Conjugate Addition-Enantioselective Protonation of N-Aryl Glycines to #-Branched 2-Vinylazaarenes via Cooperative Photoredox and Asymmetric Catalysis

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Conjugate Addition–Enantioselective Protonation of *N*-Aryl Glycines to α-Branched 2-Vinylazaarenes via Cooperative Photoredox and Asymmetric Catalysis

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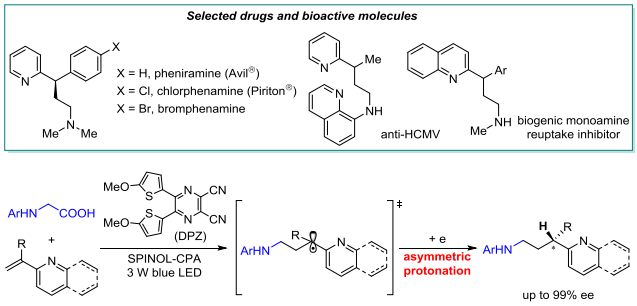
ABSTRACT: An enantioselective protonation strategy has been successfully applied to the synthesis of chiral α-tertiary azaarenes. With a dual catalytic system involving a chiral phosphoric acid and a dicyanopyrazine-derived chromophore (DPZ) photosensitizer that is mediated by visible light, a variety of α-branched 2-vinylpyridines and 2-vinylquinolines with *N*-aryl glycines underwent a redox-neutral, radical conjugate addition–protonation process and provided valuable chiral 3-(2-pyridine/quinoline)-3-substituted amines in high yields with good to excellent enantioselectivities (up to >99% ee). An application of this methodology to a two-step synthesis of the enantiomerically pure medicinal compound pheniramine (Avil®) is also presented.

INTRODUCTION

Enantioselective protonation is a bio-inspired method widely used to synthesize valuable carbonyl compounds with various chiral α-tertiary carbon scaffolds.[1] Notably, azaarenes bearing embedded C=N imine fragments such as pyridines and quinolines are electron deficient. In the past few years, the direct exploitation of such azaarenes as the analogs of carbonyls to trigger the reaction, thus furnishing the enantioselective functionalization of prochiral azaarenes, has become an attractive method due to its atom and step economy.[2-8] In this regard, a synthetic methodology involving an enantioselective protonation would provide an expedient and complementary[3] approach to accessing significantly enantioenriched α-tertiary azaarenes, which are ubiquitous in pharmaceuticals, agrochemicals and natural products,[9] thus leveraging the broad applicability of this modular strategy.

Among the established enantioselective protonation protocols, conjugate addition–protonation to α-branched carbonyl-activated terminal alkenes can be used to assemble a range of crucial molecular motifs at the β-position of carbonyls in a straightforward manner.[1h-m] Accordingly, the platform of using α-branched vinylazaarenes as electrophiles would be a viable and productive strategy. However, the ground-state ionic reaction approach is likely not tolerant of terminal alkenes given that no examples of such substrates have been reported;

Scheme 1. Outline of This Work.



this is probably due to the unfavorable formation of the *tetra*-substituted enamine intermediates via a transient dearomatization step. This dilemma has inspired the exploration of visible-light-driven photoredox catalysis, which often permits otherwise inaccessible modes of molecular transformations.[10] As a result, in recent years, the groups of Rueping,[11a] Ngai,[11b] Ravelli[11c] and Ley[11d] have developed racemic conjugate addition reactions of distinct radical species to α-branched vinylpyridines by exploiting this powerful synthetic technique. Radical-based approaches of this type feature high reactivity, and in most cases, an extra catalyst is not required for promoting the transformation. This catalyst-free reactivity is a substantial problem for the development of an enantioselective version of the reaction since it means a competitive achiral background reaction that would deteriorate the enan-

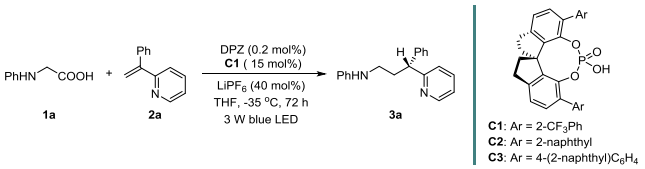
tioselectivity would be active. More importantly, controlling the stereochemistry during the construction of chiral azaarenes via asymmetric photoredox catalysis still constitutes a formidable challenge.[12]

