Visible-Light Driven Enantioselective Radical Addition to Imines Enabled by Excitation of Chiral Phosphoric Acid–Imine Complex

Tatsuhiro Uchikura, Nanami Kamiyama, Toshiki Mouri, Takahiko Akiyama*

Department of Chemistry, Gakushuin University, 1-5-1, Mejiro, Toshima-ku, Tokyo 171-8588, Japan

ABSTRACT: A visible-light driven enantioselective radical addition to imines enabled by the direct excitation of a chiral phosphoric acid-imine complex was developed. By using benzothiazolines as the radical precursors, chiral amine products were obtained with high enantioselectivities (up to 98% ee). Mechanistic studies elucidated that the chiral phosphoric acid-imine complex has photoredox activities for oxidizing benzothiazolines.

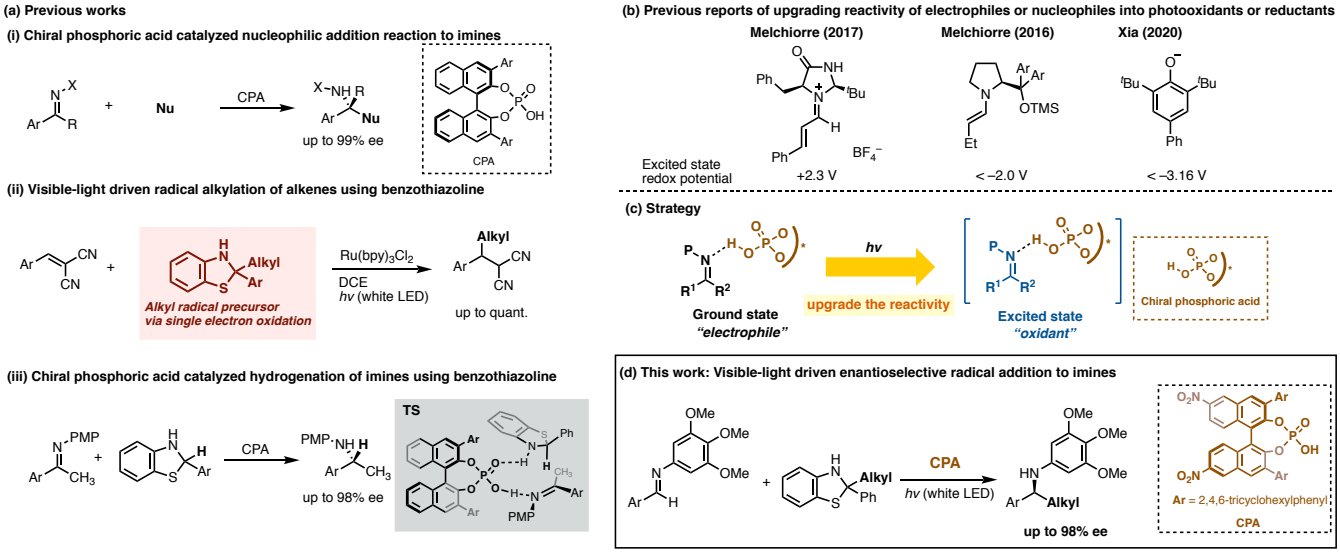
Because chiral amines occur widely in natural products and pharmaceuticals, the development of efficient methods for the synthesis of chiral amines continues to be an important issue in organic chemistry.[1] The enantioselective nucleophilic addition to imines is one of the most useful methods for the construction of chiral amines, and a range of chiral acid-catalyzed enantioselective nucleophilic addition reactions with imines have been reported.[2] We have reported chiral phosphoric acid catalyzed nucleophilic addition reactions with imines, such as the Mannich-type reactions and the Friedel–Crafts alkylation reactions (Scheme 1a-i).[3,4]

