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Enantioselective Chemodivergent Three-Component Radical Tandem Reactions through Asymmetric Photoredox Catalysis

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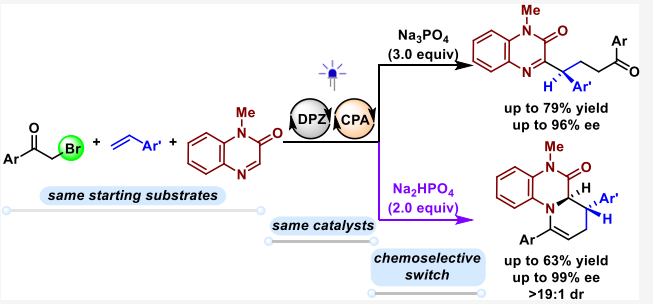
ABSTRACT: Chemodivergent synthesis has been achieved in asymmetric photocatalysis. Under a dual catalyst system consisting of a chiral phosphoric acid and DPZ as a photosensitizer, different inorganic bases enabled the formation of two sets of valuable products from the three-component radical tandem transformations of 2-bromo-1-arylenthan-1-ones, styrenes, and quinoxalin-2(1*H*)-ones. The key to success was the distinct pK_a environment, in which the radicals that formed on the quinoxalin-2(1*H*)-one rings after two radical addition processes underwent either single-electron oxidation or single-electron reduction. In addition, this work represents the first use of quinoxalin-2(1*H*)-ones in asymmetric photoredox catalysis.



INTRODUCTION

Controlling the chemoselectivity during the generation of distinct products from the same set of starting substrates can effectively improve molecular diversity and is thus a very useful tool for drug discovery.[1,2] As such, the development of chemodivergent synthesis has attracted extensive interest from chemists over the past few decades.[1,2] Several elegant examples[2] of visible-light-driven photocatalysis[3] have been established, although radical species can readily undergo diverse transformations in the reaction system, usually resulting in the loss of chemoselectivity. Central to success is the elaborate modulation of reaction parameters, such as photosensitizers, media, temperature, and additives, suggesting that distinct chemoselective events are sensitive to the reaction conditions.[2] Under such a specific environment and owing to the high reactivity of radicals, it is difficult for chiral catalysts to achieve sufficient enantiocontrol of the formation of stereocenters.

In recent years, the prominent synthetic capacity of photocatalysis has inspired us to develop enantioselective reactions by combining asymmetric organocatalysis with this sustainable tool of radical chemistry.[4] Based on the accumulation of these studies, we anticipated challenging chemodivergent photocatalytic asymmetric synthesis, a task with great importance in radical chemistry and the pharmaceutical industry. Herein, we report the first realization of this synthesis; when using a dual catalyst system[5] involving DPZ as a photosensitizer and a chiral phosphoric acid (CPA), the three-component transformations of 2-bromo-1-arylenthan-1-ones, styrenes, and quinoxalin-2(1*H*)-ones can efficiently result in two different radical-based pathways, with an inorganic base as a chemoselective switch (Scheme 1). A wide variety of quinoxalin-2(1*H*)-one derivatives bearing α-tertiary stereocenters and dihydroquinoxalin-2-one-based bicyclic variants featuring two adjacent tertiary stereocenters, both of which are prevalent in pharmaceutically important molecules (e.g., molecules **I**−**IV**),[6,7] were obtained in high yields with good to excellent enantio- and diastereoselectivities. Preliminary studies suggested that different pK_a environments effectively induced the radicals that formed on the quinoxalin-2(1*H*)-ones after the second radical addition to undergo either single-electron oxidation (i.e., Minisci-type reaction) or single-electron reduction. In the latter event, the bromide anion (Br^-) released from ketones was determined to be the crucial reductant, enabling the successful synthesis of the bicyclic products in the absence of an external reductant.

Because of their extensive range of biological and pharmacological activities,[6,8] considerable efforts[9,10] have been devoted to developing methodologies for constructing quinoxalin-2(1*H*)-one derivatives. Due to the readily accessible feedstocks and mild reaction conditions, photocatalysis has been widely used to devise various direct C3−H functionalization strategies based on radical addition.[10] Notably, the enantioselective manifolds remain unmet, although other

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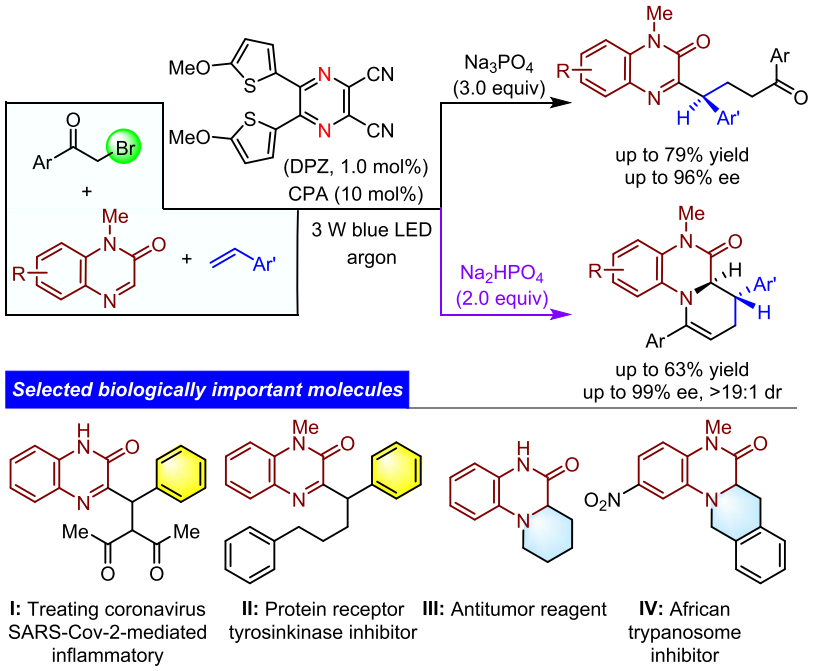
Scheme 1. Outline of This Work



