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Communication

All-Carbon Quaternary Stereocenters α to Azaarenes via Radical-Based Asymmetric Olefin Difunctionalization

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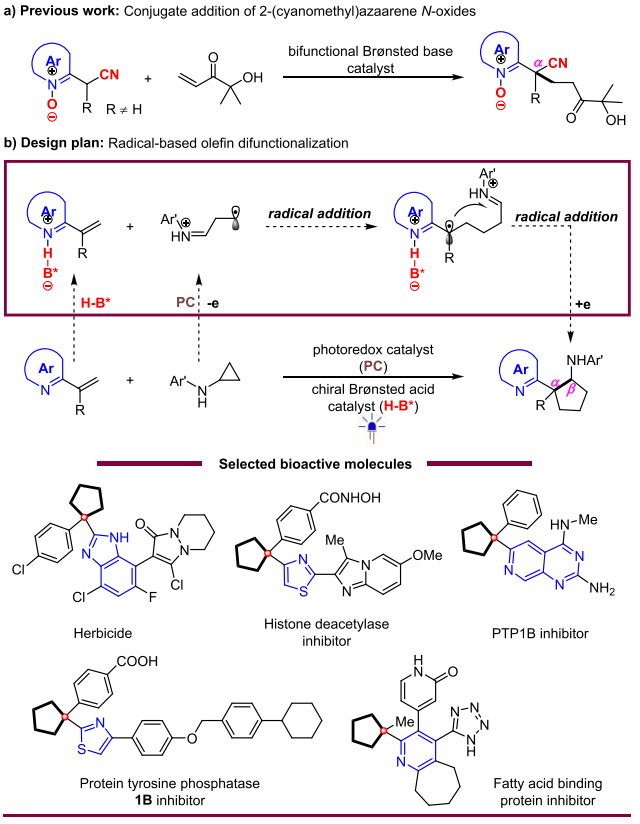
ABSTRACT: A radical-based asymmetric olefin difunctionalization strategy for rapidly forging all-carbon quaternary stereocenters α to diverse azaarenes is reported. Under cooperative photoredox and chiral Brønsted acid catalysis, cyclopropylamines with α-branched 2-vinylazaarenes can undergo a sequential two-step radical process, furnishing various valuable chiral azaarene-substituted cyclopentanes. The use of the rigid and confined C_2-symmetric imidodiphosphoric acid catalysts achieves high enantio- and diastereo-selectivities for these asymmetric [3 + 2] cycloadditions.

Azaarenes are important structural motifs that are diverse and ubiquitous in bioactive natural and non-natural products, drugs, ligands, and functional materials. The synthesis of azaarene-containing compounds, especially the development of enantioselective variants, continues to be an attractive task in synthetic chemistry. In recent years, the direct exploitation of the electronic properties of the azaarene itself to trigger catalytic asymmetric transformations of azaarene-based prochiral substrates has been recognized as an effective and efficient strategy.[1−21] Among such reactions, many elegant methods for accessing imine-bearing azaarene-based chiral compounds with different stereocenters at distinct positions have been established.[3−21] To construct an all-carbon quaternary stereocenter at the α-position of azaarenes, the Palomo group developed 2-(cyanomethyl)azaarene oxides as the nucleophiles, in which using a strongly electron-withdrawing cyano group and the prepared azaarene *N*-oxide as the substituents can tremendously increase the acidity of the C−H bond, resulting in efficient deprotonation (Scheme 1a).[8] However, the formation of such a challenging stereogenic center without introducing an activating functional group as a more general and direct synthetic approach has not been reported. The fact that these azaarenes are less able than carbonyl moieties to activate functional groups makes the development of new and highly reactive protocols of great importance.

