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Catalytic Enantioselective Addition of Prochiral Radicals to Vinylpyridines

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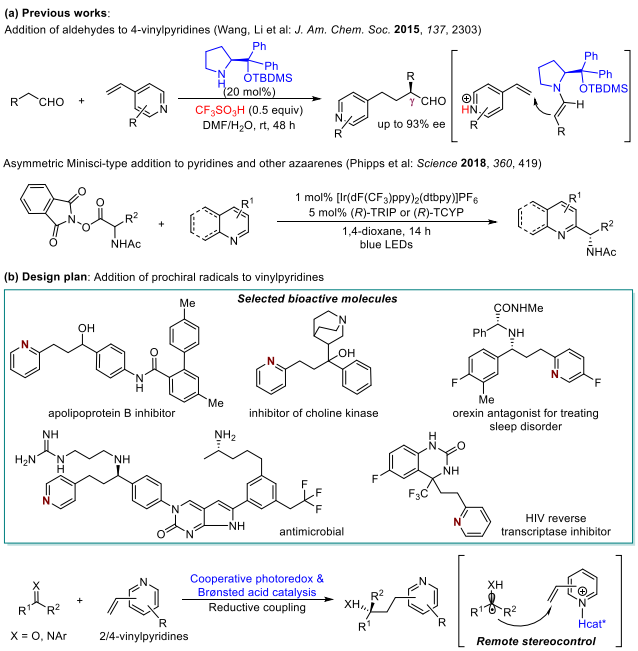
ABSTRACT: Pyridine, one of the most important azaarenes, is ubiquitous in functional molecules. The electronic properties of pyridine have been exploited to trigger asymmetric transformations of prochiral species as a direct approach for accessing chiral pyridine derivatives. However, the full potential of this synthetic strategy for the construction of enantioenriched γ-functionalized pyridines remains untapped. Here, we describe the first enantioselective addition of prochiral radicals to vinylpyridines under cooperative photoredox and asymmetric catalysis mediated by visible light. The enantioselective reductive couplings of vinylpyridines with aldehydes, ketones and imines were achieved by employing a chiral Brønsted acid to activate the reaction partners and provide stereocontrol *via* H-bonding interactions. Valuable chiral γ-secondary/tertiary hydroxyl- and amino-substituted pyridines were obtained in high yields with good to excellent enantioselectivities.

INTRODUCTION

Pyridine is an important azaarene commonly found in pharmaceuticals,[1] agrochemicals,[2] functional materials,[3] ligands[4] and natural products.[5] The synthesis of pyridine-containing chiral architectures has been the subject of intense research in recent years.[6-7] One widely accepted protocol for the formation of such species is the enantioselective functionalization of prochiral pyridines triggered by the electron-deficient nature of the pyridine. In addition to the advantage of being direct, this attractive strategy is well-suited for various ground-up approaches, allowing the construction of diverse stereocentres at the *α*- and *β*-positions of pyridines.[8-15] In particular, in 2015, Wang and co-workers reported a chiral secondary amine-catalysed enantioselective conjugate addition of aldehydes to 4-vinylpyridines, and this procedure generated *γ*-tertiary carbon stereocentres for the first time (Scheme 1a).[16] The combinatorial use of a strong Brønsted acid to activate the weakly electrophilic vinylpyridines and enamine catalysis to provide a stereocontrolled environment for nucleophiles was responsible for the high reactivity and enantioselectivity. To improve the diversity of the suitable prochiral nucleophiles, especially for challenging tertiary variants to furnish important tetrasubstituted stereocentres, the development of a more reactive protocol with a practical stereocontrol strategy is of great interest.

Scheme 1. Development of an Enantioselective Radical Addition Protocol to Access γ-Functionalized Pyridines



Radical-based transformations are well known to proceed with high reactivity.[17] In recent years, visible-light-driven photoredox catalysis[18-19] has been utilized as a powerful and sustainable tool in radical chemistry to accomplish various addition reactions of radical species to vinylpyridines.[20-27] In most cases, an extra catalyst to

