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Research Article

Stereoselective Radical Cross-Coupling of Amino Acids and Imines via Hydrogen-Bond Catalysis

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Cite This: ACS Catal. 2025, 15, 21033−21041

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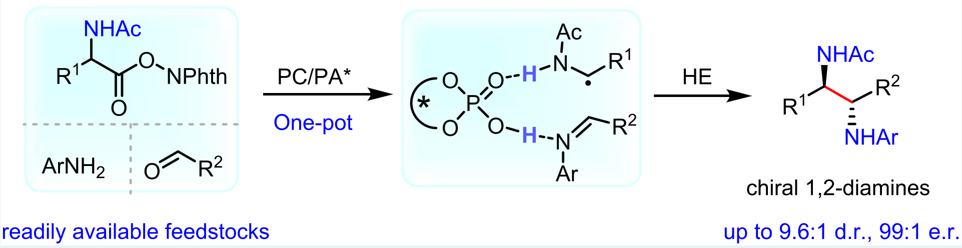


ABSTRACT: Stereochemical control remains one of the most challenging obstacles in developing practical radical transformations. Recent progress in transition-metal-catalyzed radical reactions has shed light on methods for stereoselectively constructing $C(sp^3)-C(sp^3)$ bonds through a single electron transfer mechanism. However, the field of chiral Brønsted acid-catalyzed stereoselective radical reactions is relatively less studied. Herein, we present a stereoselective radical cross-coupling between abundant amino acids and readily available imine substrates (prepared in situ from aldehydes and anilines) via cooperative catalysis of photoredox and phosphoric acid. This method features good functional group compatibility, providing a diverse range of chiral 1,2-diamine products which are valuable in synthetic utility. Preliminary mechanistic studies indicate that this reaction probably proceeds via both radical−radical cross-coupling pathway and radical nucleophilic addition mechanism.

KEYWORDS: *radical cross-coupling, stereoselective, hydrogen-bond catalysis, photocatalysis, 1,2-diamine*

■ INTRODUCTION

The advancement of free carbon radical transformations has paved the way for a diverse array of retrosynthetic disconnections, enabling the fast approach to complex functional molecules by leveraging their high reactivity.[1−4] As an illustration, one of the simplest retrosynthetic strategies for 1,2-diamines involves homolytically breaking the C−C bond to produce two α-amino radicals, which subsequently undergo cross-coupling to yield the desired products. However, the intricate pathways of homo- and cross-coupling, combined with the racemization of chiral centers in a planar radical intermediate, present significant challenges in achieving both chemoselectivity and stereochemical control in these reactions[5] (Figure 1a). In the past decades, several strategies have been formulated to surmount the barriers to enantioselective radical reactions.[6] The early endeavors involve introducing a chiral center into the substrate (the so-called chiral auxiliary), which can govern the stereoselectivity when the substrate reacts with a free radical.[7−13] These reactions are highly reliant on the structure of the substrates, thus restricting their broad applications in organic synthesis. Another widely adopted reaction paradigm is to capture the free radical using a preformed chiral organometallic species. By manipulating diverse transition metals and chiral ligands, a series of carbon−carbon and carbon−heteroatom bonds can be fashioned in a stereoselective manner.[14−26] In 2007, non-metal-engaged catalytic enantioselective radical reactions were also demonstrated by MacMillan et al. as part of the development of organocatalysis, which involves a Singly Occupied Molecular Orbital (SOMO) activation of enamines.[27−29] In recent years, hydrogen-bond interactions have also emerged as a powerful strategy to induce the stereoselectivity in radical reactions, with chiral phosphoric acids being the most used organocatalysts.[30−38]

Given the importance of chiral 1,2-diamine skeletons in agrochemicals and bioactive small molecules, we are interested in synthesizing these architectures from readily available starting materials using a chiral phosphoric acid-catalyzed radical reaction. Conventional methods for preparing 1,2-diamines involve the diamination and diazidation reactions of alkene substrates under the catalysis of transition metals, which typically require special diamination reagents such as diaziridinone and azido-iodine.[39−46] Another issue that needs