Although the enantioselective nucleophilic addition to imines through an ionic process has been widely explored, the radical version of the reaction is still limited in spite of its high substituent tolerance[5–7] because the enantio-control of free radical is not a trivial issue.[8] Ooi and coworkers[8b] and Jiang and coworkers[9] have reported the organo- and photocatalytic enantioselective radical addition of imines employing substrates containing a hydrogen bonding acceptor. In order to upgrade the reactivity of imine into a radical reaction, the excited state of iminium ions is useful due to its high oxidation potential. There are several reports of upgrading reactivity of electrophiles or nucloephiles into photooxidants or reductants (Scheme 1b). [10–12] Melchiorre and coworkers developed an enantioselective β-alkylation of enals via the excitation of iminium ions, wherein the iminium cations behaved as strong photooxidants (E = +2.3 V vs SCE) to generate radical anions. According to this phenomenon, we hypothesize that the protonation of imines by chiral acids will result in a high oxidation potential (Scheme 1c).

We have reported the alkyl and acyl transfer reactions of alkenes using benzothiazoline derivatives under photoirradiation[13] or thermal conditions (Scheme 1a-ii).[14] The benzothiazoline derivatives work as radical precursors by single-electron oxidation wherein free radicals are not generated, and the alkyl radicals are considered to be directly transferred to the radical acceptors because the formation of radical dimers was not observed at all.

We have also developed a chiral phosphoric acid catalyzed enantioselective transfer hydrogenation of ketimines using benzothiazoline derivatives as the hydrogen donor (Scheme 1a-iii).[15] Because of the bifunctional nature of chiral phosphoric acid, the transfer hydrogenation of ketimines proceeded in a highly enantioselective manner using benzothiazoline derivatives. Hence, we hypothesize that 2-alkyl benzothiazoline is applicable to the enantioselective radical transfer reactions with imines.

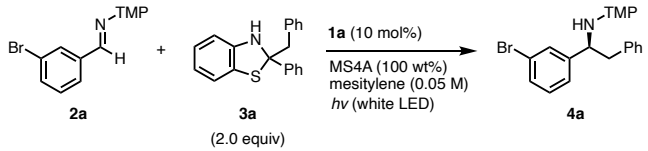
We wish to report herein a chiral phosphoric acid catalyzed visible-light driven enantioselective radical addition to imines by using benzothiazoline derivatives as the radical precursors (Scheme 1d).[16]



Scheme 1. Strategy of this study

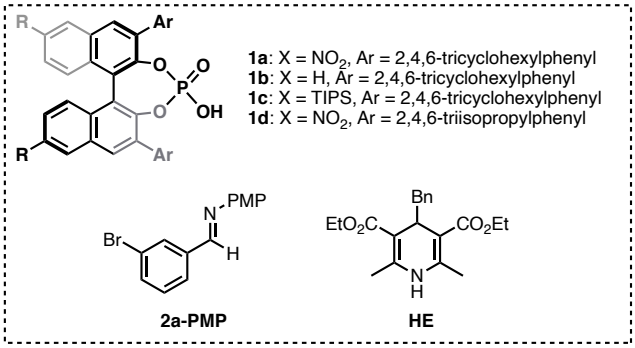
At the outset, *N*-3,4,5-trimethoxyphenyl (TMP)-substituted aldimine **2a** and benzothiazoline **3a** were mixed in mesitylene in the presence of chiral phosphoric acid (*R*)-**1** under photoirradiation conditions (Table 1). Among the chiral phosphoric acids examined, the nitrated BINOL skeleton containing **1a** afforded the most favorable result (99%, 90% ee). The nitro groups at the 6,6'-positions of BINOL phosphoric acid[17] were necessary for the high reactivity and enantioselectivity[18] (entries 1–4). The presence of the TMP group on the nitrogen atom of **2a** was critical, and the use of *N*-*p*-methoxyphenyl (PMP)-substituted aldimine **2a-PMP** in place of *N*-TMP-substituted aldimine **2a** lowered both enantioselectivity and reactivity (entry 5). Mesitylene was found to be the solvent of choice (entries 6 and 7). Furthermore, Hantzsch ester (**HE**), which is known as an alkyl radical precursor by single-electron oxidation, was not suitable (entry 8). Control experiments clarified that both **1a** and photoirradiation were critical to promote the reaction (entries 9 and 10). The enantioselectivity slightly decreased in the absence of MS4A (entry 11). The addition reaction was completely suppressed in air (entry 12).[19]