Visible-light-driven photoredox catalysis,[22,23] a powerful tool in organic synthesis, has recently been employed to construct azaarene-based variants by enabling radical-based transformations.[5−7,18,20,24−30] Specifically, radical conjugate additions to alkenylazaarenes have been revealed as a promising and fruitful synthetic approach due to the high reactivity and diversity of radical species.[6,18,20,24−30] Among such reactions, a radical conjugate−enantioselective protonation strategy has been developed to build azaarene-substituted tertiary carbon stereocenters.[6] The reduction of the α-azaarene radical species, which is generated from the conjugate addition of radical species to alkenes, furnishes anions, allowing the enantiose-

Scheme 1. Enantioselective Construction of All-Carbon Quaternary Stereocenters α to Azaarenes



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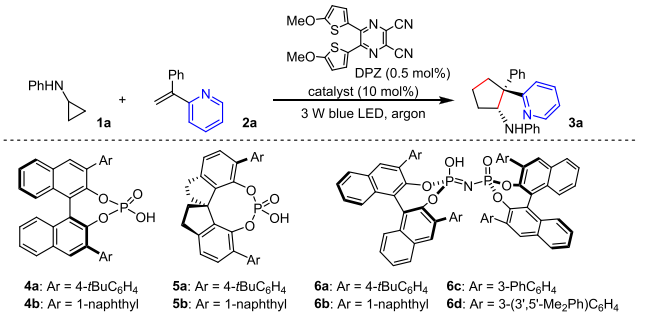
lective protonation. We wondered if such radical intermediates could subsequently add to an unsaturated double bond, thereby affording the desired all-carbon quaternary stereocenter α to azaarenes. In consideration of the high reactivity of radicals in additions to imines,[31,32] we were fascinated by the possibility of an enantioselective [3 + 2] cycloaddition between cyclopropylamines[33−36] and α-branched 2-vinylazaarenes under cooperative photoredox and chiral Brønsted acid catalysis (Scheme 1b).[5−7,18,20,31,32] The envisaged bimolecular chemical transformation might involve a sequential two-step radical process, namely, a radical conjugate addition of distonic ions to alkenes and radical addition to iminium ions. The method would provide the first access to the biologically important highly enantioenriched molecular architectures that are azaarene-substituted cyclopentanes featuring an all-carbon quaternary stereocenter.[37−40]

The implementation of this reaction scenario will inarguably face two significant challenges. (a) Chemoselectivity. Because α-azaarene radicals can act as oxidants,[6,18,41,42] the high steric hindrance is likely to make the competitive single-electron reduction and protonation more favorable. (b) Enantioselectivity. Through H-bonding interactions with the N atom of azaarenes, a chiral Brønsted acid catalyst can provide a chiral environment for the formation of stereocenters by activating the system for the radical conjugate addition.[6,20] However, this interaction will decrease the electron density on the α-azaarene radical species, which disfavors the subsequent radical addition to the iminium. To overcome this deactivation, the H-bonding interaction tends to dissociate, which weakens the stereocontrolling effect of the chiral Brønsted acid in the simultaneous formation of the two stereocenters. In addition, the highly enantioselective construction of all-carbon quaternary stereocenters is always a formidable challenge in radical chemistry.[32,43−45]

