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Catalytic Reductive Cross Coupling and Enantioselective Protonation of Olefins to Construct Remote Stereocenters for Azaarenes

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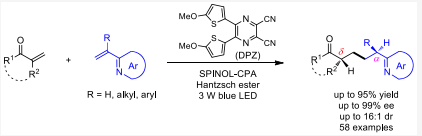
ABSTRACT: A novel enantioselective protonation protocol that is triggered by reductive cross coupling of olefins is reported. When under cooperative photoredox and chiral hydrogen-bonding catalytic conditions and using a terminal reductant, various α-branched vinylketones with diverse vinylazaarenes could provide important enantioenriched azaarene derivatives containing tertiary stereocenters at their remote δ-position with high yields and enantioselectivities. This reaction system is also suitable for α-branched vinylazaarenes, thus successfully assembling elusive 1,4-stereocenters. The convenient late-stage modifications of products, especially the formation of remote ε-tertiary and ε-heteroquaternary carbon stereocenters, further highlight the important synthetic value of this method. Control experiments and density functional theory (DFT) calculations were conducted to elucidate the plausible reaction mechanism and origins of regioselectivity and stereoselectivity.

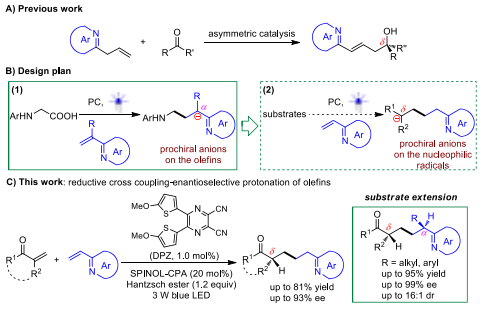


INTRODUCTION

Structurally diverse azaarenes exist widely in numerous natural products, pharmaceuticals, and agrochemicals as well as ligands and catalysts in catalysis. The prominent importance has inspired continuous pursuits for developing efficient catalytic synthetic protocols to access azaarene derivatives, especially in an enantioselective fashion.[1,2] Among them, exploiting the inherent electronic properties of azaarenes to directly trigger transformations has been appreciated as an expedient and practical strategy owing to the potential advantages of using simple and readily accessible feedstocks and avoiding tedious operations in the late-stage modifications of products. For instance, with respect to imine-containing azaarenes that feature an electron-withdrawing ability, a variety of catalytic asymmetric methods using 2-alkylazaarenes as pronucleophiles and 2-alkenylazaarenes as electrophiles have been established;[1c,3−6] substantial enantioenriched azaarene derivatives bearing various α-,[3] α,β-,[4] β-,[5] and γ-stereocenters[6] were obtained. By contrast, directly constructing relatively remote δ-stereocenters remains underdeveloped. As the only strategy, unstable 2-allylazaarenes have been devised to perform enantioselective γ-selective addition to ketones (Scheme 1A).[7] Given the prevalence of such structural motifs in bioactive molecules,[8] exploring new, convenient, and general synthetic methods is always highly desirable.

Due to the weaker electron-withdrawing ability of azaarenes as compared to that of carbonyls, in recent years, photoredox catalysis[9] has been extensively used in the synthesis of azaarene derivatives.[2] In particular, the high reactivity of radicals has enabled various radical species to be successfully embedded on 2-alkyenylazaarenes via an addition−hydrogen atom transfer (HAT)/protonation process.[3b,4e,5i,6b,10] Furthermore, by merging extrinsic, chiral Brønsted acid catalysis,[11] our group reported an efficient method to construct tertiary carbon stereocenters α to azaarenes through radical addition−enantioselective protonation of *N*-aryl glycines with α-branched 2-vinylazaarenes,[3b] in which prochiral anion intermediates were formed on the electrophilic olefins (Scheme 1B1). This work provided us with an important hypothesis that if prochiral anions could be generated on

Scheme 1. Enantioselective Construction of δ-Stereocenters for Azaarenes



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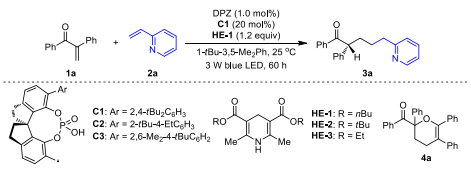
nucleophilic radical species, then the desired remote stereogenic centers could be achieved (Scheme 1B2). To this end, we conceived that α-branched vinylketones might be viable precursors of desired radicals, given the proven capability of vinyl ketones to produce α-enolate radicals via single-electron reduction.[12]