Table 1. Optimization of conditions.[a]



entry	Deviation from standard conditions	yield (%)	ee (%)
1	none	99	90
2	**1b** was used instead of **1a**	72	69
3	**1c** was used instead of **1a**	83	79
4	**1d** was used instead of **1a**	83	77
5	PMP protected imine **2a-PMP** was used instead of **2a**	31	56
6	In *m*-xylene	94	78
7	In toluene	85	75
8	HE was employed instead of **3a**	15	65
9	Without **1a**	0	-
10	Without photoirradiation	6	90
11	Without MS4A	83	86
12	Under air	0	-

[a]Reaction conditions: **2a** (0.050 mmol), **3a** (0.10 mmol), **1** (0.0050 mmol), and MS4A (17.5 mg) in mesitylene (1.0 mL).

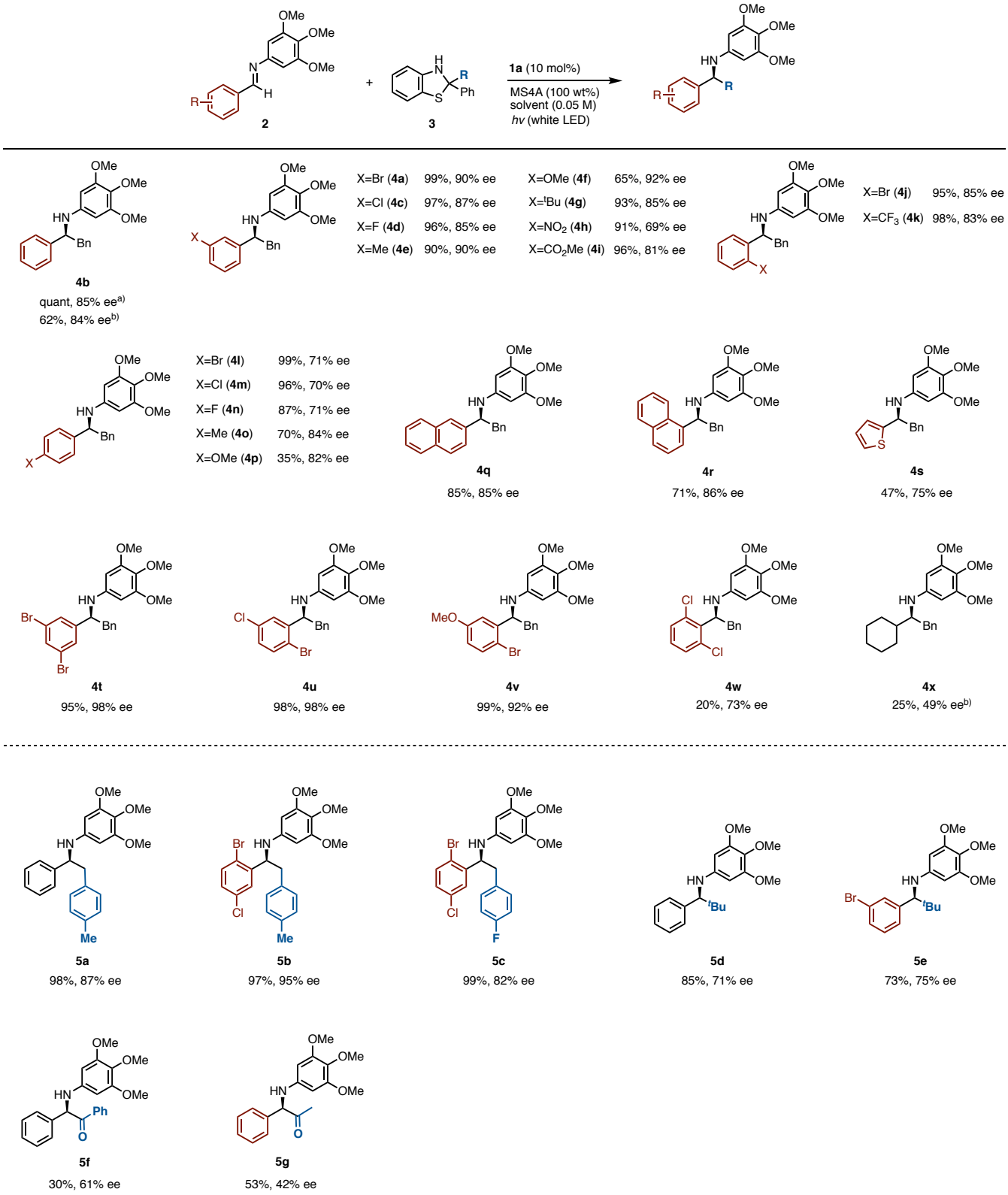


TMP: 3,4,5-trimethoxyphenyl, PMP: *p*-methoxyphenyl.

Next, we studied the substrate scope under the optimized reaction conditions (Figure 1). First, the effect of aryl groups was investigated. Aldimine **2b**, derived from benzaldehyde, gave corresponding adduct **4b** with 85% ee by employing 1.3 equiv of **3a**. Three-component synthesis starting from benzaldehyde, 3,4,5-trimethoxyaniline, and benzothiazoline **3a** was also successful to afford **4b** with almost same enantioselectivity (84% ee) albeit in moderate yield (62%). *Meta*-substituted aromatic imines were suitable substrates, affording the corresponding adducts with high enantioselectivities, and various *meta*-substituents were tolerated. A range of *meta*-substituents such as chloro, fluoro, methyl, methoxy, and *tert*-butyl groups were tolerated (**4c**–**4g**, 85–92% ee). Aldimine **2h** bearing the *m*-nitrophenyl moiety gave adduct **4h** with moderate enantioselectivity. The methoxycarbonyl group was tolerated and **4i** was obtained with