Received: October 15, 2025
Revised: December 2, 2025
Accepted: December 3, 2025

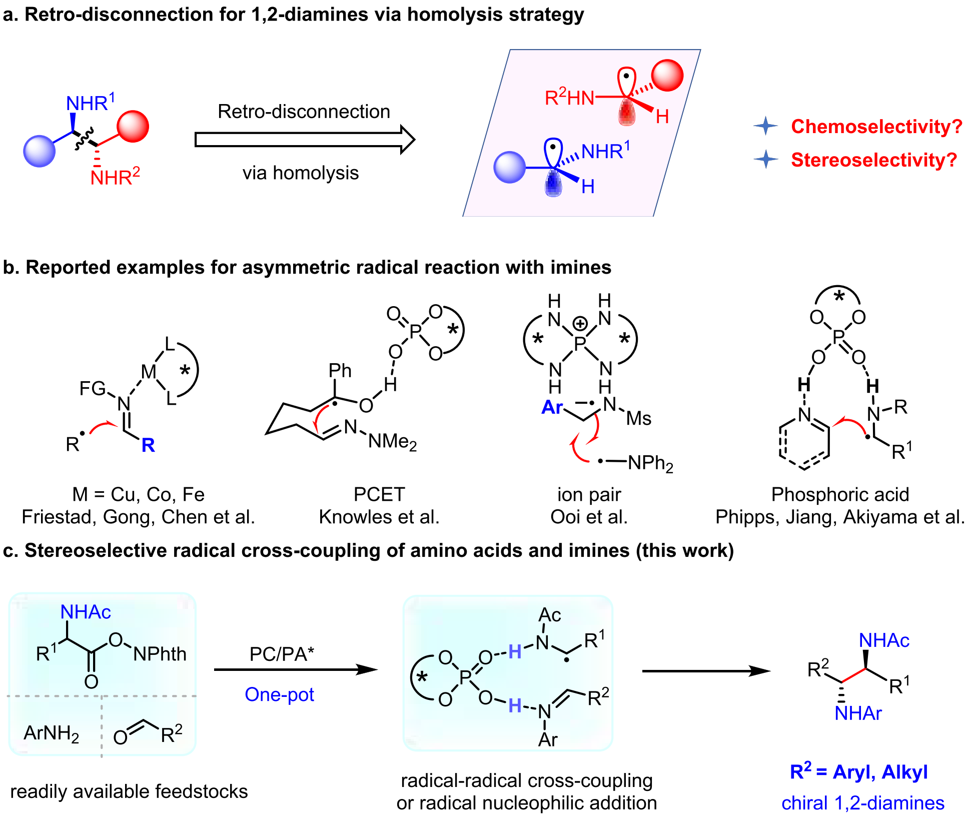


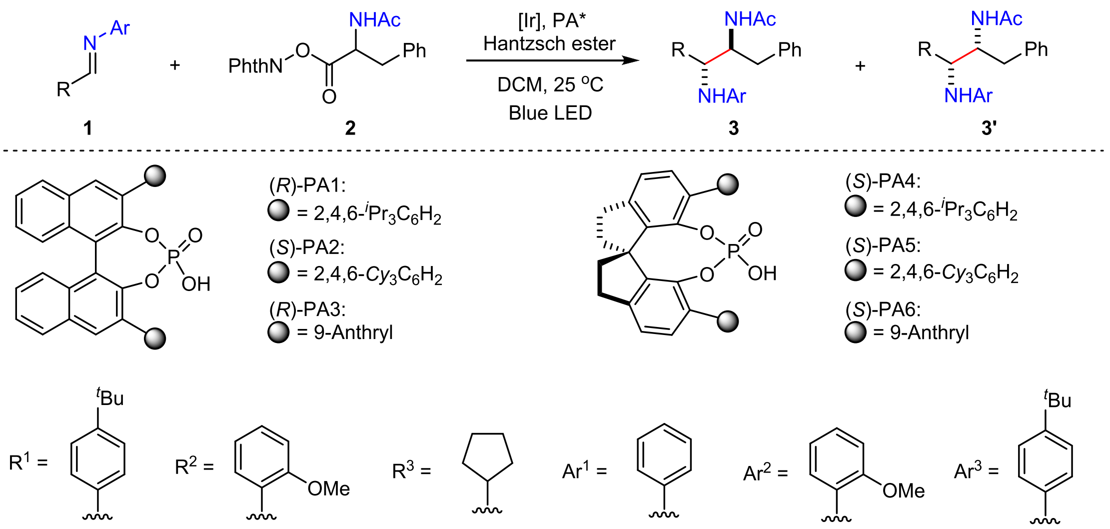
Figure 1. Challenges in enantioselective radical reactions and hydrogen-bond-catalyzed radical cross-coupling for the synthesis of chiral 1,2-diamines. (a), Retro-disconnection for 1,2-diamines via homolysis strategy. (b), Reported examples for asymmetric radical reaction with imines. (c), Stereoselective radical cross-coupling of amino acids and imines (this work).

to be tackled in these reactions is the stereoselective control, and only a few examples have been reported to date regarding the asymmetric diamination of alkenes.[47−49] The primary work on radical reaction with imines was carried out by Porta et al. in 1990, where $TiCl_3$ was used as a single electron donor and facilitated the addition of the benzene radical to imines.[50] The asymmetric version of this reaction was reported in 2000 by Naito et al. using α-carbonyl oxime ether as substrate and copper/chiral bisoxazoline as catalyst, albeit with poor enantioselectivity.[51] Later works by Friestad and Gong's group on asymmetric types of these reactions typically focused on aromatic hydrazones or indoline-2,3-diones substrates employing a similar catalytic system.[52−55] More recently, Chen's group reported a series of elegant works on Co- and Fe-catalyzed asymmetric radical addition with imines to generate a variety of chiral amino acids.[56−58] In 2013, a chiral phosphoric acid-catalyzed enantioselective intramolecular Aza-Pinacol cyclization reaction was reported by Knowles et al., in which the phosphoric acid acted as a Proton Couple Electron Transfer (PCET) catalyst.[59] In 2015, the Ooi group also reported a radical reaction with aromatic imines using an ion pair catalyst.[60] In recent years, phosphoric acid-catalyzed asymmetric radical reactions with imines were also reported by Phipps, Akiyama, and Jiang's group, providing various chiral amine products[61−66] (Figure 1b). Nevertheless, the existing radical reactions involving imines have primarily focused on aromatic imines and aza-heterocycles, and there is no report on radical reactions with aliphatic imines to date. Imines (which could be generated in situ from aldehydes and amines) and α-amino acids represent two of the most abundant building blocks in modern synthetic chemistry. Our aim is to utilize α-amino acids as precursors for the α-amino radical.[25,35,61,62] This radical can be stereoselectively captured by imine substrates, facilitated by hydrogen-bond interactions that arise from a chiral phosphoric acid (Figure 1c). To achieve chemoselectivity and stereoselectivity, the two substrates must be designed to include functional groups that can act as hydrogen-bond donors and acceptors, respectively.