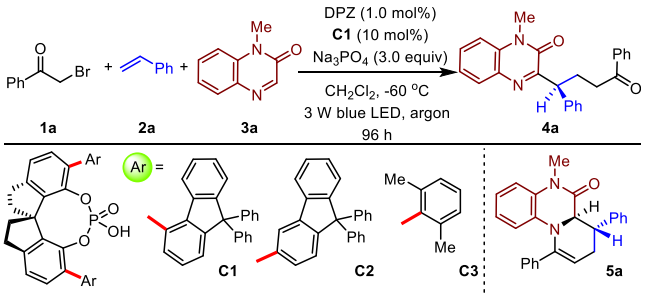
azaarenes such as pyridines and quinolines have been successfully extended to asymmetric Minisci-type reactions.[11] We speculated that such a dilemma might originate from the high reactivity since no extra acid is required to induce transformation in many cases.[10] Accordingly, the effective inhibition of the racemic background reaction is critical for chiral Brønsted acid catalysts to provide sufficient enantiocontrol. In addition, the current asymmetric Minisci-type reactions via noncovalent-bonding catalysis are limited to assembling α-amino and α-hydroxy radicals onto azaarenes,[11a−f] indicating the significance of the acidic proton on the radical species as a hydrogen-bond donor to the precise enantiofacial control of chiral Brønsted acid−base catalysts.

RESULTS AND DISCUSSION

Asymmetric three-component reactions of quinoxalin-2(1*H*)-ones[10g−i,12] using styrenes to engage in radical relays have become our preferred research target given the attractive bioactivities of the resultant products[6] (e.g., molecules **I** and **II**, Scheme 1). Moreover, the synthetic versatility of ketones led us to evaluate the unprecedented 2-bromo-1-arylenthan-1-ones as radical precursors. Accordingly, the study was begun by selecting 2-bromoacetophenone (**1a**), styrene (**2a**), and 1-methylquinoxalin-2(1*H*)-one (**3a**) as model substrates (Tables 1 and S1 in the Supporting Information (SI)). To test the feasibility of this process, the transformation was first carried out using 1.0 mol % DPZ in CH_2Cl_2 as the solvent at 25 °C and irradiated by a 3 W blue light-emitting diode (LED) (entry 1, Table S1). The desired product **4a** was obtained in 81% yield after 24 h. Although the result suggested that a strong racemic background reaction would occur in the enantioselective manifold, we still conducted a systematic investigation by probing diverse chiral CPAs and other parameters (Table S1).

To our delight, the reaction conducted in CH_2Cl_2 at −50 °C for 96 h using 1.0 mol % DPZ, 10 mol % SPINOL-CPA (**C1**), and 3.0 equiv of Na_3PO_4 afforded the chiral product **4a** in 68% yield with 93% ee (entry 1, Table 1). The control experiments

Table 1. Optimization of the Reaction Conditions[a]



entry	alteration to conditions	yield (%)[b]	ee (%)[c]
1	none	68	93
2	**C2** instead of **C1**	66	−77
3	**C3** instead of **C1**	56	−33
4	3DPAFIPN instead of DPZ	50	86
5	$[Ru(bpy)_3](PF_6)_2$ instead of DPZ	41	90
6[d]	no Na_3PO_4	21	83
7	no **C1**	5	n.a.
8	no DPZ	n.r.	n.a.
9	no light	n.r.	n.a.
10	under air	n.r.	n.a.

[a]Reaction conditions: **1a** (0.10 mmol), **2a** (0.20 mmol), **3a** (0.10 mmol), DPZ (1.0×10^{-3} mmol), **C1** (0.01 mmol), and Na_3PO_4 (0.3 mmol) in degassed DCM (3.0 mL) and at −60 °C. [b]Yield of isolated product. [c]ee was determined by HPLC analysis. [d]**5a** was obtained in 31% yield, 83% ee, and 7.7:1 dr. N.R., no reaction. N.A., not available.

revealed that the enantioselectivity is sensitive to the substituents at the 6,6′-positions of SPINOL (entries 2−3). Other feasible photosensitizers, such as 3DPAFIPN and $[Ru(bpy)_3](PF_6)_2$, were also evaluated, but both the yield and ee of **4a** decreased (entries 4−5). The transformation was then tested without Na_3PO_4 (entry 6). As a result, **4a** was obtained in only 21% yield with 86% ee, and the dihydroquinoxalin-2-one-based bicyclic compound **5a** was determined to be the major product (31% yield, 83% ee, 7.7:1 dr). In the absence of the

