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

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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. 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. 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). 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 because the enantio-control of free radical is not a trivial issue. Ooi and coworkers and Jiang and coworkers 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 nucleophiles into photooxidants or reductants (Scheme 1b). Melchiorre and coworkers developed an enantioselective β-alkylation of enals via the excitation of iminium ions, wherein the iminium cations behaved as strong photooxidents (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 or thermal conditions (Scheme 1a-ii). 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). 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).
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 were necessary for the high reactivity and enantioselectivity (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).

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 |
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 \textit{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.
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). After benzylation, the ee of 6 was determined and the absolute configuration of 4a was found to

Figure 1. Generality of substrate.
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.\textsuperscript{21} The absolute stereochemistry of the other products was surmised by analogy.

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

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 ($\Phi = 0.57\%$) also supported the non-radical chain mechanism (Figure 2c).\textsuperscript{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.\textsuperscript{16} 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-Ds (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).\textsuperscript{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 $E_{1/2} = -1.04$ 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).

In addition, the reduction potential of 2b@1a at the lowest excited state was estimated to be $+1.58$ V vs SCE.\textsuperscript{24} Thus, 3a ($E_{ox} = 0.70$ V vs SCE) could be oxidized by the excited state of 2b@1a.\textsuperscript{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-pyridyl)indium (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),\textsuperscript{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 ($k_0/k_D = 0.85$). Thus, the radical addition to imine, in which the carbon center of the C–H or C–D bond is converted from C(sp$^3$) into C(sp$^3$), is suggested to be the rate-determining step.\textsuperscript{27}
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 benzo-thiazoline 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 aildmines 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 aildmines bearing the 3,4,5-trimethoxyphenyl group on nitrogen is critical and the N-ary 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 ($E_{\text{red}}^\circ = +1.58$ 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 photoiniated reaction enabled by the excitation of an acid-imine complex. 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.

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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 1H 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.

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