■ METHODS

The redox-active ester of amino acids (0.1 mmol, 1.0 equiv), Ir photocatalyst (0.002 mmol, 2 mol %), chiral phosphoric acid (0.01 mmol, 10 mol %), and Hantzsch ester (0.1 mmol, 1.0 equiv) were weighed into a 10 mL vial containing a stir bar. The vial was purged with nitrogen gas three times. Then, a dichloromethane solution of the corresponding aldehyde (0.22 mmol, 2.2 equiv) and aniline (0.2 mmol, 2.0 equiv) was added to the vial via syringe under an inert atmosphere. The reaction mixture was stirred at 25 °C for 24 h under the emission of blue LEDs (λ_{max} = 450 nm, 8 W). Upon reaction completion, the crude product was washed with aqueous potassium carbonate solution (1.0 mol/L), and the aqueous phase was extracted with dichloromethane (5 mL) 2 times. The organic layer was dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by preparative thin-layer chromatography using hexane/ethyl acetate (4:1 to 2:1) as the eluent to provide the desired 1,2-diamine products. Full experimental details and characterization of compounds are given in the Supporting Information.

Table 1. Optimization of Reaction Conditions[a]



Entry	R	Ar	PA*	Yield[b]	d.r.	e.r.[c]
1	R^1	Ar^1	(R)-PA1	67%	2.4:1	89:11
2	R^1	Ar^1	(S)-PA2	70%	2.5:1	13:87
3	R^1	Ar^1	(R)-PA3	58%	3.7:1	84:16
4	R^1	Ar^1	(S)-PA6	55%	3.4:1	89:11
5	R^1	Ar^2	(R)-PA1	51%	1.2:1	95:5
6	R^1	Ar^2	(S)-PA2	53%	1.3:1	6.5:93.5
7	R^1	Ar^2	(R)-PA3	49%	1.1:1	90.5:9.5
8	R^1	Ar^2	(S)-PA4	53%	1.1:1	50.3:49.7
9	R^1	Ar^2	(S)-PA5	53%	1.3:1	50:50
10	**R^1**	**Ar^2**	**(S)-PA6**	**56%**	1.1:1	98:2
11	**R^2**	**Ar^3**	**(S)-PA6**	**51%**	1.2:1	99:1
12	**R^3**	**Ar^3**	**(S)-PA6**	**62%**	9:1	4:96
13	R^3	Ar^3	(S)-PA4	68%	4:1	48:52