81% ee. *Ortho*-substituted phenyl moieties were also suitable to give **4j** and **4k** in high yields and with slightly low enantioselectivities. Although the *para*-substituted phenyl group decreased the enantioselectivity compared with the *ortho*-substituted phenyl group, the radical addition consistently proceeded to give adducts **4l**–**4p** in high yields and with approximately 70% ee (**4l**–**4p**). 1- and 2-Naphthyl imines also generated adducts **4q** and **4r** with high enantioselectivities. 2-Thienyl imine afforded **4s** in moderate yield and enantioselectivity. On the other hand, the disubstituted phenyl group showed excellent enantioselectivities. 3,5-Dibromophenyl aldimine **2t** afforded **4t** in 95% yield with 98% ee. 2,5-Disubstituted phenyl aldimines **2u** and **2v** afforded **4u** and **4v** with 98% ee and 92% ee, respectively. 2,6-Dichlorophenyl aldimine **2w,** which was generated *in situ*, exhibited low reactivity due to the steric effect, with moderate ee. Aliphatic aldimine **2x** showed low reactivity probably due to the reduced absorption of visible light.

The transfer of other alkyl or acyl groups on benzothiazoline was investigated. *p*-Methyl and *p*-fluorobenzyl groups underwent the transfer reaction smoothly to give **5a**–**5c** with high to excellent enantioselectivities. The *tert*-butyl group gave **5d** and **5e** with 71% ee and 75% ee, respectively. The transfer of benzoyl and acetyl groups also proceeded to furnish **5f** and **5g** in modest yields and with moderate enantioselectivities probably due to the undesired interaction of the carbonyl moiety with **1a**.