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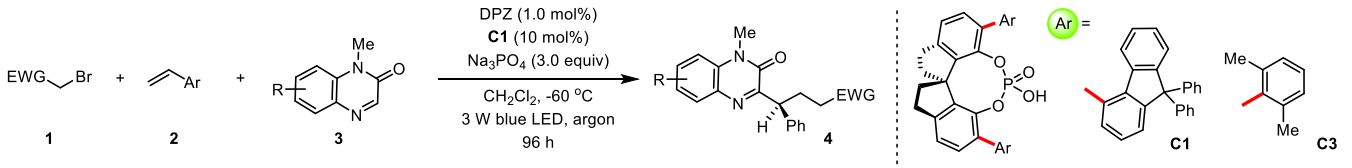
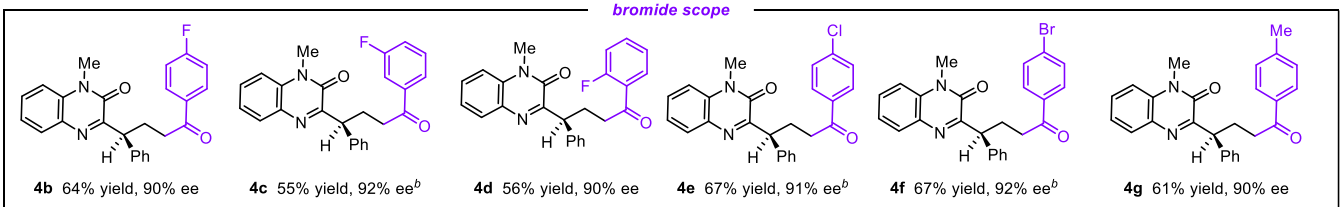
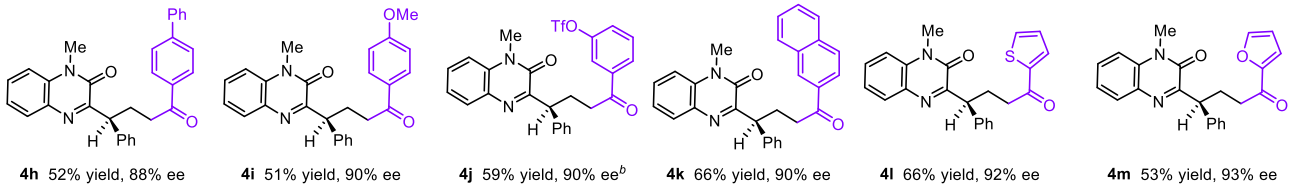
Table 2. Scope of Accessing Enantioenriched 3-Functionalized Quinoxalin-2(1*H*)-ones[a,b,c,d,e,f,g,h]



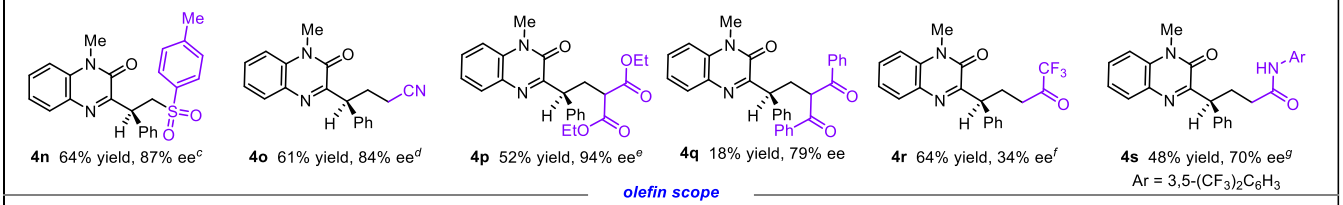
bromide scope



4b 64% yield, 90% ee; **4c** 55% yield, 92% ee[b]; **4d** 56% yield, 90% ee; **4e** 67% yield, 91% ee[b]; **4f** 67% yield, 92% ee[b]; **4g** 61% yield, 90% ee

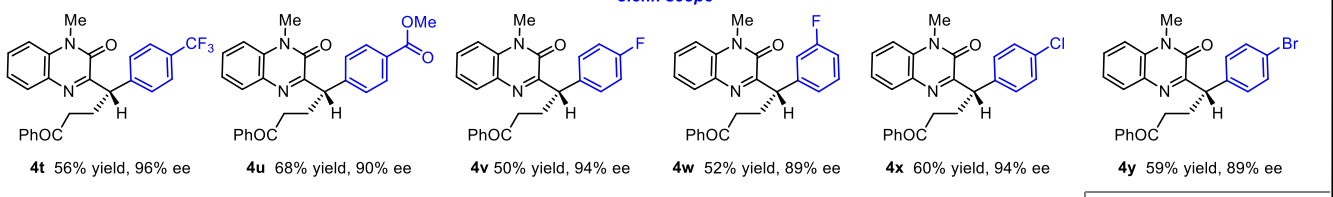


4h 52% yield, 88% ee; **4i** 51% yield, 90% ee; **4j** 59% yield, 90% ee[b]; **4k** 66% yield, 90% ee; **4l** 66% yield, 92% ee; **4m** 53% yield, 93% ee

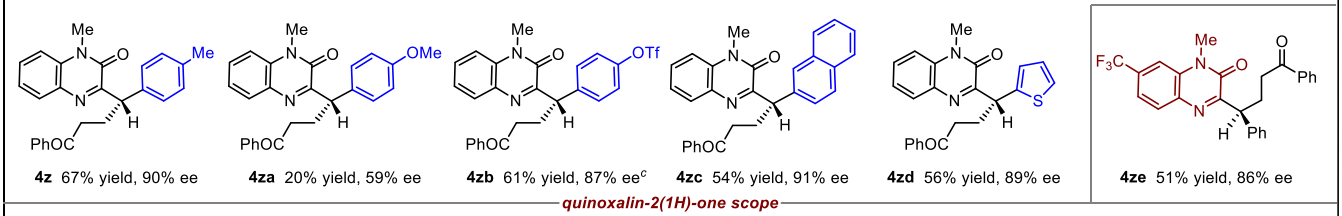


4n 64% yield, 87% ee[c]; **4o** 61% yield, 84% ee[d]; **4p** 52% yield, 94% ee[e]; **4q** 18% yield, 79% ee; **4r** 64% yield, 34% ee[f]; **4s** 48% yield, 70% ee[g] Ar = 3,5-$(CF_3)_2C_6H_3$