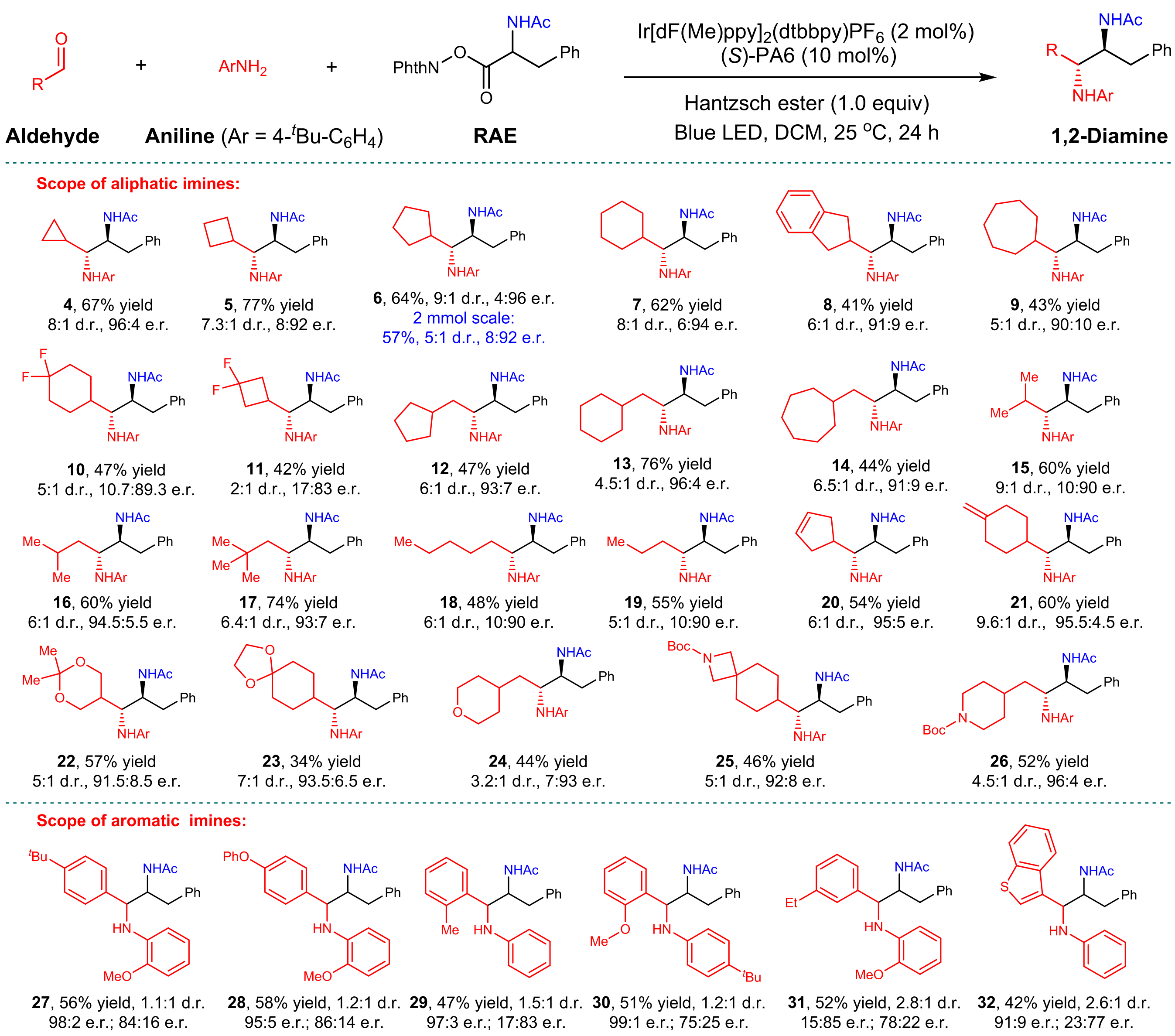
[a] Performed with imine **1** (0.2 mmol, 2.0 equiv), redox-active ester **2** (0.1 mmol, 1.0 equiv), Hantzsch ester (0.1 mmol, 1.0 equiv), Ir[dF(Me)ppy]$_2$(dtbbpy)PF$_6$ (2 mol %) and PA* (10 mol %) in 1.0 mL of dichloromethane at 25 °C under blue LED for 24 h. [b] Yields were determined by isolation. [c] The e.r. was only determined for the major isomer.

■ RESULTS AND DISCUSSION

To initiate our study of this reaction, we chose *N*-arylimine (**1**) and the phenylalanine-derived redox-active ester (**2**) presented in Table 1 as our model substrates. When using Ir[dF(Me)ppy]$_2$(dtbbpy)PF$_6$ as the photocatalyst and PA1 as the hydrogen-bond catalyst, after irradiating with blue LED light at a temperature of 25 °C, we achieved a product yield of 67%, accompanied by a diastereomeric ratio of 2.4:1 and an enantiomeric ratio of 89:11 for the major product (Table 1, Entry 1). Motivated by this initial result, a series of phosphoric acids were screened to further improve the reactivity and selectivity of this reaction. The results turned out to be not very positive when just changing the phosphoric acid (Table 1, Entries 2−4). We next screened several anilines that would form the imine substrate with aldehyde and found that 2-methoxy aniline gave the enantiomeric ratio of 95:5 under catalysis of PA1, but the diastereomeric ratio was only 1.2:1. Other phosphoric acids were also screened, and PA6 was found to be the best for the reaction, which provided the enantiomeric ratio of 98:2 (Table 1, Entries 5−10). Remarkably, the imine formed from 2-methoxy benzaldehyde and 4-*tert*-butyl aniline also exhibited an exceptional enantiomeric ratio (Table 1, Entry 11). Although the current catalytic system allows for an impressive enantiomeric ratio when working with aromatic imine substrates, achieving control over the diastereomeric ratio has proven to be challenging. To explore this reaction further, we also investigated aliphatic imines derived from aliphatic aldehydes and anilines. We were pleased to discover that *N*-(4-(*tert*-butyl)phenyl)-1-cyclopentylmethanimine yielded 62% of 1,2-diamine product with a diastereomeric ratio of 9:1 and an enantiomeric ratio of 96:4 when catalyzed by PA6 (Table 1, Entry 12). In contrast, other phosphoric acids, such as PA4, were found to be less effective in controlling the enantioselectivity (Table 1, Entry 13). Ultimately, we concluded that while aliphatic imine substrates can achieve both good diastereomeric ratios and excellent enantiomeric ratios, only exceptional enantiomeric ratios are attainable for aromatic imines under the current experimental conditions.