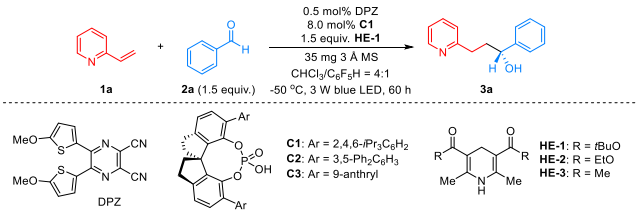
promote the transformation was not necessary, which is consistent with the higher reactivity of these systems compared to that of the ionic approach.[20-24] In addition, the groups of Melchiorre[25] and Ngai[26] revealed that both organic and inorganic acid catalysts could readily activate less reactive manifolds by interacting with the nitrogen atom of the pyridine to reduce the energy of the LUMO at the *β*-position of the alkene. Brønsted acid catalysis was recently adopted by the Phipps group and by our group to develop photoredox asymmetric Minisci-type additions (Scheme 1a)[28] and protonation[29] strategies.[30-35] While this catalysis platform has been shown to generate tertiary carbon stereocentres *α* to pyridines with high enantioselectivities,[28,29,36] the corresponding conjugate additions of *α*-amino radicals to alkenylpyridines to generate *β*-tertiary stereocentres provided poor enantioselectivities.[25] This result is likely due to the longer distance between the *α*-amino radical and the nitrogen-coordinated chiral catalyst, which reduces the efficacy of the enantiofacial induction. The formation of even more distant γ-stereocentres through the analogous conjugate addition of prochiral radicals to vinylpyridines is therefore a formidable challenge.

Among the γ-functionalized pyridines, derivatives with a secondary or tertiary alcohol or amine at the *γ*-position are especially attractive owing to their varied and significant biological activities (Scheme 1b).[37-42] We envisioned that the enantioselective addition of secondary/tertiary ketyl and *α*-aminoalkyl radicals to vinylpyridines would provide direct access to *γ*-secondary/tertiary alcohol-functionalized pyridines. Single-electron transfer reductions of aldehydes, ketones and imines under photoredox catalysis with tertiary amines as the sacrificial electron/hydrogen donors have been reported to furnish the corresponding radical species.[26,27,32,43-47] As such, we sought to perform the umpolung-type asymmetric reductive coupling reactions of aldehydes, ketones and imines with 2-vinylpyridines by exploring the viability of chiral Brønsted acid catalysis (Scheme 1b).

RESULTS AND DISCUSSION

(1) Reaction Optimization. We began our investigation by selecting 2-vinylpyridine (**1a**) and benzaldehyde (**2a**) as model substrates (Table 1). The initial study revealed that the reaction proceeded well when using our developed dicyanopyrazine-derived chromophore (DPZ) as the photoredox catalyst with a catalytic amount of a phosphoric acid instead of a Lewis acid (see entry 1, Table S1 in the SI). The results prompted us to examine a range of chiral phosphoric acids, tertiary amine reductants and reaction parameters (see Table S1 in the SI). To our delight, conducting the reaction in a mixture of $CHCl_3$ and C_6F_5H as the solvent (v/v = 4:1) at −50 °C for 60 h in the presence of 0.5 mol% DPZ, 8.0 mol% chiral SPINOL-based spirocyclic chiral phosphoric acid (SPINOL-CPA) **C1**, 1.5 equiv. of Hantzsch ester (HE) **HE-1** and 35 mg of 3 Å molecular sieves (MS) as an additive furnished chiral product **3a** in 93% yield and 90% ee (entry 1). The enantioselectivity was influenced by the substituents at the 6,6'-positions of the SPINOL; for instance, catalysts **C2** and **C3** afforded **3a** in only 15% ee and 35% ee, respectively (entries 2–3). The more conveniently accessible (*S*)-BINOL-based TRIP-PA (**C21**) was also tested under the optimized reaction conditions, but **3a** was obtained in a 62% yield with only 11% ee (see entry 100, Table S1 in the SI). When the 3-substitutent of **HE-1** was changed to an ethyl ester (**HE-2**) and to a methyl

Table 1. Optimization of the Reaction Conditions[a]