Herein, we report the development of reductive cross coupling−enantioselective protonation of α-branched vinylketones to 2-vinylazaarenes (Scheme 1C). By establishing a dual catalyst system involving a dicyanopyrazine-derived chromophore (DPZ) photosensitizer and a SPINOL-based chiral phosphoric acid (CPA) and using Hantzsch ester (HE) as the terminal reductant, a variety of enantioenriched azaarene variants bearing δ-tertiary carbon stereocenters on acyclic or cyclic frameworks were obtained in high yields with good to excellent enantiomeric excesses (ee's). α-Branched 2-vinylazaarenes were also compatible, leading to products containing nonadjacent 1,4-stereocenters with satisfactory results.

RESULTS AND DISCUSSION

Reaction Optimization. We began our study by selecting 2-phenyl acrylophenone (**1a**) and 2-vinylpyridine (**2a**) as model substrates (Table 1 and Table S1 in the Supporting Information [SI]). The transformation was first tested in the presence of 1.0 mol % DPZ and 1.2 equiv of HE (**HE-3**) in CH_2Cl_2 as the solvent at 25 °C and under irradiation with a 3 W blue LED (entry 1, Table S1). It was found that the reaction proceeded smoothly, providing desired racemic product **3a** in 82% yield within 24 h. Notably, after single-electron reduction and protonation of **1a**, a neutral ketyl radical intermediate would first be generated; in addition to experiencing tautomerization to form the desired α-enolate radical,[13] the neutral ketyl radical intermediate could undergo addition to activated olefins.[10f] Accordingly, in addition to the high reactivity, the result also suggests satisfactory regioselectivity of this intermolecular reaction. The chemoselectivity is not so satisfactory given that the homocoupling product of the α-enolate radical was observed (*vide infra*), leading to the use of 2.0 equiv of **1a**. Using 10 mol % diphenyl phosphate as a racemic Brønsted acid catalyst afforded **3a** in the same yield (entry 2, Table S1).

Table 1. Optimization of the Reaction Conditions[a]



entry	variation from the standard conditions	yield[b] (%)	ee[c] (%)
1	none	73	90
2	**C2** instead of **C1**	51	52
3	**C3** instead of **C1**	trace	N.A.[d]
4	**HE-2** instead of **HE-1**	63	86
5	**HE-3** instead of **HE-1**	60	88
6	iPr$_2$NEt instead of **HE-1**	N.R.[e]	N.A.
7	$[Ir(ppy)_2(dtbbpy)]PF_6$ instead of DPZ	41	57
8	eosin Y instead of DPZ	29	88
9	no **C1**	N.R.	N.A.
10	no DPZ	0[f]	N.A.
11	no light	N.R.	N.A.
12	air	0[f]	N.A.

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.1 mmol), solvent (8.0 mL). [b]Yield of isolated product. [c]ee's were determined by HPLC analysis. [d]N.A. = not available. [e]N.R. = no reaction. [f]**1a** was transformed to **4a** via a Diels−Alder reaction.[12]

Nevertheless, we still engaged in developing the enantioselective manifold by using CPAs as chiral Brønsted acid catalysts given their robust ability in asymmetric photoredox-catalyzed synthesis of azaarene-based compounds.[3b,6a,11e] It is worth mentioning that, in addition to the inherent challenge originating from the very small volume and high mobility of protons, the arguably strong racemic background reaction would further increase the difficulty of attaining high enantioselectivity for this unprecedented enantioselective protonation reaction.[14] After careful examinations of diverse CPAs, HEs, and reaction parameters (Tables S1−S4), to our delight, product **3a** was obtained in 73% yield with 90% ee when using 20 mol % SPINOL-CPA **C1**, **HE-1**, and (*tert*-butyl)-3,5-dimethylbenzene as the solvent (entry 1, Table 1). Both the ee and yield were highly sensitive to the substituents at the 6,6′-position of the SPINOL (entries 2 and 3); for instance, when the substituents were 2,6-dimethyl-4-*tert*-butyl phenyl, roughly no **3a** was achieved (entry 3). The ester groups of HEs also affected the enantioselective result (entries 4 and 5). When iPr$_2$NEt instead of HE was used as the reductant, no reaction was observed (entry 6). Several viable photoredox catalysts were also evaluated, but the yield of **3a** deteriorated, accompanied by decreased ee (entries 7 and 8). Interestingly, transformation could not proceed when in the absence of CPA **C1**, suggesting that the current solvent could effectively suppress the racemic background reaction.[15] Other control experiments indicated that DPZ, visible light, and the oxygen-free environment are indispensable to the success of the reaction (entries 10−12).