With the optimal conditions in hand, we embarked on an investigation of the substrate scope for this reaction, as depicted in Tables 2 and 3. First, a series of aliphatic imines were examined under the optimal conditions using phenylalanine redox-active ester (**2**) as the coupling partner. It is important to highlight that during the execution of this reaction, the imines were generated in situ from the corresponding aldehydes and anilines, greatly enhancing the practicality of this protocol. The imines derived from cyclopropyl carbaldehyde, cyclobutyl carbaldehyde, cyclopentyl carbaldehyde, cyclohexyl carbaldehyde, and cycloheptyl

Table 2. Substrate Investigation for the Imines[a]



4, 67% yield
8:1 d.r., 96:4 e.r.

5, 77% yield
7.3:1 d.r., 8:92 e.r.

6, 64%, 9:1 d.r., 4:96 e.r.
2 mmol scale:
57%, 5:1 d.r., 8:92 e.r.

7, 62% yield
8:1 d.r., 6:94 e.r.

8, 41% yield
6:1 d.r., 91:9 e.r.

9, 43% yield
5:1 d.r., 90:10 e.r.

10, 47% yield
5:1 d.r., 10.7:89.3 e.r.

11, 42% yield
2:1 d.r., 17:83 e.r.

12, 47% yield
6:1 d.r., 93:7 e.r.

13, 76% yield
4.5:1 d.r., 96:4 e.r.

14, 44% yield
6.5:1 d.r., 91:9 e.r.

15, 60% yield
9:1 d.r., 10:90 e.r.

16, 60% yield
6:1 d.r., 94.5:5.5 e.r.

17, 74% yield
6.4:1 d.r., 93:7 e.r.

18, 48% yield
6:1 d.r., 10:90 e.r.

19, 55% yield
5:1 d.r., 10:90 e.r.

20, 54% yield
6:1 d.r., 95:5 e.r.

21, 60% yield
9.6:1 d.r., 95.5:4.5 e.r.

22, 57% yield
5:1 d.r., 91.5:8.5 e.r.

23, 34% yield
7:1 d.r., 93.5:6.5 e.r.

24, 44% yield
3.2:1 d.r., 7:93 e.r.

25, 46% yield
5:1 d.r., 92:8 e.r.

26, 52% yield
4.5:1 d.r., 96:4 e.r.

27, 56% yield, 1.1:1 d.r.
98:2 e.r.; 84:16 e.r.

28, 58% yield, 1.2:1 d.r.
95:5 e.r.; 86:14 e.r.

29, 47% yield, 1.5:1 d.r.
97:3 e.r.; 17:83 e.r.

30, 51% yield, 1.2:1 d.r.
99:1 e.r.; 75:25 e.r.

31, 52% yield, 2.8:1 d.r.
15:85 e.r.; 78:22 e.r.

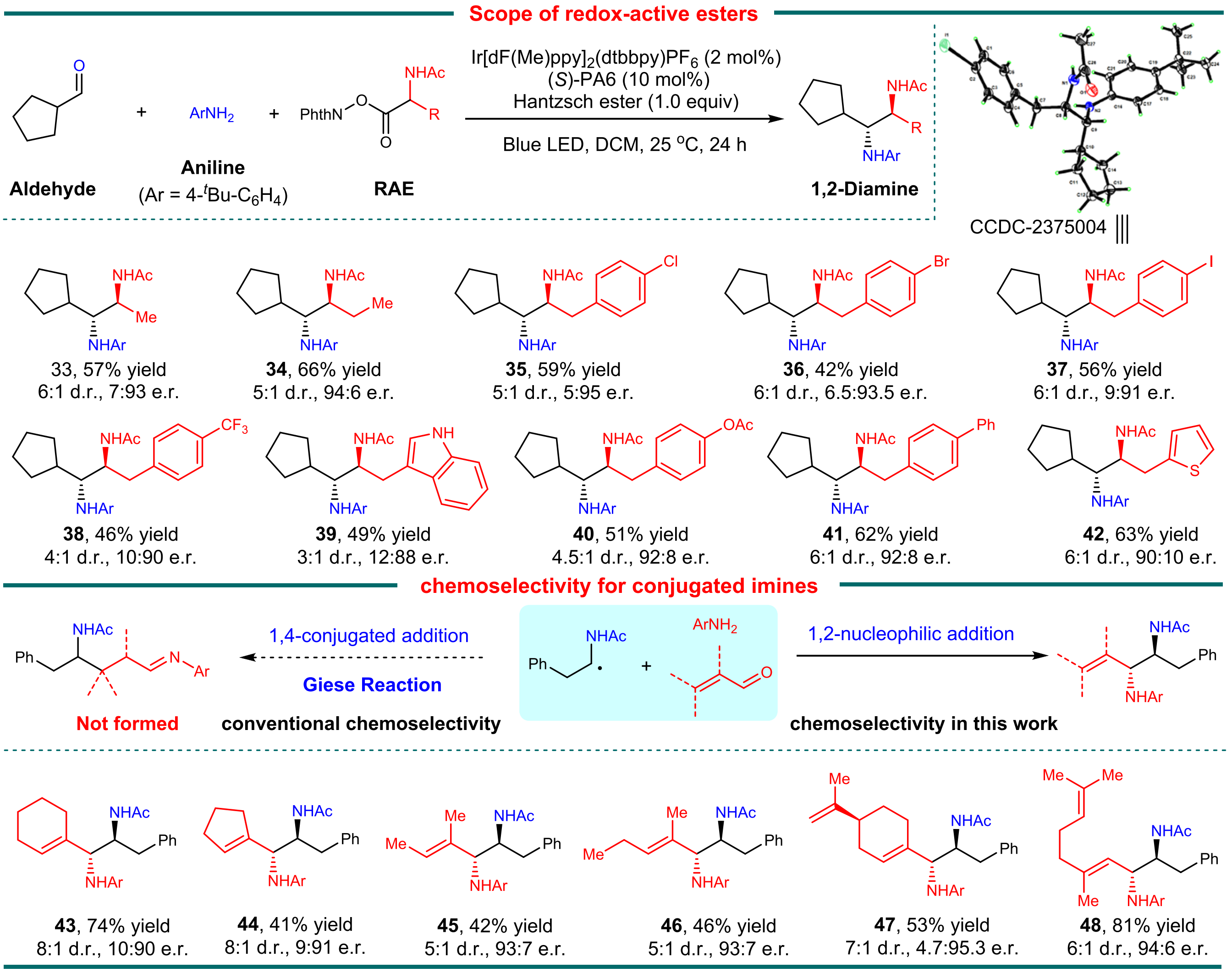
32, 42% yield, 2.6:1 d.r.
91:9 e.r.; 23:77 e.r.