olefin scope

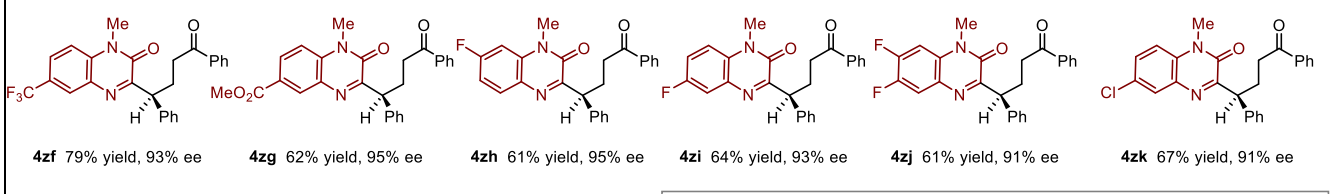


4t 56% yield, 96% ee; **4u** 68% yield, 90% ee; **4v** 50% yield, 94% ee; **4w** 52% yield, 89% ee; **4x** 60% yield, 94% ee; **4y** 59% yield, 89% ee

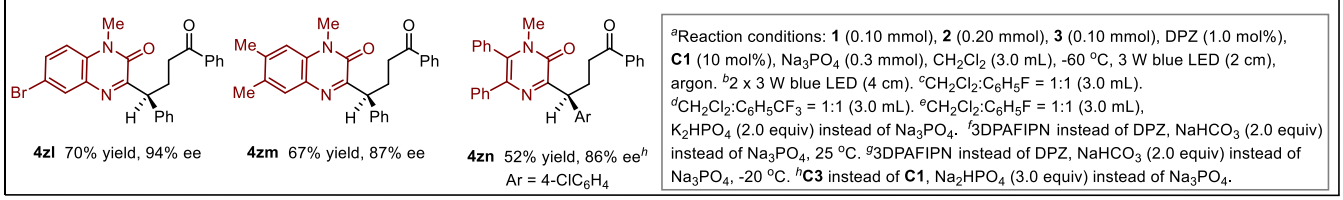


4z 67% yield, 90% ee; **4za** 20% yield, 59% ee; **4zb** 61% yield, 87% ee[c]; **4zc** 54% yield, 91% ee; **4zd** 56% yield, 89% ee; **4ze** 51% yield, 86% ee

quinoxalin-2(1H)-one scope



4zf 79% yield, 93% ee; **4zg** 62% yield, 95% ee; **4zh** 61% yield, 95% ee; **4zi** 64% yield, 93% ee; **4zj** 61% yield, 91% ee; **4zk** 67% yield, 91% ee



4zl 70% yield, 94% ee; **4zm** 67% yield, 87% ee; **4zn** 52% yield, 86% ee[h] Ar = 4-ClC_6H_4

[a]Reaction conditions: **1** (0.10 mmol), **2** (0.20 mmol), **3** (0.10 mmol), DPZ (1.0 mol%), **C1** (10 mol%), Na_3PO_4 (0.3 mmol), CH_2Cl_2 (3.0 mL), -60 °C, 3 W blue LED (2 cm), argon. [b]2 x 3 W blue LED (4 cm). [c]CH_2Cl_2:C_6H_5F = 1:1 (3.0 mL). [d]CH_2Cl_2:$C_6H_5CF_3$ = 1:1 (3.0 mL). [e]CH_2Cl_2:C_6H_5F = 1:1 (3.0 mL), K_2HPO_4 (2.0 equiv) instead of Na_3PO_4. [f]3DPAFIPN instead of DPZ, $NaHCO_3$ (2.0 equiv) instead of Na_3PO_4, 25 °C. [g]3DPAFIPN instead of DPZ, $NaHCO_3$ (2.0 equiv) instead of Na_3PO_4, -20 °C. [h]**C3** instead of **C1**, Na_2HPO_4 (3.0 equiv) instead of Na_3PO_4.

[a]Reaction conditions: **1** (0.10 mmol), **2** (0.20 mmol), **3** (0.10 mmol), DPZ (1.0 mol %), **C1** (10 mol %), Na_3PO_4 (0.3 mmol), CH_2Cl_2 (3.0 mL), −60 °C, 3 W blue LED (2 cm), argon. [b]2 × 3 W blue LED (4 cm). [c]CH_2Cl_2/C_6H_5F = 1:1 (3.0 mL). [d]$CH_2Cl_2/C_6H_5CF_3$ = 1:1 (3.0 mL). [e]CH_2Cl_2/C_6H_5F = 1:1 (3.0 mL), K_2HPO_4 (2.0 equiv) instead of Na_3PO_4. [f]3DPAFIPN instead of DPZ, $NaHCO_3$ (2.0 equiv) instead of Na_3PO_4, 25 °C. [g]3DPAFIPN instead of DPZ, $NaHCO_3$ (2.0 equiv) instead of Na_3PO_4, −20 °C. [h]**C3** instead of **C1**, Na_2HPO_4 (3.0 equiv) instead of Na_3PO_4.