Substrate Scope and Synthetic Applications. With the optimal reaction conditions, a variety of α-branched vinylketones **1** and vinylazaarenes **2** were examined to evaluate the substrate scope of this reductive cross coupling−enantioselective protonation strategy (Scheme 2). Reactions of α-phenyl vinylketones featuring diverse substituents on the ketones with vinylpyridines **2a** were first carried out (Scheme 2A). With respect to aryl groups, it was found that the corresponding products **3a**−**3q** could be obtained in 53−81% yields with 62−92% ee's within 60 h. Distinct electron-withdrawing and electron-donating groups at the *para*- and *meta*-positions of aromatic rings always presented excellent ee's, while moderate ee's were obtained when the substituent was introduced on the *ortho*-position. Ketones with fused aromatic (**3p**) and heteroaromatic (**3q**) rings as the substituents were also well tolerated. For a benzyl-substituted α-phenyl vinylketone, the transformation became sluggish, leading to product **3r** in 46% yield with 68% ee. 2-Aryl acrylophenones were subsequently tested (Scheme 2B); regardless of the electronic properties and substitution patterns of the aryls, products **3s**−**3z** could be achieved with excellent ee's. Notably, the reactions of 2-benzyl and 2-alkyl acrylophenones with **2a** afforded products in moderate yields and ee's.[15] Transformations of various 2-vinylazaarenes with 2-phenyl acrylophenone **1a** were then examined (Scheme 2C). 2-Vinylpyridines containing diverse electron-deficient and electron-rich substituents on the 3-, 4-, and 5-positions of pyridine rings generated products **3aa**−**3ai** in 35−63% yields and 82−93% ee's. The reaction did not occur for 6-substituted pyridine-derived olefins, likely because

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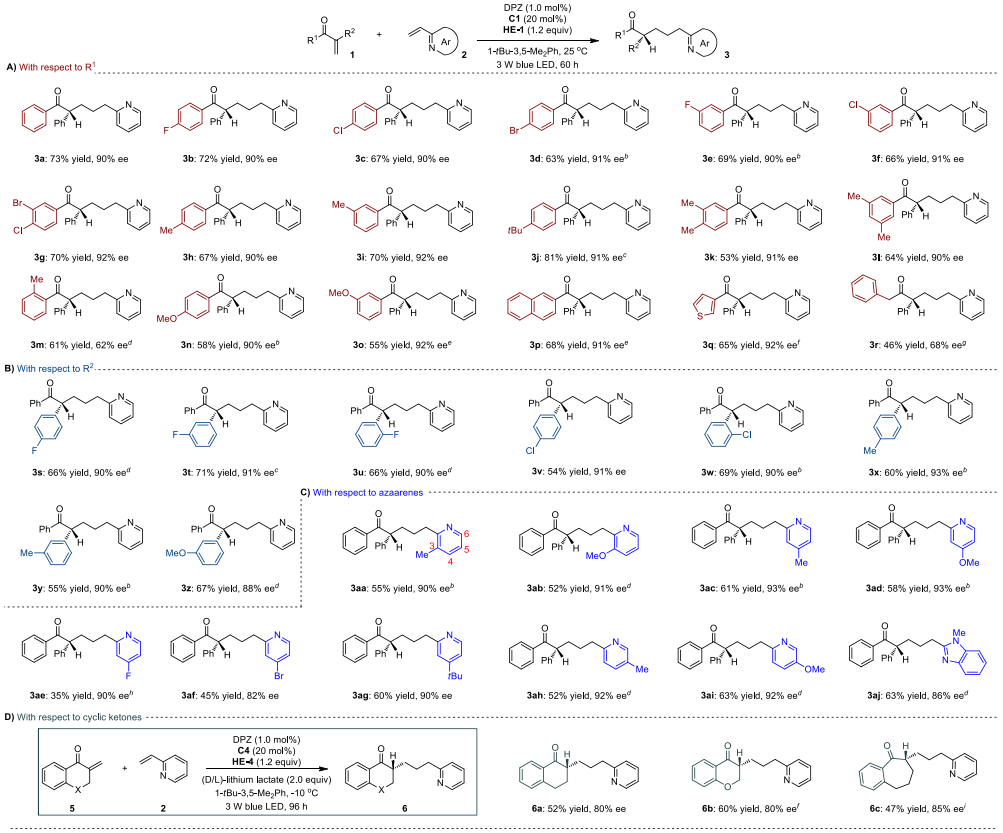
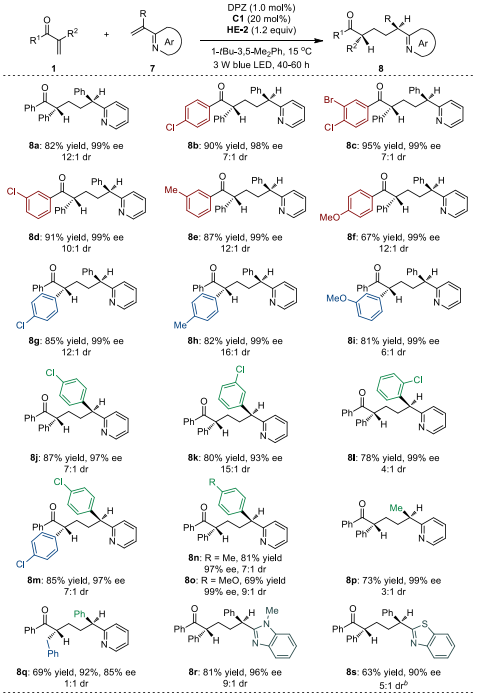
Scheme 2. Substrate Scope to Access Chiral Azaarenes Containing δ-Stereocenters[a]