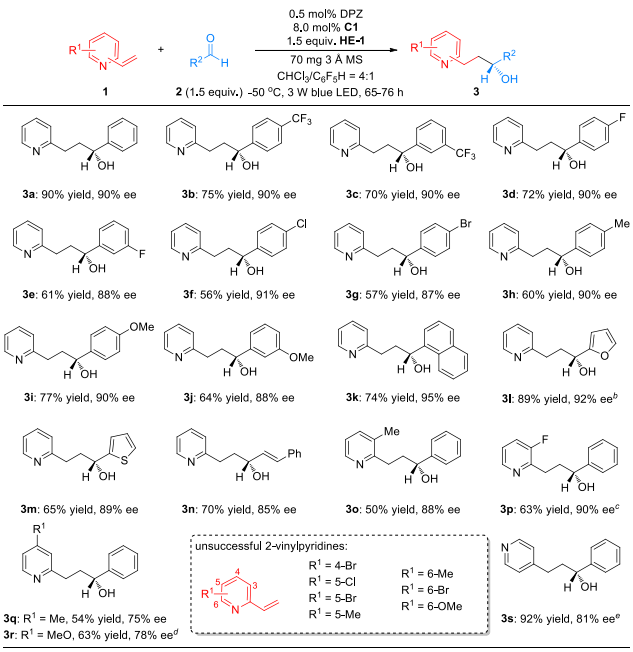
entry	variation from the standard conditions	yield (%)[b]	ee (%)[c]
1	None	93	90
2	**C2** instead of **C1**	88	15
3	**C3** instead of **C1**	72	35
4	**HE-2** instead of **HE-1**	31	80
5	**HE-3** instead of **HE-1**	25	51
6[d]	*i*Pr$_2$NEt instead of **HE-1**	N.R.	N.A.
7	[Ru(bpy)$_3$](PF$_6$)$_2$ instead of DPZ	38	66
8	[Ir(ppy)$_2$(dtbbpy)]PF$_6$ instead of DPZ	66	82
9	Eosin Y instead of DPZ	82	78
10	no 3 Å MS	85	78
11	no **C1**	N.R.	N.A.
12	no DPZ	N.R.	N.A.
13	no light	N.R.	N.A.
14	Air	N.R.	N.A.

[a]The reaction was performed on a 0.05-mmol scale. [b]Yields were determined from the isolated compounds following chromatographic purification. [c]Enantiomeric excesses were determined by HPLC analysis on a chiral stationary phase. [c]*t* = 36% h. bpy = 2,2'-bipyridine, dtbbpy = 4,4'-di-*tert*-butyl-2,2'-bipyridine, ppy = 2-phenylpyridine. N.R. = no reaction. N. A. = not available.

ketone (**HE-3**), the obtained yields and enantioselectivities decreased (entries 4–5). The reduced yield stemmed from the lower reaction rate and the unsatisfactory chemoselectivity, as an unknown by-product was formed. Furthermore, no reaction was observed when *i*Pr$_2$NEt was used instead of **HE-1** (entry 6). Other common photoredox catalysts, such as [Ru(bpy)$_3$](PF$_6$)$_2$, [Ir(ppy)$_2$(dtbbpy)]PF$_6$ and Eosin Y, were also examined (entries 7–9), but no improvement in the enantioselectivity was observed, and all isolated yields were lower. In these transformations, unknown byproducts were detected. More importantly, it was found that **HE-1** was consumed to form the corresponding pyridine in a faster manner than with DPZ as the catalyst. In the absence of 3 Å MS, the ee of **3a** fell to 78% (entry 10). Finally, control experiments verified that CPA **C1**, DPZ, visible light, and the oxygen-free environment are essential to the success of the reaction (entries 11–14).

(2) Substrate Scope and Synthetic Applications.

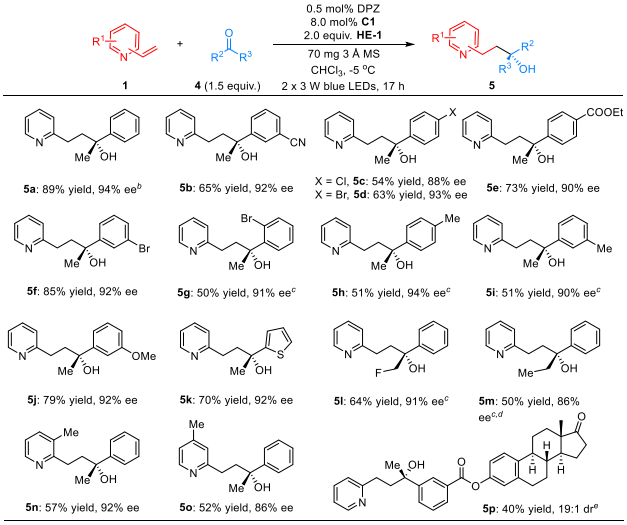
Table 2. Substrate scope with respect to the aldehyde[a]



[a]The reaction was performed on a 0.1-mmol scale. Yields were determined from the isolated compounds following chromatographic purification. Enantiomeric excesses were determined by HPLC analysis on a chiral stationary phase. [b]2.0 equiv. of **HE-1** was used. [c]$CHCl_3$ as the solvent. [d]10 mol% of **C1**, toluene as the solvent, T = −40 °C. [e]10 mol% of **C11**, 2.0 equiv. of **HE-1**, toluene as the solvent, T = −40 °C, 60 h. Note: under standard reaction conditions, no reaction was observed; when T = 25 °C, yield = 78%, ee = 0%, 36 h.