[a] All of the yields were isolated yields. The diastereomeric ratio was determined by isolation yield.

carbaldehyde all provided moderate to good yields and diastereomeric ratios, with excellent enantiomeric ratios (**4**–**9**). Notably, product **6** was synthesized on a 2 mmol scale, achieving a yield of 57%, a diastereomeric ratio of 5:1, and an enantiomeric ratio of 8:92. Substrates with fluorine atoms gave decreased stereoselectivities (**10**, **11**). Other aliphatic imines derived from acyclic carbaldehydes all provided the 1,2-diamines with moderate yields, moderate diastereomeric ratios, and good to excellent enantiomeric ratios (**12**–**19**). Importantly, olefin groups were well compatible in this reaction, offering good yields and stereoselectivities (**20**, **21**). Oxygen atom containing heterocycles (**22**–**24**) and *aza*-heterocycles (**25**, **26**) were also well tolerated in the reaction conditions and provided good yields and enantioselectivities. A series of aromatic imines derived from aryl aldehydes were also tested under the optimal conditions, and we found that all of these substrates were hard to control the diastereoselectivity. We speculate that this discrepancy arises from the weaker hydrogen-bonding interaction between aromatic imine and phosphoric acid. Additionally, the planar structure of the aromatic imine may further diminish facial selectivity during the radical addition process. Besides, a time course experiment of the d.r. value for **29** was also conducted, and the results indicated that the diastereoselectivity of this reaction was kinetic-controlled (see page 42 in the Supporting Information). The 2- and 4-substituted aromatic imines could provide very excellent enantioselectivities for one of the diastereomers and moderate enantioselectivities for another (**27**–**30**). While 3-substituted aromatic imine and heterocyclic imine gave moderate enantioselectivities for both diastereomers (**31**, **32**).

Having demonstrated the wide scope of the imine substrates in this reaction, we turned our attention to the scope of amino acid redox-active esters. The results indicated that a series of amino acid derivatives worked well under optimal conditions. Substrates derived from alanine (**33**), 2-aminobutyric acid (**34**), tryptophan (**39**), and tyrosine (**40**) all gave good to excellent enantiomeric ratios and moderate diastereomeric ratios. A series of substituted phenylalanine derivatives also

Table 3. Substrate Investigation for Redox-Active Esters and *α*, *β*-Unsaturated Imines[a]



33, 57% yield
6:1 d.r., 7:93 e.r.

34, 66% yield
5:1 d.r., 94:6 e.r.

35, 59% yield
5:1 d.r., 5:95 e.r.

36, 42% yield
6:1 d.r., 6.5:93.5 e.r.

37, 56% yield
6:1 d.r., 9:91 e.r.

38, 46% yield
4:1 d.r., 10:90 e.r.

39, 49% yield
3:1 d.r., 12:88 e.r.

40, 51% yield
4.5:1 d.r., 92:8 e.r.

41, 62% yield
6:1 d.r., 92:8 e.r.

42, 63% yield
6:1 d.r., 90:10 e.r.

43, 74% yield
8:1 d.r., 10:90 e.r.

44, 41% yield
8:1 d.r., 9:91 e.r.

45, 42% yield
5:1 d.r., 93:7 e.r.

46, 46% yield
5:1 d.r., 93:7 e.r.

47, 53% yield
7:1 d.r., 4.7:95.3 e.r.

48, 81% yield
6:1 d.r., 94:6 e.r.