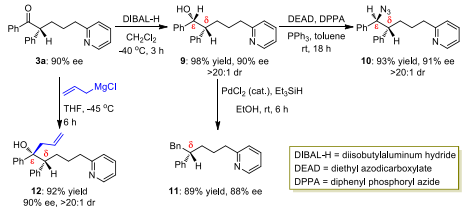
[a]0.1 mmol scale. [b]10 °C, adding 1.0 equiv of NH_3SO_3. [c]Adding 1.0 equiv of NH_3SO_3. [d]15 °C. [e]10 °C, adding 0.5 equiv of NH_3SO_3. [f]10 °C. [g]**1**/**2** = 1:1, 2 mL of solvent. [h]15 °C, adding 1.0 equiv of NH_3SO_3. [i]**C5** instead of **C4** was used and at 15 °C in 7.0 mL of solvent.

Scheme 3. Substrate Scope with Respect to α-Branched 2-Vinylazaarenes[a]



[a]0.1 mmol scale in 4.0 mL of solvent. [b]0.1 mol % DPZ was used.

Scheme 4. Synthetic Applications



the steric hindrance inhibits the hydrogen-bonding interaction between catalyst **C1** and the pyridine rings. Transformations of 3-vinylpyridines and 4-vinylpyridines with **1a** only afforded the homocoupling product of **1a** (*vide infra*), suggesting their poorer reactivity as compared to 2-vinylpyridines.[15] Gratifyingly, 2-vinylbenzimidazole was compatible, leading to product **3aj** with satisfactory results. Next, we turned our attention to vinylketones generated from cyclic ketones (**5**, Scheme 2D). It was observed that, under the modified reaction conditions, enantioenriched pyridine derivatives **6a**–**6c** were obtained with good ee's, wherein tertiary carbon stereocenters on the cyclic skeletons of α-tetralone, chromanone, and benzosuberone were successfully formed at the δ-position of pyridine.

To further demonstrate the practicality and generality of this strategy, we next attempted transformations of α-branched vinylketones **1** with α-branched vinylazaarenes **7** to simultaneously construct attractive but challenging nonadjacent 1,4-stereocenters. As depicted in Scheme 3, under the slightly modified reaction conditions, the reactions succeeded

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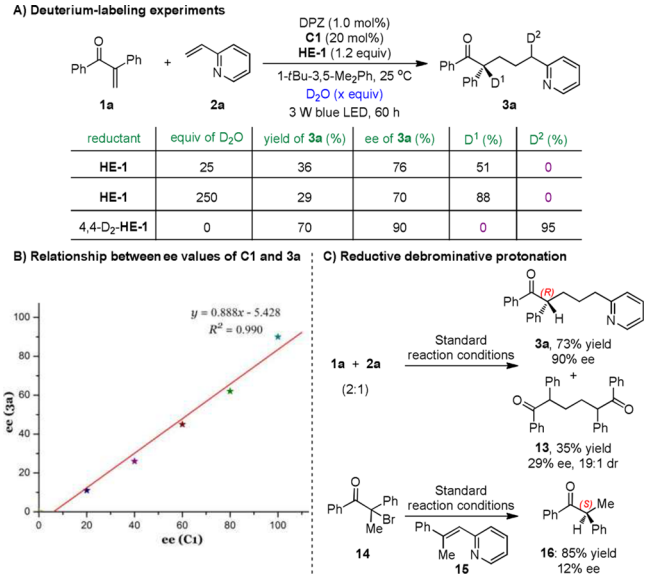