With the optimal reaction conditions in hand, we examined the scope of this asymmetric reductive coupling reaction with a wide range of aldehydes and vinylpyridines for the synthesis of chiral pyridines bearing distinct γ-secondary alcohols (Table 2). The reactions of **1a** with aromatic aldehydes containing electron-withdrawing or electron-donating substituents on the aryl ring afforded **3a-m** in 56–90% yields with 87–95% ees. The good chemical yields and excellent enantioselectivities achieved for aldehydes with fused aromatic (**3k**) and heteroaromatic (**3l-m**) ring substituents underscore the generality of this catalytic system. Cinnamaldehyde, a representative *α,β*-unsaturated aldehyde, was tested, and it provided **3n** in 70% yield with 85% ee, and an alkene was introduced on the stereogenic centre. Notably, the conditions were not suitable for alkyl aldehydes (no reaction was observed), likely because reducing them to the corresponding ketyl radicals is quite difficult. In addition, no desired product was observed when using photoredox catalysts with higher reduction potentials, such as *fac*-Ir(ppy)$_3^{3+}$ and *fac*-Ir(dF-ppy)$_3^{3+}$. 2-Vinylpyridines containing distinct substituents on the pyridine ring were then examined. 2-Vinylpyridines with 3-methyl, 3-fluoro, 4-methyl and 4-methoxy substituents generated corresponding adducts **3o-r** in 50 to 54% yields and 75 to 90% ees. However, no reaction was observed for alkenes bearing electron-withdrawing groups, e.g., bromo groups, at the 4-position or various substituents at the 5- and 6-positions. No reaction was detected when 4-vinylpyridine was subjected to the standard reaction conditions (footnote *e*). When the reaction temperature was increased to 25 °C, the desired product **3s** was obtained in 78% yield after 36 h but with 0% ee. Finally, **3s** was generated in 92% yield and 81% ee when using 10 mol% SPINOL-CPA **C11** (see Table S1 in the SI for its structure) and performing the reaction at −40 °C.

Table 3. Substrate scope with respect to ketones[a]

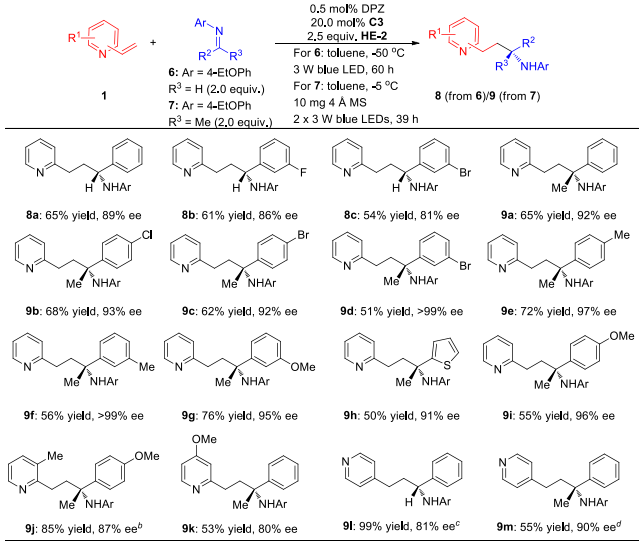


[a]The reaction was performed on a 0.1-mmol scale. The yields were determined from the isolated compounds following chromatographic purification. Enantiomeric excesses were determined by HPLC analysis on a chiral stationary phase. [b]5.0-mmol scale, t = 24 h, yield = 85%, ee = 94%. [c]3.0 equiv. of **HE-1** was used. [d]15 mol% of **C1** was used and t = 36 h. [e]For the newly formed stereocentre, ee = 90%; when a racemic phosphoric acid (diphenyl phosphate) was used, ee = 0% (i.e., dr = 1:1).