chiral catalyst **C1**, almost no product was detected, revealing that low temperatures could suppress the undesirable racemic background reaction, leading to the successful enantiocontrol of the chiral catalyst to the formation of the new C(sp^2)−C(sp^3) bond (entry 7). Subsequent experiments evaluating other reaction elements revealed that DPZ, visible light, and an

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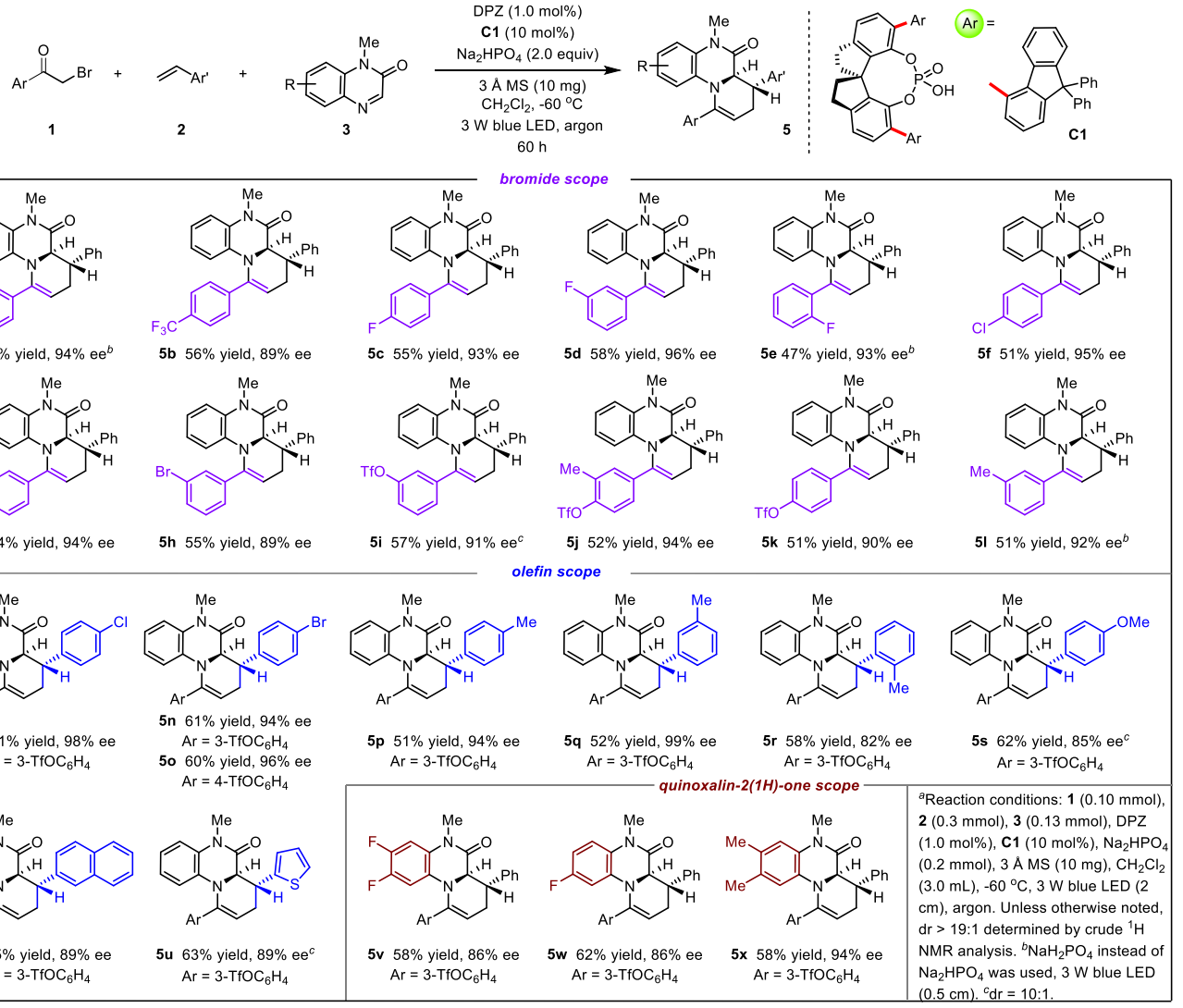
Table 3. Scope of Accessing Enantioenriched Bicyclic Compounds[a,b,c]



[a]Reaction conditions: **1** (0.10 mmol), **2** (0.3 mmol), **3** (0.13 mmol), DPZ (1.0 mol %), **C1** (10 mol %), Na_2HPO_4 (0.2 mmol), 3 Å MS (10 mg), CH_2Cl_2 (3.0 mL), −60 °C, 3 W blue LED (2 cm), argon. Unless otherwise noted, dr > 19:1 determined by crude ^{1}H NMR analysis. [b]NaH_2PO_4 instead of Na_2HPO_4 was used, 3 W blue LED (0.5 cm). [c]dr = 10:1.

oxygen-free environment are indispensable to the transformation occurring (entries 8−10).