We began our investigation by selecting cyclopropylaniline (**1a**) and 2-(1-phenylvinyl)pyridine (**2a**) as the model substrates (Table 1). Our developed dicyanopyrazine-derived chromophore (DPZ, for *DPZ, $E^{t}(S^*/S^{\bullet-})$ = +1.42 V vs SCE in CH_3CN)[46] was chosen as the photoredox catalyst because its excited state is theoretically able to perform the single-electron oxidation of **1a** ($E_{1/2}^{red}$ = +0.92 V, +1.30 V vs SCE in CH_3CN). We first evaluated the reaction using 0.5 mol % DPZ in toluene as the solvent at 25 °C with irradiation by a 3 W blue LED (entry 1). It was found that racemic [3 + 2] cycloaddition adduct **3a**, the desired product, was obtained in a 33% yield with a 1:1.5 dr. The result shows an enantiocontrol challenge due to the occurrence of the background reaction. We then tested a series of (*S*)-BINOL-based chiral phosphoric acids (CPAs), such as **4a−b** (entries 2−3), and (*S*)-SPINOL-based CPAs, such as **5a−b** (entries 4−5) (for more details, see Table S1 in the Supporting Information), which led to enantioenriched product **3a** with unsatisfactory ee values. Importantly, the diastereoselectivity was reversed and became excellent. The results indicate the suitability of chiral Brønsted acids as catalysts. We wondered if the highly rigid and confined C_2-symmetric imidodiphosphoric acids could achieve better enantioselectivity since they can provide extremely sterically demanding chiral environments, geometrically restraining the α-pyridine radical intermediate.[47−50] In addition, the greater distance between the catalytically active bifunctional acid/base pair might increase the probability of interacting with the iminium, which can weaken the negative influence of the racemic background reaction by lowering the energy barrier to

Table 1. Optimization of the Reaction Conditions[a]



entry	cat	solvent	T (°C)	yield (%)[b]	ee (%)[c]	dr[d]
1		toluene	25	33	N.A.	1:1.5
2	**4a**	toluene	25	76	11	>19:1
3	**4b**	toluene	25	79	21	>19:1
4	**5a**	toluene	25	78	16	>19:1
5	**5b**	toluene	25	74	22	>19:1
6	**6a**	toluene	25	77	31	2:1
7	**6b**	toluene	25	78	50	>19:1
8	**6c**	toluene	25	79	50	>19:1
9	**6d**	toluene	25	79	60	>19:1
10	**6d**	benzene	25	78	68	15:1
11	**6d**	Et_2O	25	60	65	15:1
12	**6d**	THF	25	63	47	>19:1
13	**6d**	CPME	25	76	61	>19:1
14	**6d**	m.s.[e]	25	80	63	>19:1
15	**6d**	m.s.[e]	−40	80	79	>19:1
16[f]	**6d**	m.s.[e]	−60	83	91	>19:1

[a]0.05 mmol scale: **1a**:**2a** = 2.0:1, 1.0 mL solvent, irradiation distance = 3.0 cm. Entries 1−14, t = 12 h. Entry 15, t = 48 h. Entry 16, t = 60 h. [b]Yield of isolated product. [c]Determined by HPLC analysis on a chiral stationary phase. [d]Determined by crude ^{1}H NMR analysis. [e]m.s. = mixed solvent: Et_2O/CPME/benzene = 1/1/1 (3.0 mL). [f]20 mol % of **6d** was used, and irradiation distance = 6.0 cm. N.A. = not available.

the radical addition. As such, we screened a range of imidodiphosphoric acids based on the BINOL backbone, such as **6a−d**, with different substituents at the 3,3′-positions (entries 6−9). To our delight, **3a** could be obtained in 60% ee with a > 19:1 dr when **6d** was used (entry 9). A solvent screening revealed that benzene, Et_2O, and cyclopentyl methyl ether (CPME) gave higher enantioselectivities (entries 10−13). However, benzene has a higher freezing point (5.5 °C), and neither Et_2O nor CPME as the medium could provide sufficient enantioselectivity even when the temperature was decreased (see Table S1). This dilemma prompted us to test mixed solvents involving on the most suitable solvent (benzene) to decrease the freezing point. As a result, **3a** was obtained with a promising 63% ee when using the mixed Et_2O/CPME/benzene in a 1:1:1 ratio as the solvent (entry 14). When the reaction was conducted at −40 °C, the ee of **3a** was improved to 78% (entry 15). Finally, **3a** was obtained in 83% yield with 91% ee and >19:1 dr after 60 h, when using 20 mol % of **6d** at −60 °C and increasing the distance to the radiation source from 3.0 to 6.0 cm (entry 16). Several control experiments supported that DPZ, chiral Brønsted acid, visible light, and an oxygen-free environment were essential to this transformation (see Table S2).