We next attempted to generate an unprecedented and challenging γ-tetrasubstituted stereocentre in a pyridine derivative as a demonstration of the practicality and generality of this radical addition reaction with ketones (Table 3). Our preliminary study showed that the transformation of **1a** with acetophenone **4a** under the established conditions afforded desired product **5a** in only 13% yield with 93% ee. This result prompted us to further investigate the reaction parameters. Finally, **5a** was obtained in 89% yield and 94% ee when the reaction was performed in $CHCl_3$ at 5 °C under irradiation with two 3 W blue LEDs. An array of ketones and 2-vinylpyridines were subsequently examined, and products **5b-p** were generated in 40–85% yields and 86–94% ees. We were pleased to find that when this reaction was conducted on a 5.0-mmol scale, a similar yield and enantioselectivity were achieved (see footnote b). 2-Fluoroacetophenone afforded corresponding product **5l**, containing an important C(sp^3)–F bond, in 64% yield with 91% ee. More importantly, this γ-tertiary alcohol–pyridine-based molecular architecture was successfully embedded in the complex natural product oestrone (product **5p**) *via* the direct use of an oestrone-derived ketone as the substrate. In this reaction, the excellent diastereoselectivity (19:1 dr) appeared to be due to the chiral catalyst **C1**, as the racemic phosphoric acid provided product **5p** with 1:1 dr (see footnote e). These results highlight the synthetic utility of this methodology. Except for the reported 2-vinylpyridines (**5n-o**), other previously tested derivatives and 4-vinylpyridine are not

suitable substrates since no reaction was observed.

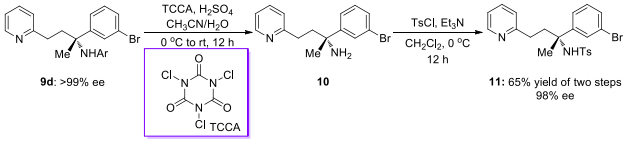
Table 4. Substrate scope with respect to imines[a]



[a]The reaction was performed on a 0.1-mmol scale. Yields were determined from the isolated compounds following chromatographic purification. Enantiomeric excesses were determined by HPLC analysis on a chiral stationary phase. [b]T = −40 °C, t = 45 h. [c]20 mol% of **C33** (See Table S1 in the SI for its structure), *p*-xylene as the solvent, T = 10 °C. [d]Toluene as the solvent, T = −25 °C.

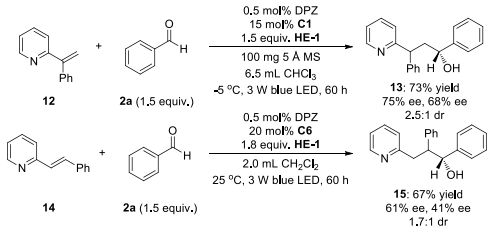
Encouraged by the results achieved with aldehydes and ketones, we tested imines as potential partners in the reductive coupling reaction with vinylpyridines (Table 4). The 2-vinylpyridines were tested first. For aldimines **6** containing 4-ethyoxyl-phenyl as the *N*-substituent, the corresponding adducts **8a-c** were obtained in 54−65% yields with 81−89% ees when the transformations were carried out in the presence of 0.5 mol% of DPZ, 20.0 mol% of CPA **C3** (See Table 1 for its structure), and 2.5 equiv. of **HE-2** in toluene at −50 °C. To access γ-tertiary amines from ketimines **7**, a higher temperature (−5 °C) and two LEDs as the energy source were necessary. Products **9a-k**, bearing aryl substituents with different electronic properties and substitution patterns on the formed stereogenic centre, were accessed in 50−76% yields with 80 to 99% ees. Notably, for 2-vinyl-3-methyl pyridine (**9j**), a lower temperature (−40 °C) was required to achieve a sufficiently high enantioselectivity. The reductive coupling did not occur for other 2-vinylpyridines and alkyl-substituted ketimines. 4-Vinylpyridine was also evaluated, and adducts **9l-m** from the transformations with an aldimine and a ketamine were produced with satisfactory results using the modified reaction conditions. The transformations of these products were then explored. As shown in Scheme 2, the treatment of **9d** with *N,N′,N″*-trichloroisocyanuric acid (TCAA) and H_2SO_4 cleaved the *N*-protecting group, i.e., the 4-ethyoxyl-phenyl moiety. The resulting free amine **10** was subsequently converted to the *N*-Ts-protected product **11** in 65% yield over two steps and with 98% ee.

Scheme 2. Modifications of γ-Chiral Amine-Containing Pyridines.