With the optimized conditions in hand, we commenced to explore the scope of this asymmetric three-component Minisci-type reaction (Table 2). A series of 2-bromo-1-arylenthan-1-ones (**1**) with diverse electron-withdrawing and electron-donating groups on the distinct positions of aromatic rings were first attempted to react with **2a** and **3a**. It was found that products **4b−j** were obtained in 51−67% yields with 88−92% ee. The excellent enantioselectivities attained with the fused aromatic (**4k**) and heteroaromatic (**4l−m**) rings as the ketone substituents underscore the versatility of the catalytic system. Moreover, other useful functional groups, such as tosyl (**4n**), cyano (**4o**), and ester (**4p**) groups, could be readily introduced onto such an important molecular scaffold by using the corresponding bromides **1**. 2-Bromo-1,3-diphenylpropane-1,3-dione rendered product **4q** with 79% ee, but the poor reactivity led to only 18% yield. Such a dilemma made it infeasible to lower the temperature for 3-bromo-1,1,1-trifluoropropan-2-one, and the adduct **4r** was obtained in 64% yield with 34% ee when the transformation was performed at 25 °C. It was found that **4s** as the amide derivative was also synthesized with a moderate yield and ee. The transformations of styrenes **2** with **1a** and **3a** were then carried out, leading to products **4t−zd** with 20−68% yields and 59−96% ee. Quinoxalin-2(1*H*)-ones featuring different substituents on the aromatic rings were subsequently evaluated, and good compatibility was demonstrated, with products **4zf−zm** obtained in 51−79% yields with 86−95% ee. The broad substrate scope of the method was further investigated by using pyrazinols instead of quinoxalin-2(1*H*)-ones, and the representative product **4zn** was obtained in 52% yield with 86% ee. It is worth mentioning that the product yields are mainly affected by the reactivity, and the chemoselectivity is excellent in most cases.

The generation of **5a** in the absence of Na_3PO_4 (footnote d) prompted us to explore the possibility of improving the yield and ee, given the biological importance of such a molecular scaffold (e.g., molecules **III**, **IV**), the lack of an asymmetric synthetic method, and the significance of verifying the viability of chemodivergent synthesis for asymmetric photocatalysis.

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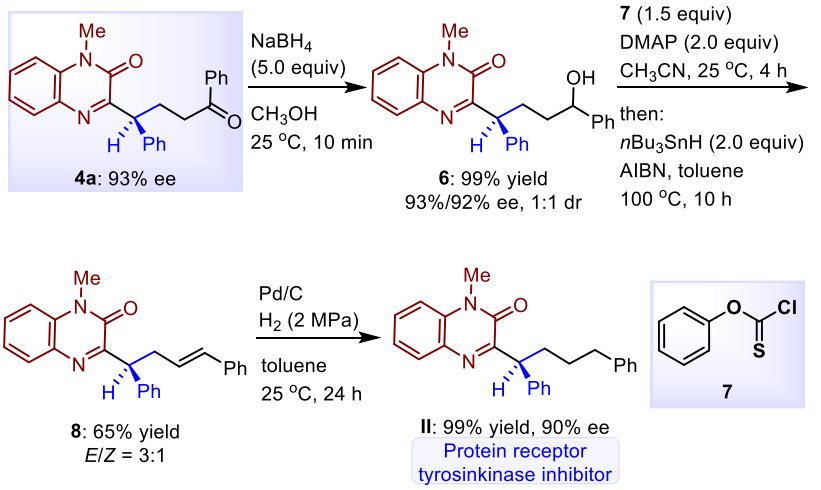
Scheme 2. Synthesis of Enantioenriched II