[a] All of the yields were isolated yields. The diastereomeric ratio was determined by isolation yield (**33**–**42**, **44**) and ^{1}H NMR analysis (**43**, **45**–**48**).

worked well and provided good stereoselectivities (**35**–**38**, **41**, and **42**). In addition, the X-ray diffraction of product **37** confirmed the absolute configuration of the 1,2-diamine products. To further investigate the characteristics of this reaction, a variety of *α*, *β*-unsaturated imines were also subjected to the reaction conditions. We were delighted to find that a series of multisubstituted enals performed well under the reaction conditions and gave 1,2-diamine products in moderate to good yields with satisfactory stereoselectivities. As illustrated in Table 3, imines derived from cyclohex-1-ene-1-carbaldehyde and cyclopent-1-ene-1-carbaldehyde both yielded promising results (**43**, **44**). Additionally, acyclic enals all gave moderate yields and good stereoselectivities (**45**, **46**). Notably, imines derived from natural aldehydes, such as perillaldehyde and geranial, also achieved good yields and stereoselectivities (**47**, **48**). This observed chemoselectivity is particularly intriguing, as traditional site selectivity for radical additions to *α*, *β*-unsaturated carbonyl compounds typically favors 1,4-selectivity, commonly referred to as the Giese reaction.[67]

To investigate the possible mechanism underlying this reaction, several control experiments were performed. First, only a trace of the product was observed when 2 equiv of TEMPO was added to the reaction system, indicating that TEMPO could inhibit this reaction. Second, this reaction only provided the product in 25% yield with a d.r. value of 2.3:1 in the absence of Ir photocatalyst, which implies that an EDA complex might form between substrates (2 or imine) and Hantzsch ester.[68] However, the significantly lower yield in the control experiment demonstrates that the EDA complex alone is insufficient to drive the reaction effectively (Figure 2a). In addition, a series of radical capture experiments were conducted for both substrates using methyl 2-phenyl acrylate (53) as a radical capture reagent. The *α*-amino radical derived from redox-active ester (2) was successfully captured by 53 to generate Giese product 54 in 32% yield. Both radical intermediates derived from aliphatic imine (49) and aromatic imine (50) were captured by 53 to provide products 55 and 56 in 41 and 65% yield, respectively. 55 and 56 can also be detected without the addition of Ir photocatalyst, albeit with lower yields. While no product was formed in the absence of Hantzsch ester (Figure 2b). These findings further confirm that the reaction proceeds via a radical mechanism with both the Ir catalyst and Hantzsch ester playing crucial roles in radical generation. To gain further insights into the roles of Ir and Hantzsch ester in the formation of radical intermediates from substrates, we conducted a series of fluorescence