With the optimal reaction conditions in hand, the scope of this asymmetric [3 + 2] cycloaddition protocol was examined (Table 2). A wide range of 2-(1-arylvinyl)pyridines (**2**)

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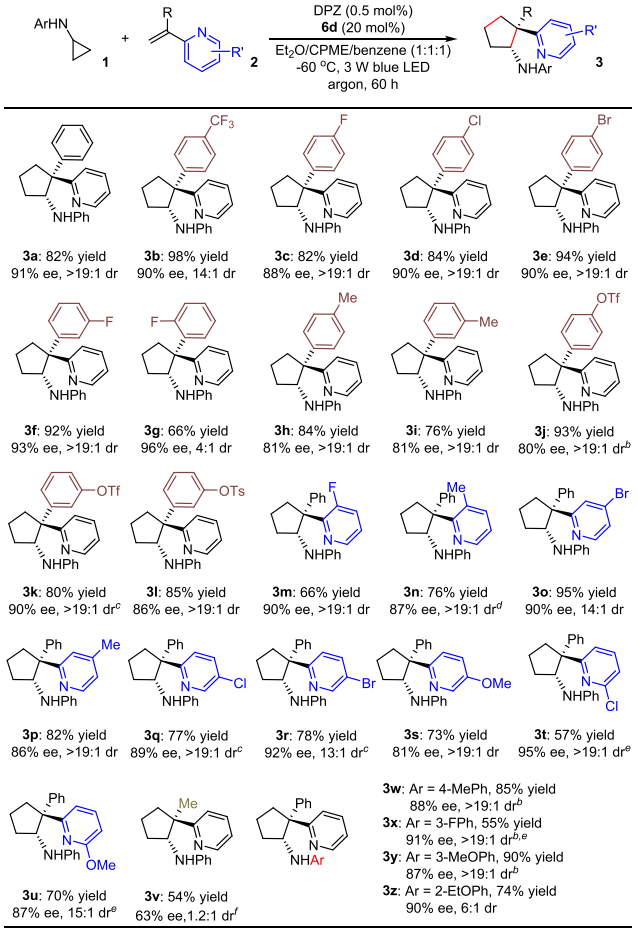
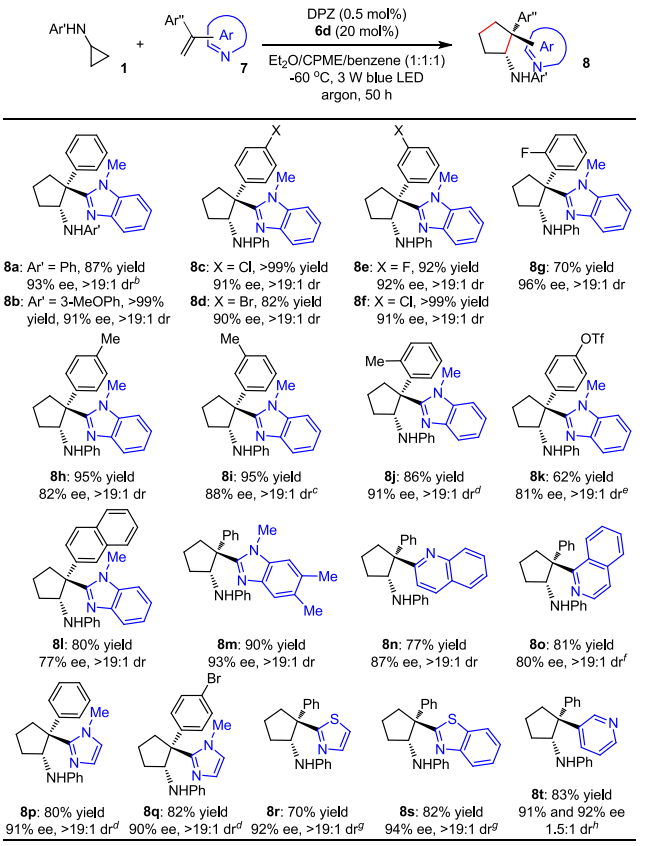
Table 2. Substrate Scope of α-Branched 2-Vinylpyridines[a]