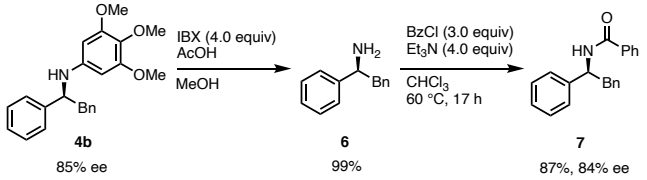
a) 1.3 equiv of **3a** was used.
b) Mixture of corresponding aldehyde, 3,4,5-trimethoxyaniline, **3a** and **1a** was irradiated under the same reaction conditions.

Figure 1. Generality of substrate.

In order to determine the absolute configuration of **4**, the TMP group of **4b** was removed by IBX to afford **6** in 99% yield without loss of optical purity (Scheme 2).[20] After benzoylation, the ee of **6** was determined and the absolute configuration of **4a** was found to

be *S* by comparison of the optical rotation sign and the retention time in the HPLC analysis of **7** with a chiral column with literature values.[21] The absolute stereochemistry of the other products was surmised by analogy.

Scheme 2. Deprotection of 3,4,5-trimethoxyphenyl group into primary amine.



4b 85% ee | **6** 99% | **7** 87%, 84% ee

In order to gain an insight into the reaction mechanism, several additional experiments were conducted.

In the presence of 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO), **4b** was not obtained at all and TEMPO adduct **8** was produced in 21% yield (Figure 2a). The generation of alkyl radical species was supported.

The reaction proceeded only under irradiation conditions (Figure 2b), suggesting that the reaction did not occur by a radical chain mechanism. Furthermore, the quantum yield of the reaction irradiated with 450 nm blue LED (Φ = 0.57%) also supported the non-radical chain mechanism (Figure 2c).[22]

According to Table 1, entry 8, **HE** was not a suitable radical precursor, and use of the benzothiazoline skeleton was crucial to attaining excellent enantioselectivity.[15c] In addition, dibenzyl, a radical dimer, was not detected under the reaction conditions. Thus, the results suggest that the free benzyl radical was not generated but direct radical transfer from the cation radical of benzothiazoline occurred in the transition state.

4b was obtained quantitatively with 85% ee using 1.3 equiv of racemic **3a** (Figure 1). If the reaction proceeds by one transition state, the racemization of **3a** is necessary. In order to confirm the racemization, we performed the deuterium scrambling experiment using **3a**. Upon mixing **3a-D$_2$** (deuterium content: 93%-D) with a stoichiometric amount of chiral phosphoric acid **1c** in mesitylene at rt for 24 h, the deuterium content at the benzylic position of **3a** decreased to 27% (Figure 2d). This result clearly shows that the chiral center of benzothiazoline was racemized under the reaction conditions by way of enamine form (Scheme S1).[23]

The UV–vis spectra of the mixture of **1a** and **2b** showed new absorbance in the visible region (Figure 2e). Therefore, the complex of **1a** and **2b** formed by hydrogen bonding (**2b@1a**) absorbed visible light. In contrast, little difference was observed by the addition of **3a**. These results suggest that the reaction proceeded not by the formation of an electron donor-acceptor complex between **2b** and **3a** but by the direct excitation of **2b@1a**. In order to verify this assumption, we conducted a fluorescence quenching experiment of **2b@1a**. The Stern-Volmer plot revealed that the fluorescence of **2b@1a** was quenched by **3a** (Figure 2f). In addition, we estimated the oxidation potential of the excited state of **2b@1a**. The cyclic voltammogram of **2b@1a** exhibited an irreversible reduction wave at $E_{p/2}$ = –1.04 V (vs SCE, Figure 2g). Furthermore, the fluorescence spectrum of **2b@1a** excited at 450 nm intersected with the absorbance spectrum at 472 nm, which indicates that the lowest excited state energy E_{00}* is 2.62 eV (Figure 2h). The reduction potential of **2b@1a** at the lowest excited state was estimated to be +1.58 V vs SCE.[24] Thus, **3a** (E_{ox} = 0.70 V vs SCE[13a]) could be oxidized by the excited state of **2b@1a**.[25]