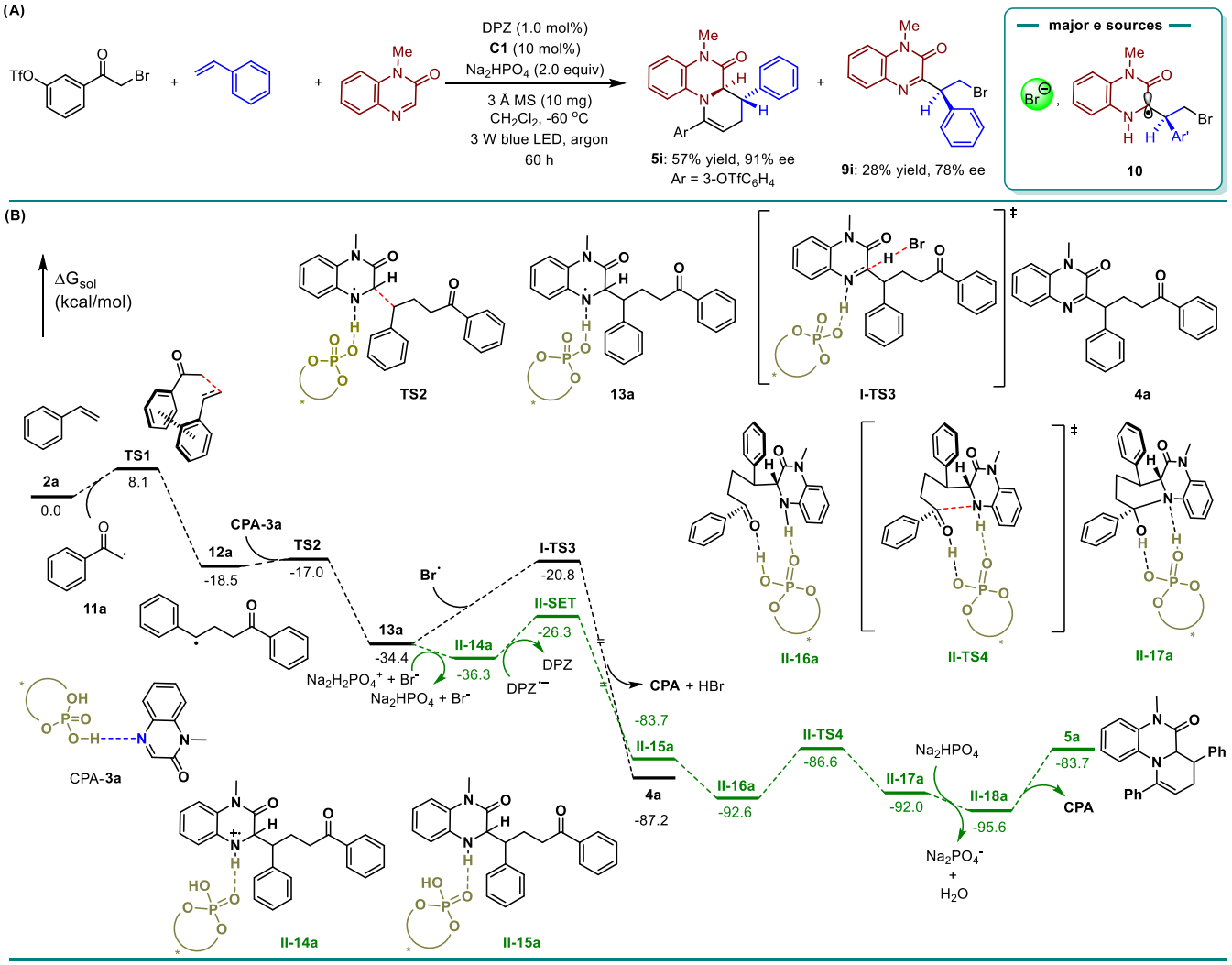


Figure 1. Mechanistic studies. (A) Determination of side products. (B) Free energy profile for the two pathways for the generation of Minisci-type (**4a**) and bicyclic (**5a**) products.

Gratifyingly, our persistent efforts toward investigating reaction conditions yielded satisfactory results. As depicted in Table 3, when using Na_2HPO_4 in place of Na_3PO_4 and a 3 Å molecular sieve (MS) as an additive, the transformations under the standard reaction conditions (Table 1) afforded an array of bicyclic compounds **5a**−**x** in 47−63% yields with 82−99% ee and 10:1 to >19:1 dr. Notably, all products were determined to be the major products in the reaction systems, and the moderate

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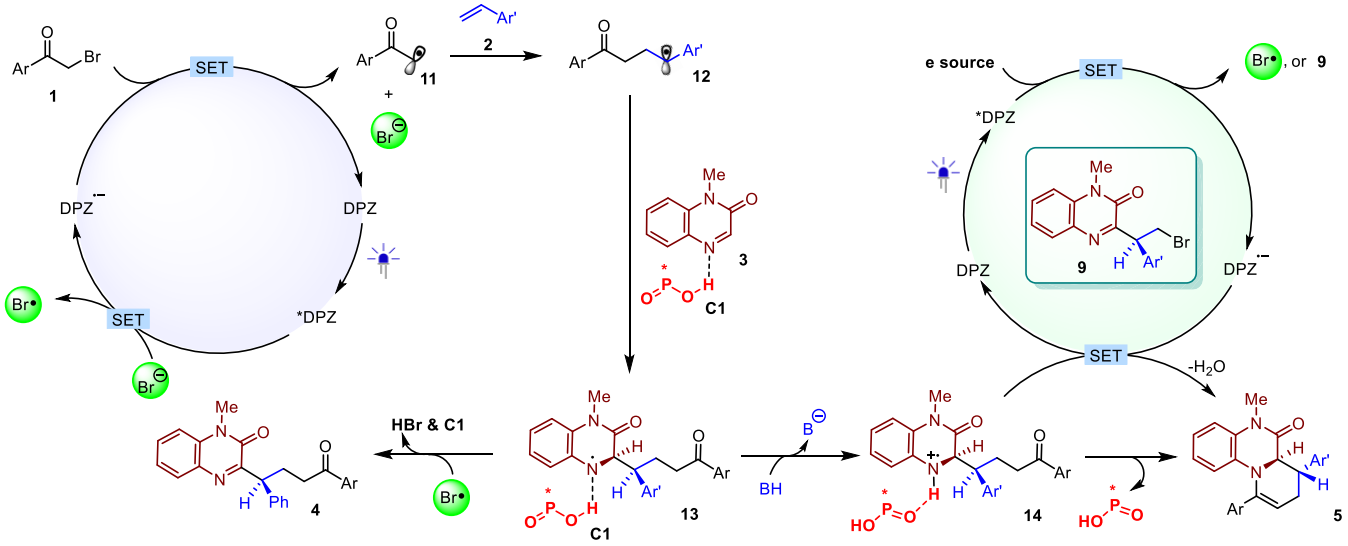

Figure 2. Proposed mechanism.

yields were mainly ascribed to the competitive reaction of quinoxalin-2(1*H*)-ones with the radical intermediates generated from the addition of the bromine radical ($Br^{\bullet}$) to olefins (vide infra).

Although the two sets of products are potentially bioactive, synthesizing known important molecules from them can further disclose the synthetic practicability of the current method. To this end, Minisci-type reaction adduct **4a** was selected to first undergo reduction by using $NaBH_4$ (Scheme 2). Alcohol **6** was obtained in 99% yield, and it could be converted to olefin **8** in 65% yield under the reaction conditions used for Barton deoxygenation. Subsequently, treatment of **8** with H_2 and Pd/C produced molecule **II**, which is a protein receptor tyrosine kinase inhibitor, in 98% yield with 90% ee.