Figure 1. Control experiments.

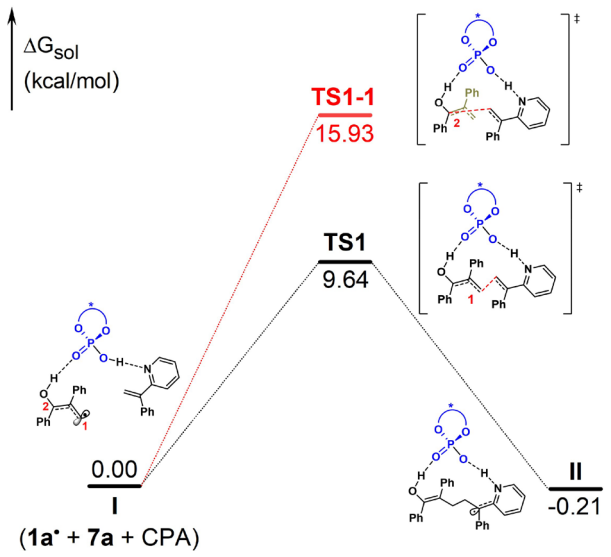

Figure 3. Gibbs free energy profiles (ΔG_{sol}, in kcal/mol) for the radical addition step.

smoothly, leading to a large array of desired products **8a**–**8s** in 63–95% yields with 85–99% ee's and 1:1 to 16:1 dr.[16] In addition to the extensive substituent patterns for the aromatic rings of α-branched vinylketones **1**, diverse α-aryl vinylpyridines **7** were well tolerated. Furthermore, α-alkyl vinylpyridine (**8p**) and 2-benzyl acrylophenone (**8q**) were compatible. Notably, benzimidazolyl (**8r**) and benzothiazolyl (**8s**) were also revealed as viable azaarene groups for substrates **7**.

With respect to this developed strategy, in addition to providing access to constructing ketone-substituted δ-tertiary stereogenic centers for azaarenes, the ketone moiety of products, as a versatile functional group, offers important opportunities to synthesize various optically pure azaarene derivatives with potential bioactivities. For example, reduction of **3a** by using DIBAL-H furnished product **9** in 98% yield with 90% ee and >20:1 dr (Scheme 4). In this regard, this work accomplished the formation of ε-stereocenters for azaarenes. The hydroxy group of **9** was then readily transformed to azide (**10**) under the Mitsunobu reaction conditions, further expanding the synthetic utility owing to the robust ability of azide for convenient and diverse modifications. Moreover, by treatment of $PdCl_2$ and Et_3SiH,[17] hydrogenation of **9** was accomplished, producing an enantioenriched pyridine derivative **11** bearing an attractive δ-stereocenter that is substituted by a phenyl and a benzyl group. Importantly, the reaction of **3a** with allylmagnesium chloride could generate **12** with satisfactory results; in addition to embedding a readily modified allyl group into the molecule, a heteroquaternary carbon stereocenter ε to pyridine was successfully assembled.

Mechanistic Studies. We next investigated the plausible mechanism of the reactions. Stern–Volmer experiments were first conducted,[15] and no measurable luminescence quenching of *DPZ by 2-phenyl acrylophenone (**1a**) or 2-vinylpyridine (**2a**) was observed.[18] Based on previous works,[6b,10f,19] accordingly, the reduction of α-branched vinylketones **1** by $DPZ^{\bullet-}$ may undergo an exothermic proton-coupled electron transfer (PCET) process enabled by CPA and PyH^+, which was generated from the oxidation of HE$^\bullet$ by *DPZ. Subsequently, the transformation of **1a** with **2a** was performed under standard conditions and in the presence of D_2O or using 4,4-D_2-**HE-1** as the reductant (Figure 1A). The results suggest that protonation is a viable pathway to construct C–H bonds of α-ketones, and HAT is responsible for the formation of C–H bonds of α-azaarenes. Similar outcomes were observed for reactions using α-branched vinylazaarenes as partners.[15] Therefore, the construction of tertiary stereocenters α to azaarenes of products **8** should experience enantioselective HAT, which is an unprecedented example of the asymmetric photoredox synthesis of enantioenriched azaarene variants.