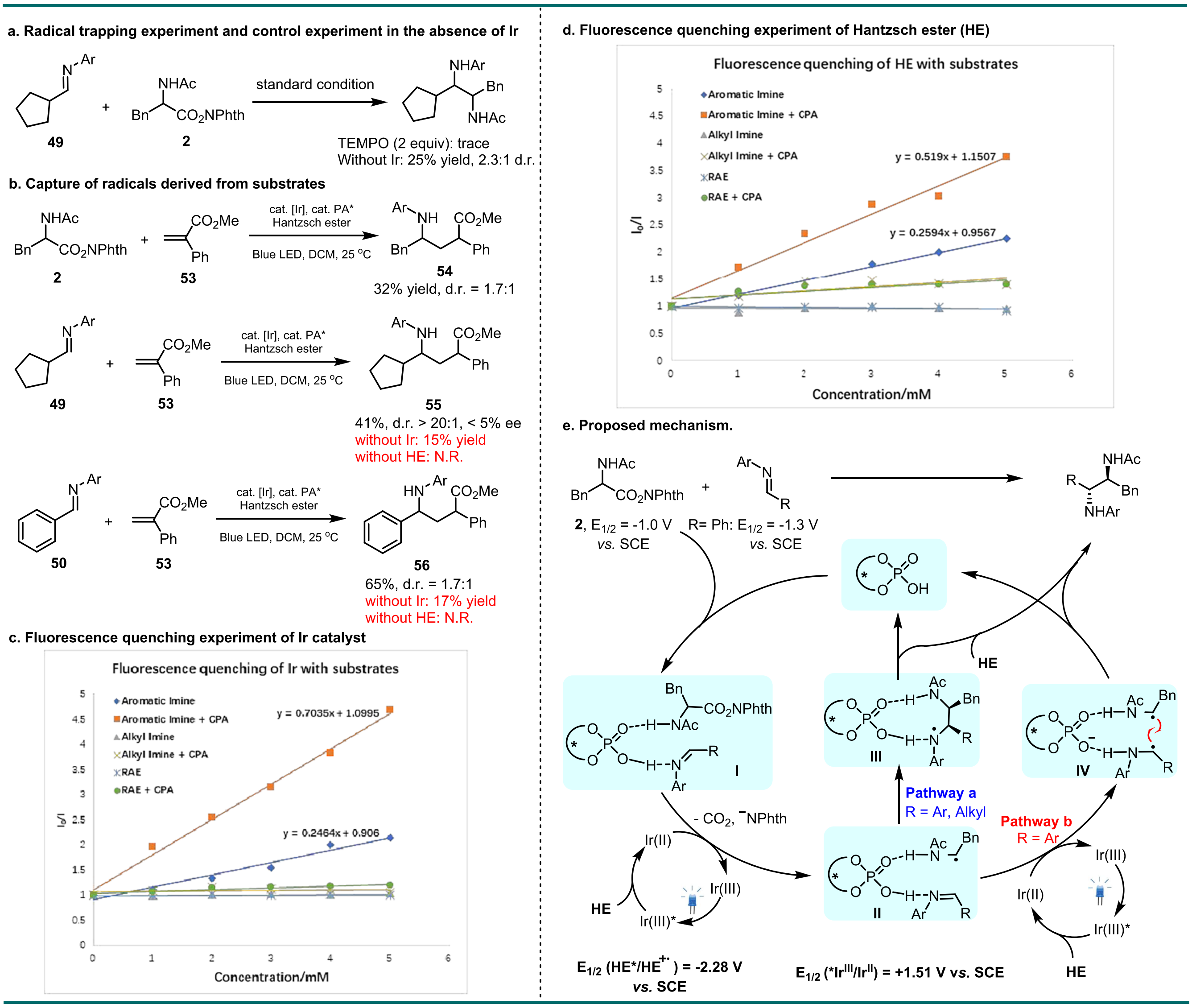


Figure 2. Mechanistic investigation of the reaction. (a), Radical trapping experiment and control experiment in the absence of Ir. (b), Capture of radicals derived from substrates. (c), Fluorescence quenching experiment of the Ir catalyst. (d), Fluorescence quenching experiment of Hantzsch ester (HE). (e), Proposed mechanism.

quenching experiments. The results revealed that only aromatic imine exhibited significant fluorescence quenching of both the Ir catalyst and Hantzsch ester. Notably, this quenching effect was enhanced by the addition of phosphoric acid, with a more pronounced enhancement observed for the Ir catalyst (Figure 2c,2d). These observations suggest that the formation of α-amino radicals from aromatic imines likely involves a proton-coupled electron transfer (PCET) process, wherein the Ir(II) catalyst, assisted by phosphoric acid, donates an electron to the imine. In contrast, redox-active ester (2) and alkyl imine substrates showed minimal fluorescence quenching of either the Ir catalyst or Hantzsch ester, with a slight increase in the quenching effect upon the addition of phosphoric acid. This indicates that these substrates (2 and alkyl imines) have a lower propensity to form stable electron donor−acceptor (EDA) complexes with Ir or Hantzsch ester. Based on these findings, we proposed a plausible reaction mechanism illustrated in Figure 2e. The redox-active ester (2, $E_{1/2}$ = −1.0 V vs. SCE, see Figure S14 in the Supporting Information) and imine substrate (R = 2-OMe-C_6H_4, $E_{1/2}$ = −1.3 V vs. SCE, see Figure S15 in the Supporting Information) initially form intermediate I through hydrogen-bond interaction with phosphoric acid. The photoactivated $[Ir^{III}]^*$ catalyst ($E_{1/2}$ = +1.51 V vs. SCE)[69] undergoes reduction by Hantzsch ester ($E_{1/2}$ = −2.28 V vs. SCE)[70] to generate $[Ir^{II}]$, which subsequently transfers an electron to substrate 2, yielding radical intermediate II. This intermediate then undergoes nucleophilic addition to alkyl imine, producing N-centered radical intermediate III, which is finally reduced by Hantzsch ester to form the desired product (Figure 2e, pathway a).[50−56,71] For aromatic imine substrates, an alternative radical−radical cross-coupling pathway also becomes possible. In this scenario, $[Ir^{II}]$ donates an electron to the aromatic imine, generating another α-amino radical that forms intermediate IV, ultimately leading to product formation (Figure 2e, pathway b).

■ CONCLUSIONS

In conclusion, we have developed a stereoselective approach for the modular synthesis of chiral 1,2-diamines through a phosphoric acid-catalyzed radical nucleophilic addition reaction to imines. This protocol demonstrates a wide range of substrate compatibilities, resulting in moderate to good yields of diamine products with high stereoselectivity. Notably, an unusual site selectivity was also observed for the α, β-unsaturated imine substrates, which preferentially undergoes 1,2-radical nucleophilic addition instead of the conventional 1,4-conjugate addition. The strategy of leveraging hydrogen-bond interactions to enhance stereoselectivity and promote substrate reactivity toward radical species paved the way for future development and the exploration of other challenging enantioselective radical transformations.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.5c07372.

> Experimental details and procedures, characterization and spectra of all unknown compounds, and X-ray crystal structure (PDF)

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Author Contributions

§W.S. and W.C. contributed equally to this work. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We gratefully acknowledge the financial support from the Chinese Academy of Sciences, the National Natural Science Foundation of China (22271297), and the Program for Talented Young Investigators of Guangdong Province (2021QN020533).

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