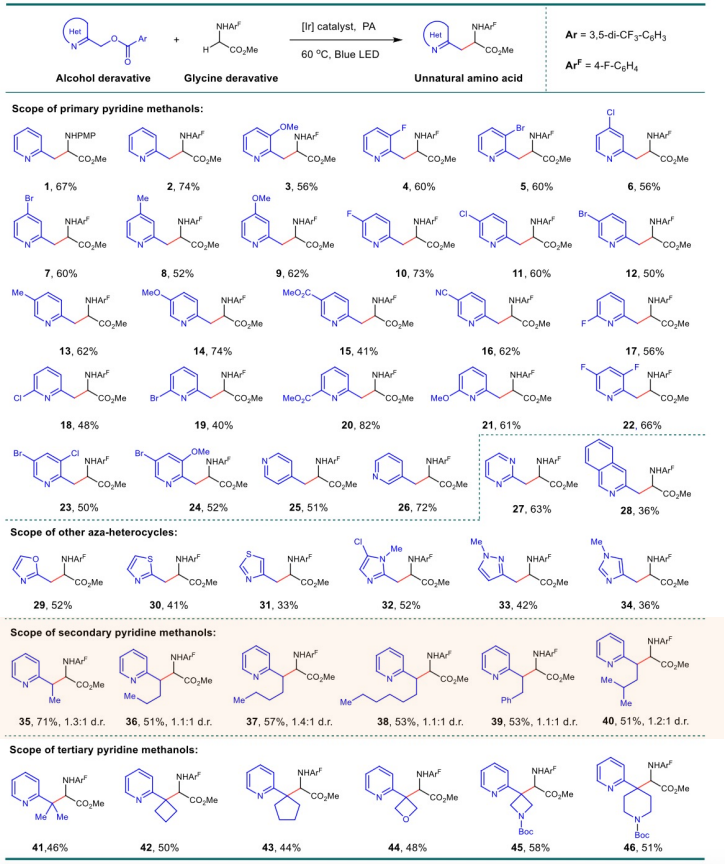
Substrate Scope – Alcohol derivative-



- Secondary alcohol derivatives: moderate to good yields,
- limited diastereoselectivity (35–40)

- Tertiary alcohols + glycinate derivatives: enable formation of quaternary carbon centers

✓ Effective for transformations challenging in traditional transition-metal-catalyzed reactions (41–46)

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Substrate Scope – amino ketones and peptides-

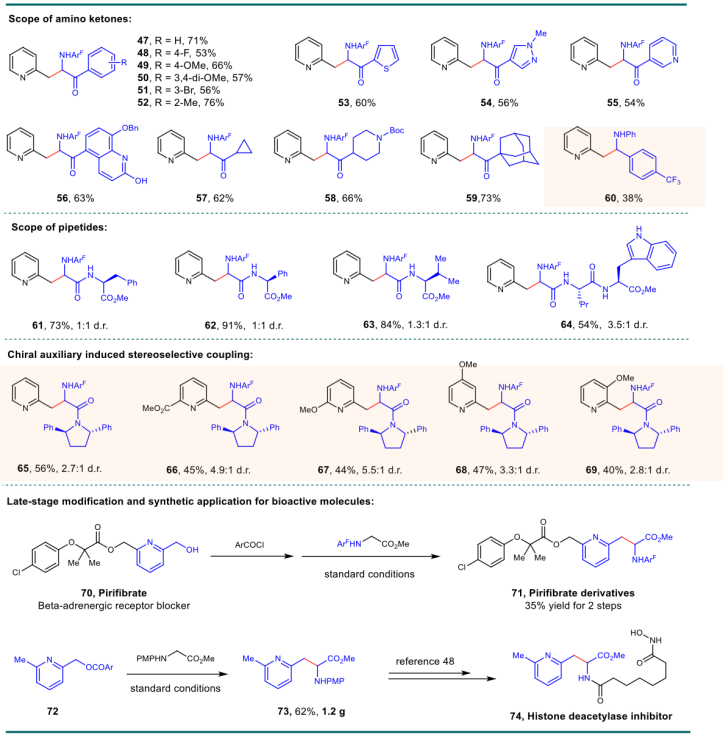

Fig. 3 | Substrate investigation for the amines and synthetic applications. All of the yields were isolated yields. The diastereomeric ratio was determined by isolation yield.

- α-Amino ketones & di-/tri-peptides:
  - moderate to good yields, tolerant to EDGs and EWGs

  ※ Benzylamine reacts only when an EWG is present on the benzene ring (60)

- Stereoselectivity control
  - Chiral auxiliaries introduced to glycinate substrates
  - Best: chiral 2,5-diphenylpyrrolidine → highest diastereoselectivity (65–69)

- Applications
  - Late-stage modification of β-adrenergic receptor blocker Piribrate (71)
  - Synthesis of histone deacetylase inhibitors (74)