[a]0.1 mmol scale. [b]Et_2O as the solvent and at −65 °C. [c]**6f** as the catalyst, and MTBE/CPME/benzene = 1:1:1 as the solvent. [d]**6e** as the catalyst, and Et_2O/toluene/benzene = 1:1:1 as the solvent. [e]t = 100 h. [f]**4m** as the catalyst, THF as the solvent, at −60 °C for 120 h.

Table 3. Substrate Scope of Other α-Branched Vinylazaarenes[a]



[a]0.1 mmol scale. [b]3.0 mmol scale, t = 72 h, yield = 90%, ee = 93%. [c]**6e** as the catalyst, and Et_2O/toluene/benzene = 1:1:1 as the solvent. [d]**6f** as the catalyst, MTBE/CPME/benzene = 1:1:1 as the solvent and at −25 °C. [e]Et_2O as the solvent and at −65 °C. [f]**6f** as the catalyst, CPME as the solvent and at −70 °C. [g]**6f** as the catalyst, MTBE/CPME/benzene = 1:1:1 as the solvent and irradiation distance = 2.0 cm. [h]**5q** as the catalyst, tBuPh as the solvent and at −45 °C within 60 h.

containing diverse substituents on either the aromatic or pyridyl ring were first evaluated in the reaction with **1a**. All the tested substrates were well tolerated regardless of their electronic properties or substitution patterns, and corresponding products **3a**−**u** were obtained in 57−98% yields with 80−96% ee and 4:1 to >19:1 dr, and in most cases, the diastereoselectivity was excellent. Notably, when there was a methoxy group present on the aromatic ring, the enantioselectivity was poor even after the careful examination of the reaction conditions (<30% ee). We reasoned that its strong electron-donating ability caused the α-pyridine radical intermediate to be highly nucleophilic, which made enantiocontrol more difficult. Accordingly, we suggested using an oxygen-derived electron-withdrawing group instead of methoxy to solve this problem. As a result, products **3j**−**l** with OTf and OTs as the substituent were obtained with satisfactory results. An α-methyl-substituted terminal alkene was then examined, and it provided product **3v** in 54% yield with 63% ee and 1.2:1 dr; the moderate yield was due to poor reactivity. On the other hand, distinct *N*-cyclopropyl arylamines reacted with **2a** to provide products **3w**−**z** with a high yield and stereoselectivity.

The success encouraged us to evaluate this method for the formation of other azaarene-substituted chiral cyclopentane variants. As depicted in Table 3, a variety of α-branched 2-vinylazaarenes with various important azaarenes, such as benzimidazole (**8a**−**m**), quinoline (**8n**), isoquinoline (**8o**), imidazole (**8p**−**q**), thiazole (**8r**), and benzothiazole (**8s**), are compatible with the catalytic system, leading to products **8a**−**s** in 62 to >99% yields with a 77−96% ee and >19:1 dr. In addition, α-phenyl 3-vinylpyridine afforded product **8t** in 83% yield with excellent enantioselectivity but poor diastereoselectivity. The broad substrate scope, the satisfactory results for constructing azaarene-substituted all-carbon quaternary stereocenters and the bioactive potential of the products highlight the generality and importance of this strategy.