We explored the application of this catalytic method to alkenylpyridines by utilizing benzaldehyde (**2a**) as a representative reaction partner (Scheme 3). 2-(1-Phenylvinyl)pyridine (**12**), an *α*-branched vinylpyridine,[29] was first examined under the reaction conditions depicted in entry 1, Table 1, and no reaction was observed, indicating that **12** is less reactive than **1a**. When the amount of catalyst **C1** was increased to 15 mol%, the temperature was increased to −5 °C, and 100 mg of 5 Å MS was used as an additive, adduct **13** was obtained in 73% yield with 75% (major diastereomer) and 68% ee (minor diastereomer) and 2.5:1 dr after 60 h. (*E*)-2-Styrylpyridine (**14**),[25] a *β*-substituted alkenylpyridine, was then tested, and it exhibited similarly poor reactivity. Moreover, no enantioselectivity was found when the reaction was conducted under standard conditions (entry 1, Table 1) but at 25 °C. The reaction parameters were therefore further investigated. As a result, desired product **15** was achieved in 67% yield with 61% (major diastereomer) and 41% ee (minor diastereomer) and 1.7:1 dr when SPINOL-CPA **C6** (see Table S1 in the SI for its structure) was used as the chiral catalyst. Notably, methyl acrylate was also tested, and although it could be consumed within 48 h, the reaction was messy, and no desired reductive coupling product was observed.

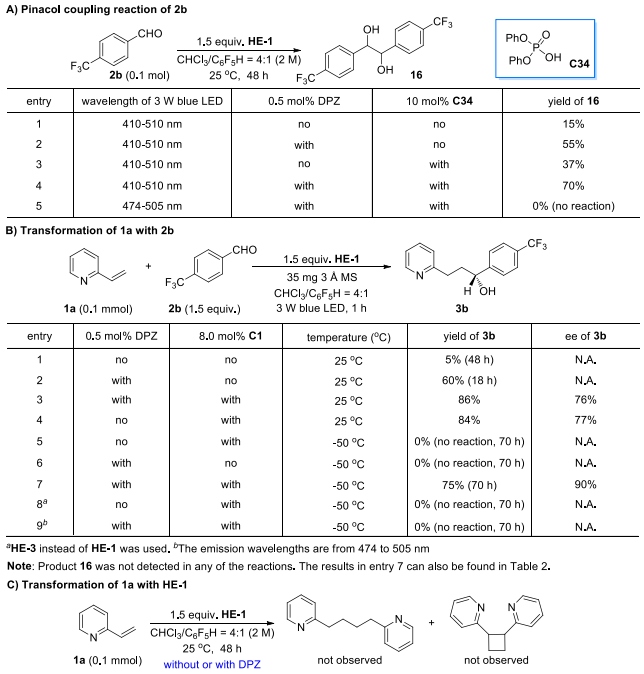
Scheme 3. Coupling reactions of alkenylpyridines with benzaldehyde 2a.



(3) Mechanistic Studies.

We next explored the mechanism of this umpolung-type conjugate addition reaction. Stern−Volmer experiments with an excitation wavelength of 448 nm showed no measurable luminescence quenching of *DPZ ($E^t(S^*/S^{\bullet-})$ = +0.91 V vs. SCE, $E^t(S^*/S^{\bullet+})$ = −1.17 V vs. SCE in CH_3CN) by **HE-1** ($E_{1/2}^{red}$ = +0.95 V vs. SCE in CH_3CN), benzaldehyde (**2a**) ($E_{1/2}^{red}$ = −1.70 V vs. SCE in CH_3CN) or 2-vinylpyridine (**1a**) ($E_{1/2}^{red}$ = −2.27 V vs. SCE in CH_3CN) (in the absence and presence of a Brønsted acid). The results are similar to those reported by Ngai in the Lewis acid-catalysed reductive couplings of aldehydes with 4-vinylpyridines.[26] Indeed, their elegant work has included systematic investigations on the mechanism. Nevertheless, since a different chiral Brønsted acid catalysis[32] was used in our reaction system, control experiments and theoretical studies *via* DFT calculations were carried out to explore the mechanisms of the onset of the transformations, the reduction process of carbonyls and the most stable transition state of the CPA providing the stereocontrol.