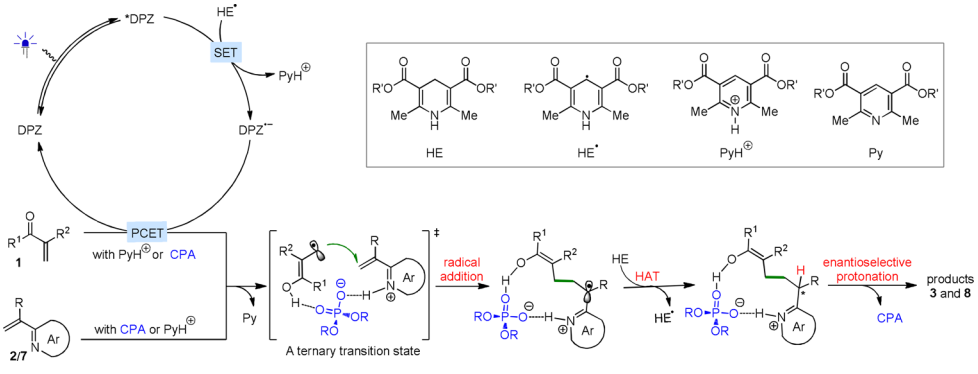

Figure 2. Proposed catalytic cycle.

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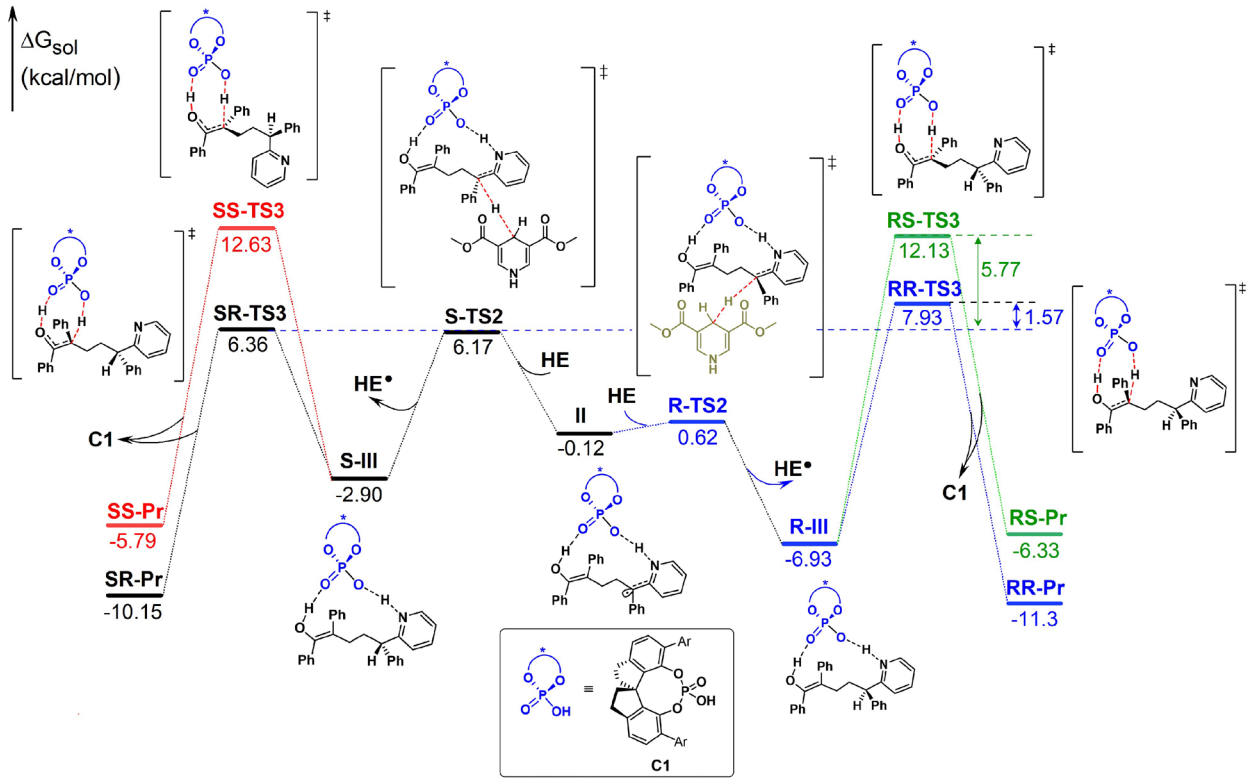