To further reveal the synthetic utility of this method, **8a** was synthesized on a 3.0 mmol scale, and a similar yield and stereoselectivity were achieved (footnote b, Table 3). Moreover, **3y** could be oxidized by *m*-chloroperbenzoic acid (*m*CPBA), leading to ketone **9** in 80% yield and without compromising the ee (eq 1). After a single recrystallization, **9** was obtained with 99% ee, and its pyridine *N*-oxide could be reduced by PCl_3, resulting in α,α-diaryl-substituted ketone **10** in 82% yield with 98% ee. Inarguably, the formation of carbonyl group tremendously enriches the application potentials of this method.

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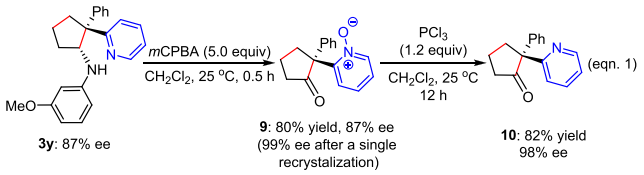

With regard to a plausible mechanism of this enantioselective [3 + 2] cycloaddition, Stern–Volmer experiments suggested that the transformations are triggered by the reductive quenching of *DPZ with cyclopropylamines (see the SI), with a quantum yield (Φ) of 0.079. Furthermore, the relationship between the ee of chiral Brønsted acid **6d** and the ee of product **3a** was evaluated (see the SI), and a linear correlation was identified, indicating that a single molecule of the chiral imidodiphosphoric acid is involved in the stereocenter-forming step. Given the remarkable difference in the enantioselectivities observed with electron-withdrawing and electron-donating substituents on the aromatic ring of the 2-(1-arylvinyl)pyridine, a ternary transition state with the chiral Brønsted acid acting as a bifunctional catalyst was proposed and plausible pathways of the cyclization reactions were calculated at the wB97X-D/6-31G(d) level of theory with ONIOM approach (see the SI for details). Two key transition states were located for the cyclization step leading to both enantiomers (Figure 1). Consistent with the experimental

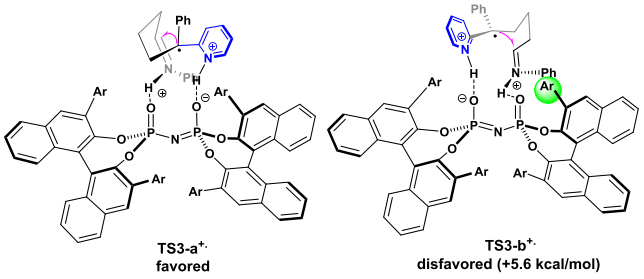

Figure 1. Stereoselectivity model.

observations, **TS3-a**$^{+\cdot}$ was found to be more favorable than **TS3-b**$^{+\cdot}$. The steric interactions between the iminium substituent (Ph) originated from cyclopropylaniline and the 3,3′-aryl groups (Ar) of the chiral Brønsted acid are crucial for the radical addition-based cyclization to attain high enantioselectivity.

In summary, these studies reveal the robust ability of radical chemistry to achieve the formation of all-carbon quaternary stereocenters for azaarenes. Under cooperative photoredox and Brønsted acid catalysis, readily accessible cyclopropylamines and α-branched 2-vinylazaarenes can efficiently undergo a tandem two-step radical addition process, accomplishing a formal [3 + 2] cycloaddition. A series of azaarene-substituted cyclopentane derivatives featuring all-carbon quaternary stereocenters at the α-position of the azaarenes have been synthesized in high yields with good to excellent enantio- and diastereo-selectivities. The substrate scope is extremely broad, and the excellent compatibility for diverse azaarenes is especially notable.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.0c08329.

General information, optimization of reaction conditions, general experimental procedures, mechanistic studies, synthetic transformations, determination of the absolute configurations, characterization data, and HPLC and NMR spectra (PDF)

Crystallographic information for C21H22N3Br (CCDC 1959655, compound **8q**, file: YZ21030) (CIF)

Crystallographic information for C16H15NO2 (CCDC 1959654, compound **9**, file: wgh0188) (CIF)

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Notes

The authors declare no competing financial interest.

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