To study the mechanisms of the two chemodivergent transformations, a series of experiments were carried out. First, Stern−Volmer experiments with an excitation wavelength of 448 nm were performed,[13] and no measurable luminescence quenching of the photoexcited DPZ (*DPZ) was observed by 2-bromoacetophenone (**1a**), styrene (**2a**), or 1-methylquinoxalin-2(1*H*)-one (**3a**). These results are similar to those of many previous reports on photoredox catalytic Minisci-type reactions via reductive quenching.[10i,j,11a−d] On the other hand, in the transformation of forming **5i**, we noted that **9i** as a major side product could be obtained in 28% yield with 78% ee, suggesting that $Br^{\bullet}$ was formed in the reaction system (Figure 1A).[14] As such, the corresponding Stern−Volmer experiment was performed, which verified the capacity of *DPZ to oxidize Br^{-}. In addition, the production of **9i** reveals radicals **10** as another viable electron source. Notably, the linear correlation between the ee of **C1** and the ee of products **4** or **5** suggests that only a single molecule of the chiral catalyst was involved in the new bond-forming process. Furthermore, 78% ee of **9i** could support the indispensability of hydrogen-bonding interactions between CPA and quinoxalin-2-ones.

With these experimental results as a guide, we subsequently performed density functional theory (DFT) calculations.[13] As a result, the reaction starts with the generation of radical **11a** from bromides **1a** through the single-electron reduction by the resultant $DPZ^{\bullet-}$ (Figure 1B). Then, **11a** undergoes addition to styrenes **2a** through the transition state **TS1** (ΔG = 8.1 kcal/mol), providing α-aryl radicals **12a**, which then adds to the complex CPA-**3a** through **TS2** with a low barrier of 1.5 kcal/mol. In the more basic condition (i.e., using Na_3PO_4), the resulting radical **13a** can experience hydrogen atom abstraction by the bromine radical to form the Minisic product **4a** and release the forming HBr and catalyst CPA. The barrier for this HAT process through **I-TS3** is 13.6 kcal/mol, which is 8.7 and 4.5 kcal/mol lower than those of the single-electron oxidation and reduction of radical **13a**, respectively (Figure S14). Hence, Minisic product **4a** is obtained as the major product.

On the other hand, inspired by MacMillan's study,[15] we explored whether the barrier of the single-electron reduction of **13a** could be reduced by recruiting a proton in the presence of Na_2HPO_4 and the small amount of HBr generated along with the side products, such as **9i**. Indeed, the single-electron reduction of the protonated **II-14a** by $DPZ^{\bullet-}$ leading to the neutral intermediate **II-15a** is preferred over the hydrogen atom abstraction process (**I-TS3**) and is exergonic by 47.4 kcal/mol. Subsequently, a more stable conformation **II-16a** displaying double H-bonding interactions (N−H···O and additional O−H···O interactions) could be transformed from **II-15a**. Intermediate **II-16a** then proceeds through a concerted proton transfer/cyclization transition state **II-TS4** to form bicyclic alcohols **II-17a** with an energy barrier of 6.0 kcal/mol. Finally, the dehydration of **II-17a** with the aid of Na_2HPO_4 leads to the bicyclic products **5a**. Therefore, in the less basic condition in the presence of Na_2HPO_4, radical **13a** could be promoted to form the radical cation **II-14a**, and the barrier of the single-electron reduction could be further reduced, resulting in bicyclic products **5a**.

From the above, plausible mechanisms on this chemodivergent enantioselective three-component reaction are proposed and summarized in Figure 2. With respect to the transformations of yielding products **4**, photoredox catalysis should be triggered from the single-electron oxidation of the bromine anion (Br^{-}) by *DPZ. The resultant $DPZ^{\bullet-}$ ($E_{red}^{1/2}$ = −1.07 V versus the saturated calomel electrode (SCE) in CH_3CN) subsequently reduced bromides **1** (e.g., **1a**: $E_{p/2}$ = −0.81 V versus SCE in CH_3CN) to complete the catalytic cycle of DPZ and produced radicals **11**. After addition of **11** to styrenes **2**, α-aryl radicals **12** were generated, which could attack the 3-position of quinoxalin-2-ones **3** upon activation of the crucial CPA **C1** (entry 7, Table 1), resulting in intermediates

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13. Subsequently, 13 are prone to generating products 4 through the hydrogen atom abstraction by the bromine radical rather than the sequential single-electron oxidation and deprotonation. On the other hand, 13 are also the key intermediates for the formation of bicyclic products 5. The DFT calculation results support that Na_2HPO_4, as a weaker inorganic base than Na_3PO_4, may lead to forming a protonated radical 14 and allow it to preferentially undergo single-electron reduction, finally resulting in 5.

CONCLUSIONS

In summary, we have demonstrated the viability of chemodivergent photocatalytic asymmetric synthesis. As a paradigm, the three-component transformations of 2-bromo-1-arylenthan-1-ones, styrenes, and quinoxalin-2(1*H*)-ones could afford two series of valuable products with high yields and ee values in the presence of the same dual catalyst system, with distinct inorganic bases to modulate the chemoselectivity. Moreover, this work represents the first enantioselective photocatalytic example of quinoxalin-2(1*H*)-ones. We anticipate that this result will encourage the pursuit of more kinds of chemodivergent asymmetric photocatalytic reactions, although the highly reactive radicals constitute a central challenge, thus robustly promoting the advancement of the pharmaceutical industry.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.3c08883.

General information; optimization of reaction conditions; experimental procedures; mechanistic studies; characterization data; X-ray of products **4e** and **5o**; and NMR spectra (PDF)

Accession Codes

CCDC 2191793−2191794 contain 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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