Figure 4. Calculated energy profiles for processes of enantioselective HAT and enantioselective protonation. All energies relative to the radical complex II. M06-2X/6-31+G(d,p)/SMD(Mesitylene)//B3LYP-D3/6-31G(d,p).

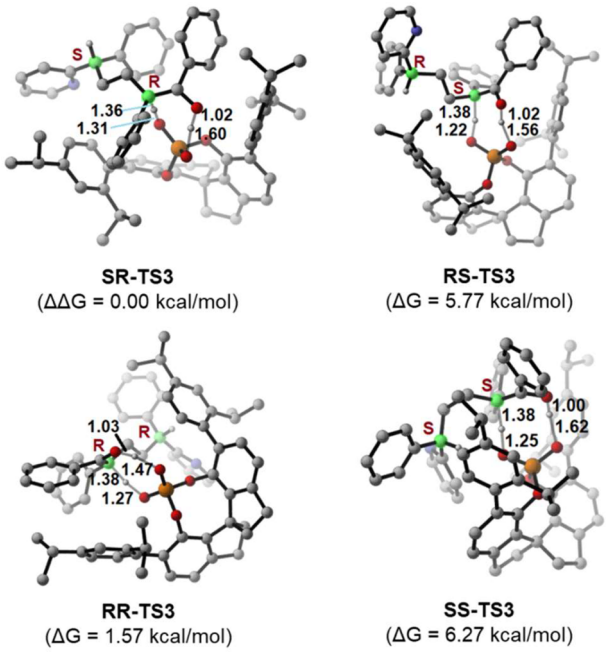

Figure 5. DFT-optimized enantiodetermining transition states for **SR-TS3**, **RS-TS3**, **RR-TS3**, and **SS-TS3**.

The relationship between the ee of CPA **C1** and the ee of product **3a** was also evaluated (Figure 1B); the linear correlation result strongly suggests that only a single molecule of the chiral phosphate is included in the C−H bond-forming step. Notably, in the reaction between **1a** and **2a**, molecule **13**, which was generated from two molecules of **1a**, was obtained with 29% ee (Figure 1C). Moreover, under the established reaction conditions and in the presence of pyridine-substituted olefin **15**, 2-bromo-1,2-diphenylpropan-1-one **14** afforded the reductive debrominative protonation product **16** with 12% ee,[20] of which the absolute configuration of the stereocenter was determined to be *S* but not *R*.[21] The results suggest that the enantioselective protonation of enolates is most likely after radical addition to vinylazaarenes. From the above, a plausible mechanism is proposed as shown in Figure 2.[15]

To gain further insights into the mechanism and origins of selectivity, we performed DFT calculations on the reaction of 2-phenyl acrylophenone (**1a**) and 2-(1-phenylvinyl)pyridine (**7a**) with CPA **C1** as catalyst.[15] In the initial step, a neutral ketyl radical **1a•** is generated from **1a** through a PCET process. Then, CPA **C1** interacts with **1a•** and **7a** through two H-bonding interactions, leading to a relatively stable complex **I** (Figure 3). Complex **I** will undergo radical addition via **TS1** (9.64 kcal/mol) and **TS1-1** (15.93 kcal/mol), which occurs at the C1 and C2 position on radical **1a•**, respectively. The results show that transition state **TS1** is highly favored due to the less distortion of radical **1a•** in **TS1** than that in **TS1-1**, perfectly validating the good regioselectivity of the radical addition process.