There are the two possible pathways for the radical addition: (1) to radical anion of **2@1a** (**A**) or (2) to neutral **2@1a** (Figure S5, see Supporting Information). In order to determine which pathway is plausible, a highly reductive but low oxidative photocatalyst was added to the reaction. In the presence of 5 mol% of tris(2-phenylpyridyl)iridium ($Ir(ppy)_3$) as the photocatalyst, almost the same enantioselectivity was observed (Figure 2i). Using $Ir(ppy)_3$, protonated imines were firstly reduced by the excited state of $Ir(ppy)_3$ (E^*_{ox} = –1.73 V, E^*_{red} = 0.31 V vs SCE),[26] and **3a** (E_{ox} = 0.70 V vs SCE) could not be oxidized. Thus, the radical-radical coupling between **A** and the alkyl radical from the radical cation of **3a** is the plausible pathway for the reaction.

In order to clarify the rate-determining step, we conducted deuterium labeling studies (Figure 2j). When a 1:1 mixture of **2b** and **2b-D** was employed, the negative secondary kinetic isotope effect was observed (k_H/k_D = 0.85). Thus, the radical addition to imine, in which the carbon center of the C–H or C–D bond is converted from $C(sp^2)$ into $C(sp^3)$, is suggested to be the rate-determining step.[27]