Scheme 4. Control experiments.



entry	wavelength of 3 W blue LED	0.5 mol% DPZ	10 mol% **C34**	yield of **16**
1	410-510 nm	no	no	15%
2	410-510 nm	with	no	55%
3	410-510 nm	no	with	37%
4	410-510 nm	with	with	70%
5	474-505 nm	with	with	0% (no reaction)

B) Transformation of 1a with 2b

entry	0.5 mol% DPZ	8.0 mol% **C1**	temperature (°C)	yield of **3b**	ee of **3b**
1	no	no	25 °C	5% (48 h)	N.A.
2	with	no	25 °C	60% (18 h)	N.A.
3	with	with	25 °C	86%	76%
4	no	with	25 °C	84%	77%
5	no	with	-50 °C	0% (no reaction, 70 h)	N.A.
6	with	no	-50 °C	0% (no reaction, 70 h)	N.A.
7	with	with	-50 °C	75% (70 h)	90%
8[a]	no	with	-50 °C	0% (no reaction, 70 h)	N.A.
9[b]	with	with	-50 °C	0% (no reaction, 70 h)	N.A.

[a]**HE-3** instead of **HE-1** was used. [b]The emission wavelengths are from 474 to 505 nm

Note: Product **16** was not detected in any of the reactions. The results in entry 7 can also be found in Table 2.

C) Transformation of 1a with HE-1

In Ngai's work, several experiments involving the pinacol coupling of **2b** were performed.[26] We repeated these transformations and evaluated the role of the phosphoric acid catalyst (Scheme 4A). The pinacol coupling product **16** was obtained in 15% yield when **2b** was reacted in the presence of only **HE-1** and irradiated by a 3 W blue LED (entry 1, the emission wavelengths of the LED light are from 410 nm to 510 nm, see the SI). The addition of a catalytic amount of DPZ could enhance the yield (entry 2, Scheme 4A). Furthermore, the use of phosphoric acid **C34** as a catalyst also provided a higher yield of **16** (entries 3 and 4, Scheme 4A). Since excitation of **HE-1** to ***HE-1** is impossible at $\lambda > 445$ nm, we tested the reaction with a laser line filter (CWL = 488 ± 2 nm, FWHM = 10 ± 2 nm, the emission wavelengths are from 474 nm to 505 nm, which can excite DPZ to *DPZ, see SI). As expected, no reaction was observed (entry 5, Scheme 4A). These results support the conclusions of Ngai that photoactivated HE (*HE, $E^t(S^*/S^{\bullet-}) = -2.28$ V vs. SCE)[48] is necessary, the HE radical (HE•, $E_{1/2}^{red} = -0.76$ V vs. SCE)[26] should be generated, DPZ will engage in a SET process to facilitate the reaction and phosphoric acid can improve the transformation. The results of the additional Stern-Volmer experiments using an excitation wavelength of 415 nm could further manifest these suggestions (See SI).

Subsequently, control experiments for the reaction of **1a** with **2b** were carried out (Scheme 4B). Under the standard reaction conditions but without the catalysts DPZ and CPA **C1** and at 25 °C, the transformation was very sluggish and provided adduct **3b** in 5% yield after 48 h, and product **16** was not observed (entry 1). This chemoselectivity indicates that conjugate addition was favoured over pinacol coupling when the radical species derived from **2b** encounters a much higher concentration of **1a**. The use of DPZ as a catalyst can increase the yield to 60% in a shorter time (entry 2). The presence of both DPZ and CPA **C1** furnished **3b** in 86% yield with 76% ee after only 1 h (entry 3). Interestingly, the absence of DPZ presented similar results (entry 4). When the temperature was decreased to −50 °C, no reaction was observed in the absence of either DPZ or **C1** (entries 5 and 6). As depicted in entry 7, the transformation under the standard reaction conditions furnished **3b** in 75% yield with 90% ee. We also evaluated the transformation using **C1** and **HE-3** with less steric hindrance than **HE-1** and in the absence of DPZ, and the transformation still could not work (entry 8). The reaction under the standard reaction conditions but irradiated by visible light with emission wavelengths from 474 nm to 505 nm did not furnish **3b** (entry 9). In addition, no homocoupling products of **1a** were observed, i.e., linear hydrodimers and cyclobutane,[49] which can exclude the possibility of the reaction starting from the reduction of vinylpyridines. All results suggest the high possibility of the catalytic cycle beginning from the single-electron reduction of the excited DPZ (*DPZ) with trace HE•, which is generated from *HE and the carbonyl and imine compounds under irradiation with visible light. Due to the low temperature, the $DPZ^{\bullet-}$ engaging in the SET reduction to provide more α-carbon radical species becomes indispensable. Furthermore, CPA is crucial to promoting the transformation. Of note, the ee value of **3a** at different reaction times with **HE-2** or **HE-3** as the reductant was maintained in both transformations (see SI). As such, we speculated that the achievement of diverse enantioselective results when using distinct HEs is likely owing to the different rates of yielding the corresponding pyridines, which would affect the H-bonding induction of CPA to substrates via a ternary transition state (*vide infra*). Accordingly, both CPA and PyH^+ to perform the exothermic proton-coupled electron transfer (PCET) in the reduction of carbonyls, described by Knowles[32] and Ngai[26] respectively, are plausible in our reaction systems.