Subsequently, the HAT from HE to the radical intermediate **II** occurs via **R-TS2** (0.62 kcal/mol) and **S-TS2** (6.17 kcal/mol) to afford intermediates **R-III** and **S-III** (Figure 4). The lower-energy pathway was calculated to be **R-TS2**, which is lower in energy by 5.55 kcal/mol relative to **S-TS2**. Herein, the possibility of the protonation process for intermediate **II** was also considered, but the energy barrier is too high to proceed under this reaction conditions (see Figure S11 in the SI). From intermediates **R-III** and **S-III**, the subsequent intermolecular proton transfer process occurs through four possible diastereomeric transition states **S,R-TS3**, **S,S-TS3**, **R,R-TS3**,

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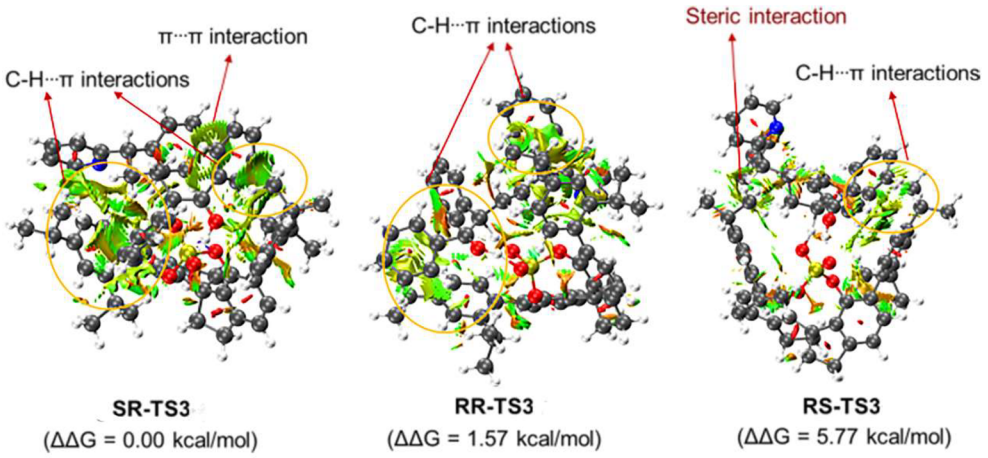

Figure 6. Noncovalent interaction (NCI) plots for the key transition states **SR-TS3**, **RR-TS3**, and **RS-TS3**. The blue, green, and red regions represent strong, weak, and repulsive interactions, respectively.

and **R,S-TS3** (Figure 5). The results suggest that both the rate-determining and enantiodetermining step for this reaction are the protonation step. The geometries of transition states **S,R-TS3**, **S,S-TS3**, **R,R-TS3**, and **R,S-TS3** were explored. As shown in Figure 4, **S,R-TS3** possesses the most stabilized structure, followed by **R,R-TS3** and **R,S-TS3**, and the energy differences between **S,R-TS3**, **R,R-TS3**, and **R,S-TS3** are 1.57 and 5.77 kcal/mol, respectively, in good accord with the experimentally obtained 99% ee and 12:1 dr.

Further, the enantioselectivity seems to be provided by the subtle combination of steric and hydrogen bonding interactions. As depicted in Figure 6, noncovalent interaction (NCI) analysis indicates that there are more noncovalent C−H···π interactions between tertiary butyl groups on the substituents of **C1** and the phenyl (or pyridine) groups on the substrate fragment, as well as the π···π interactions between the two phenyl groups on substrate fragment. Compared with the transition state **S,R-TS3**, there are fewer C−H···π interactions and no π···π interaction present in the transition sate **R,R-TS3** and **R,S-TS3**, and the weak steric interaction between the tertiary butyl group on **C1** and methylene group was also found in **R,S-TS3**. This is the key contribution to the preference for the formation of the major product.

CONCLUSIONS

In summary, we developed a reductive cross coupling−enantioselective protonation of α-branched vinylketones to vinylazaarenes via visible-light-mediated cooperative photoredox and chiral hydrogen-bonding catalysis. This method offers highly efficient access to valuable enantioenriched azaarene derivatives featuring diverse tertiary stereocenters δ to azaarenes in high yields and ee's. It is also effective for α-branched vinylazaarenes, thus successfully assembling elusive 1,4-stereocenters. In addition, the ketone moiety of products offers versatile approaches to constructing remote ε-tertiary and ε-heteroquaternary carbon stereocenters for azaarenes. Control experiments and theoretical studies via DFT calculations suggested that the reactions should experience a tandem radical addition, (enantioselective) HAT, and enantioselective protonation process. This work represents an unprecedented enantioselective protonation strategy, which will further inspire the pursuit of novel enantioselective protonation reactions via highly reactive radical-based asymmetric photoredox catalysis.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.1c01073.

General information, optimization of reaction conditions, general experimental procedures, mechanistic studies, characterization data, X-ray of product **8g**, and NMR spectra (PDF)

Accession Codes

CCDC 2020078 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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