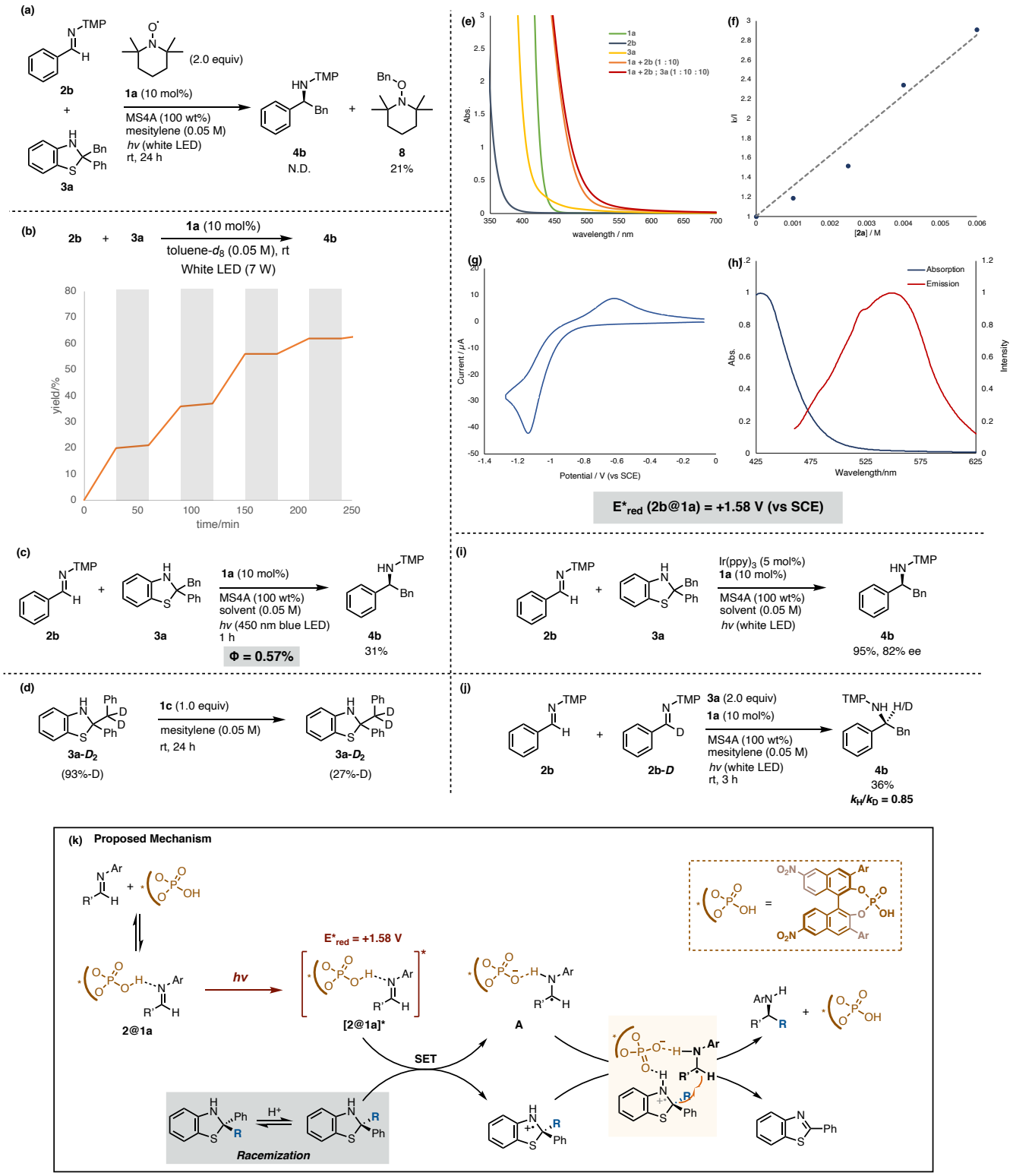


Figure 2. Mechanistic studies. (a) Radical scavenging experiment. (b) ON/OFF experiment. (c) Quantum yield measurement. (d) Deuterium exchange experiment if 3a. (e) UV–Vis spectra. (f) Stern–Volmer plot of 2b@1a. (g) Cyclic Voltammogram of 2b@1a. (h) Intersected of UV–Vis spectrum and emission spectrum of 2b@1a. (i) Photocatalytic experiment using $Ir(ppy)_3$. (j) Estimation of kinetic isotope effect. (k) Proposed mechanism of reaction.

According to these results, we propose a reaction mechanism (Figure 1k). First, protonated imines are excited by visible light and the resultant excited state of the chiral phosphoric acid-imine complex, which has high reduction potential, oxidizes benzothiazoline by

single electron transfer (SET) to generate the amino radical and the radical cation of benzothiazoline. Both of these effectively interact with chiral phosphate anion, and the radical transfer proceeds enantioselectively to afford chiral amine and benzothiazole. Under these reaction conditions, the racemization of benzothiazoline occurs and the matched enantiomer selectively participates in the radical addition.

In summary, we have developed a visible-light driven enantioselective radical addition to imines by the combined use of chiral phosphoric acid and benzothiazoline derivatives. A range of aromatic aldimines participated in the radical addition, and high to excellent enantioselectivities were observed. Several alkyl and acyl radicals were suitable for this reaction system. The use of aromatic aldimines bearing the 3,4,5-trimethoxyphenyl group on nitrogen is critical and the *N*-aryl moiety can be removed quantitatively without loss of enantioselectivity to give chiral primary amines. Mechanistic studies revealed that the key step of the reaction is the excitation of the chiral phosphoric acid-imine complex, which has high reduction potential (E_{red}^* = +1.58 V) for oxidizing benzothiazolines. Furthermore, the asymmetric carbon center of benzothiazoline is racemized under the reaction conditions and this skeleton is crucial for the interaction with chiral phosphoric acid to exhibit high enantioselectivity.

To the best of our knowledge, this is the first report of a photoinduced electron transfer mediated reaction enabled by the excitation of an acid-imine complex.[28] The highly oxidative excited state of the protonated imine is expected to make possible various photoreactions in the future.

ASSOCIATED CONTENT

Supporting Information

Additional experimental details and characterization data for new compounds.