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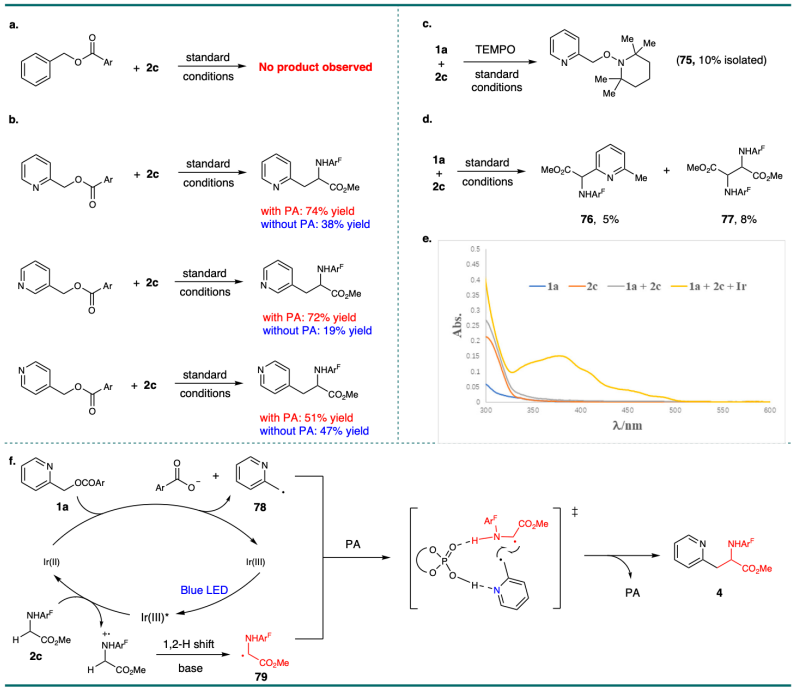
Mechanistic Insights (Control Experiments)



- Nitrogen is essential: Benzyl alcohol fails (a)

→ N atom stabilizes radical and provides H-bonding site

- Role of phosphoric acid: Absence lowers yields (b)

→ Promotes cross-coupling via H-bond + radical polarity matching

- Radical formation confirmed:
  TEMPO-trapped product (75) observed (c)
  Minisci-type (76) and homo-coupling products (77) observed (d)

- No significant red shift observed for the 1a–2c mixture (e)

→ EDA complex is weak:

→ SET mediated by Ir photocatalyst is the main pathway

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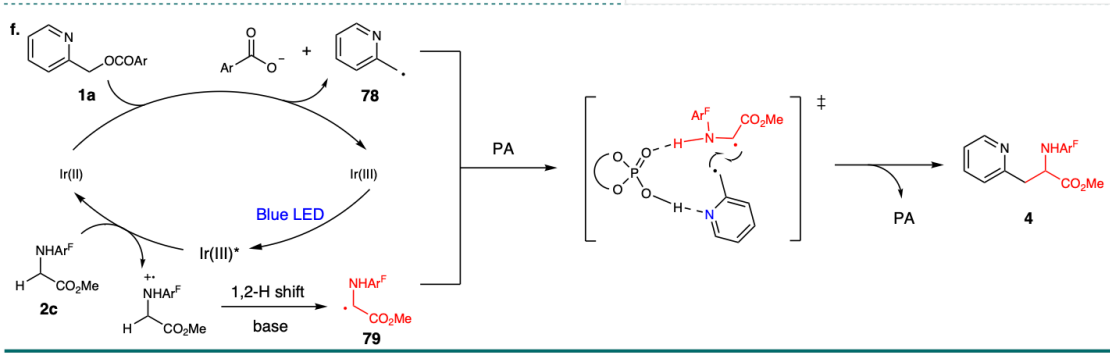
Proposed reaction pathway



- 1a + Ir(III) → pyridyl methylene radical (78)
- 2c + Ir(III) → α-amino radical (79)
- 78 + 79 → (H-bond with phosphoric acid) → formation of $C(sp^3)$–$C(sp^3)$ bond

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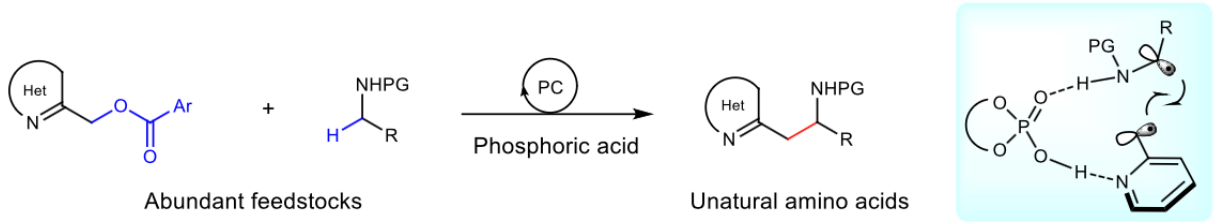
Short Summary



Abundant feedstocks

Unatural amino acids

This work:
Hydrogen-bond promoted

- Developed a deoxygenative C(sp^3)–C(sp^3) radical cross-coupling of heterobenzylic alcohols and amines under hydrogen-bond control
- Broad substrate scope and functional group tolerance
- Diastereoselectivity controlled using chiral auxiliary 2,5-diphenylpyrrolidine
- Enables efficient synthesis of heterocyclic unnatural amino acids

→ applicable to drug discovery and chemical biology.

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Contents

Summary

1. Persistent Radical Generation via NHC Catalysis
   - First example of C-radical–O-radical coupling under NHC catalysis
   - Applicable to C–C bond formation, including 1,3-diketones

2. Lewis acid complex formation
   - Dual coordination using a Lewis acid enables control of cross- and enantioselectivity
   - Allows efficient synthesis of substituted quaternary β-keto amino acids

3. Hydrogen-Bond Control
   - Deoxygenative radical cross-coupling of heterobenzylic alcohols and amines
   - Diastereoselectivity controlled via chiral auxiliary