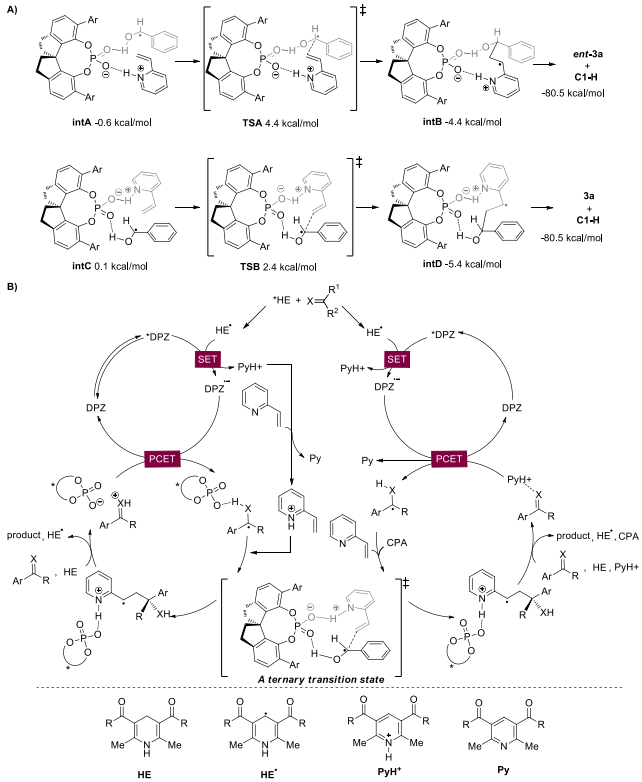


Figure 1. Density functional theory modelling of reduced 2a radical addition to 1a with catalyst C1 and the proposed mechanisms.

The relationship between the ee of CPA **C1** and the ee of product **5a** was next evaluated, and a linear correlation was determined (see SI). It could be concluded that only a single molecule of the chiral phosphate is involved in the C–C bond-forming step. We then calculated the transition state (TS) energies for the radical conjugate addition of reduced **2a** to **1a** bound to **C1** as the catalyst (see Figure 1A), and the most stable TS, through a cooperative **TSB** forming *R*-**3a** as the product, is consistent with the experimental results. As predicted, catalyst **C1** provides an enantio-discriminating environment that favours the *R*-pathway over the *S*-pathway and directs the C–C bond formation between reduced **2a** and **1a** through H-bonding. From the above, two plausible mechanisms with only a difference in the PCET process are proposed, as depicted in Figure 1B.

CONCLUSIONS

In summary, we have developed an enantioselective addition of prochiral radicals to vinylpyridines *via* visible-light-driven cooperative photoredox and asymmetric catalysis. With a chiral Brønsted acid catalyst to activate the substrate and control the enantioselectivity, a series of prochiral ketyl and α-aminoalkyl radical species generated from aldehydes, ketones and imines through single-electron transfer reductions could readily undergo conjugate addition to vinylpyridines, leading to various pharmaceutically and biologically important chiral γ-secondary/tertiary hydroxyl- and amine-substituted pyridines in high yields and ees. Control experiments and theoretical studies *via* DFT calculations suggested a plausible mechanism, including the initiation of the photoredox catalytic cycle and a PCET process, and the role of phosphoric acid in the asymmetric induction. The current organocatalytic method is the first system for constructing chiral tetrasubstituted stereocentres γ to pyridines. Moreover, such an asymmetric reductive coupling reaction is an unprecedented type of intermolecular transformation. Given the demonstrated practicality of this electrophile-involving chiral Brønsted acid catalysis in controlling the formation of distant γ-stereocentres for azaarenes, a generic pathway for the synthesis of valuable γ-functionalized azaarenes and their derivatives can be anticipated.

ASSOCIATED CONTENT

Supporting Information Available: [General information, optimization of reaction conditions, general experimental procedures, mechanistic studies, computational methods, synthetic applications, determination of the absolute configurations, characterization data, HPLC chromatograms and NMR spectra.] This material is available free of charge *via* the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interests.

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