AUTHOR INFORMATION

Corresponding Author

Takahiko Akiyama – *Department of Chemistry, Faculty of Science, Gakushuin University, 1-5-1, Mejiro, Toshima-ku, Tokyo, Japan;* ORCID: 0000-0003-4709-4107
Email: takahiko.akiyama@gakushuin.ac.jp

Authors

Tatsuhiro Uchikura – *Department of Chemistry, Faculty of Science, Gakushuin University, 1-5-1, Mejiro, Toshima-ku, Tokyo, Japan;* ORCID: 0000-0002-0327-3675
Email: tatsuhiro.uchikura@gakushuin.ac.jp

Nanami Kamiyama – *Department of Chemistry, Faculty of Science, Gakushuin University, 1-5-1, Mejiro, Toshima-ku, Tokyo, Japan*

Toshiki Mouri – *Department of Chemistry, Faculty of Science, Gakushuin University, 1-5-1, Mejiro, Toshima-ku, Tokyo, Japan*

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[18] Detail of comparison of **1a** and **1b** to realize the reason of necessity of nitro group at 6,6'-position of BINOL skeleton was shown in Supporting Information. **1a** was associated with **2b** more favorable than **1b** observed by ^{1}H NMR (Figure S6, see Supporting Information).

[19] Detail screening of conditions were investigated in the presence of photocatalyst (Table S1: See Supporting Information).

[20] Ee of **6** was determined after benzoylation of primary amine. The detail was shown in Supporting Information.

[21] (a) Wu, M. J.; Pridgen, L. N. Synthesis of Chiral α-Alkyl Phenethylamines via Organometallic Addition to Chiral 2-Aryl-1,3-oxazolidines. *J. Org. Chem.* **1991**, *56*, 1340–1344. (b) Kanta De, C.; Klauber, E. G.; Seidel, D. Merging Nucleophilic and Hydrogen Bonding Catalysis: An Anion Binding Approach to the Kinetic Resolution of Amines. *J. Am. Chem. Soc.* **2009**, *131*, 17060–17061. (c) Kim, S.; Choi, Y. K.; Hong, J.; Park, J.; Kim, M.-J. *Candida Antarctica* Lipase A and *Pseudomonas Stutzeri* Lipase as a Pair of Stereocomplementary Enzymes for the Resolution of 1,2-Diarylethanols and 1,2-Diarylethanamines. *Tetrahedron Lett.* **2013**, *54*, 1185–1188.

[22] The photon flux of the 450 nm blue LED was determined by standard ferrioxalate actinometry. The detail of the method was shown in Supporting Information. Representative example of reference, see: Cismesia, M. A.; Yoon, T. P. Characterizing Chain processes in Visible Light Photoredox Catalysis. *Chem. Sci.* **2015**, *6*, 5426–5434.

[23] Deuterium exchange pathway via racemization of **3a** was shown in Scheme S1 (See Supporting Information).

[24] E^* was calculated by the equation: $E^* = E_{red} + E_{00}$. Buzzetti, L.; Crisenza, G. E. M.; Melchiorre, P., Mechanistic Studies in Photocatalysis. *Angew. Chem. Int. Ed.* **2019**, *58*, 3730–3747.

[25] Using **1b** instead of **1a**, the reduction potential of excited state was calculated to $E_{red}^* = +1.47$ V, which is large enough to oxidize **3a** (Figure S3 and S4, see Supporting Information). Therefore, the reduction potential of excited state was not crucial factor of the nitro group of chiral phosphoric acid.

[26] Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. Visible Light Photoredox Catalysis with Transition Metal Complexes: Applications in Organic Synthesis. *Chem. Rev.* **2013**, *113*, 5322–5363.

[27] Simons, J. W.; Rabinovitch, B. S. Deuterium Isotope Effects in Rates of Methylene Radical Insertion into Carbon–Hydrogen Bonds and Across Carbon Double Bonds. *J. Am. Chem. Soc.* **1963**, *85*, 1023–1024

[28] Donor-acceptor type imines could be used as photoredox catalyst ($E^*_{ox} = -1.45$ - -1.52 V vs SCE) to reduce electron deficient alkyl halides, see: Uraguchi, D.; Tsuchiya, Y.; Ohtani, T.; Enomoto, T.; Masaoka, S.; Yokogawa, D.; Ooi, T. Unveiling Latent Photoreactivity of Imines. *Angew. Chem. Int. Ed.* **2020**, *59*, 3665–3670.