Recently, we reported visible-light-driven, organocatalytic enantioselective photoreductions of 1,2-diketones and α-keto ketimines.[13a] The hydrogen-bonding interaction between the chiral catalysts and the ketyl intermediates effectively overcame the remarkable background reaction and allowed precise kinetic control of the delivery of a proton. Although the substantially lower electronegativity of the neutral N atom of the azaarene over the strongly basic oxygen anion of the ketyl radical[14] should considerably deteriorate the enantiocontrol effect,[12] we were inspired to explore this highly desirable but elusive task via H-bonding catalysis. In particular, we sought to solve asymmetric conjugate addition of α-amino radicals[15e,g,j] to α-branched 2-vinylpyridines and 2-vinylquinolines since the produced chiral 3-(2-pyridine/quinoline)-3-substituted amines are featured in many drugs and bioactive molecules (Figure 1).[9b-e] Asymmetric hydrogenations of 3-aryl-3-(2-pyridyl)allylamines catalyzed by chiral transition-metal complexes is the only reported method of approaching the pyridine entities.[3a-b] However, this methods suffers from unsatisfactory enantioselectivity, and the low yield stemmed from the unavoidable hydrogenolysis of the C–N bond. Here, we report the development of a redox-neutral, enantioselective radical conjugate addition–protonation of *N*-aryl glycines to α-branched 2-vinylpyridines and 2-vinylquinolines under the cooperative catalysis[14-15] of a dicyanopyrazine-derived chromophore (DPZ) photosensitizer[13] and a 1,1'-spirobiindane-7,7'-diol (SPINOL)-based chiral phosphoric acid (CPA, Figure 1). The desired chiral amine entities were prepared in high yields with good to excellent enantioselectivities.

RESULTS AND DISCUSSION

α-Amino acids are non-fossil fuel-based, environmentally benign carbon sources and have therefore been pursued as starting substrates for organic synthesis.[16] Many research groups, with the MacMillan group as a representative,[15h,17] have reported that *N*-protected α-amino acids can undergo visible-light-driven, single-electron oxidative decarboxylation to efficiently generate α-amino radicals. As such, we began our investigation by exploring the model reaction between *N*-phenyl glycine (**1a**) and 2-(1-phenylvinyl)pyridine (**2a**) with our developed metal-free[10e] DPZ as the photoredox catalyst (Table 1). The initial study showed that the transformation furnished racemic product **3a** in 87% yield after 12 hours when only using 0.5 mol% DPZ at 25 °C, revealing a high reactivity of this radical-based transformation (See entry 1, Table S1 in the Supporting Information [SI]). Nevertheless, we explored a range of chiral H-bonding catalysts and reaction parameters (See Table S1 in SI). To our delight, the reaction performed in THF at –35 °C for 72 hours in the presence of 0.2 mol% DPZ, 15 mol% chiral SPINOL-CPA[18] (**C1**) and 40 mol% $LiPF_6$ as an additive afforded chiral product **3a** in 90% yield and 94% ee (entry 1). The substituents at the 6,6'-positions of SPINOL have a substantial influence on the enantioselectivity of the reaction; as an example, catalysts **C2** and **C3** afforded **3a** in 56% ee and 72% ee, respectively (entries 2–3). In the absence of $LiPF_6$, the ee of **3a** fell to 88% (entry 4). Other plausible photoredox catalysts, including rose bengal and $[Ru(bpy)_3]Cl_2$, were tested (entries 5–6), but the reaction became very sluggish, and trace or no **3a** was obtained probably due to the very low catalyst loading. Interestingly, the reaction conducted under the standard conditions but in the absence of catalyst **C1** did not produce **3a** (entry 7). The control experiments confirmed that DPZ, visible light and the oxygen-free environment are essential to the transformation (entries 8–10).

Table 1. Optimization of Reaction Conditions[a]



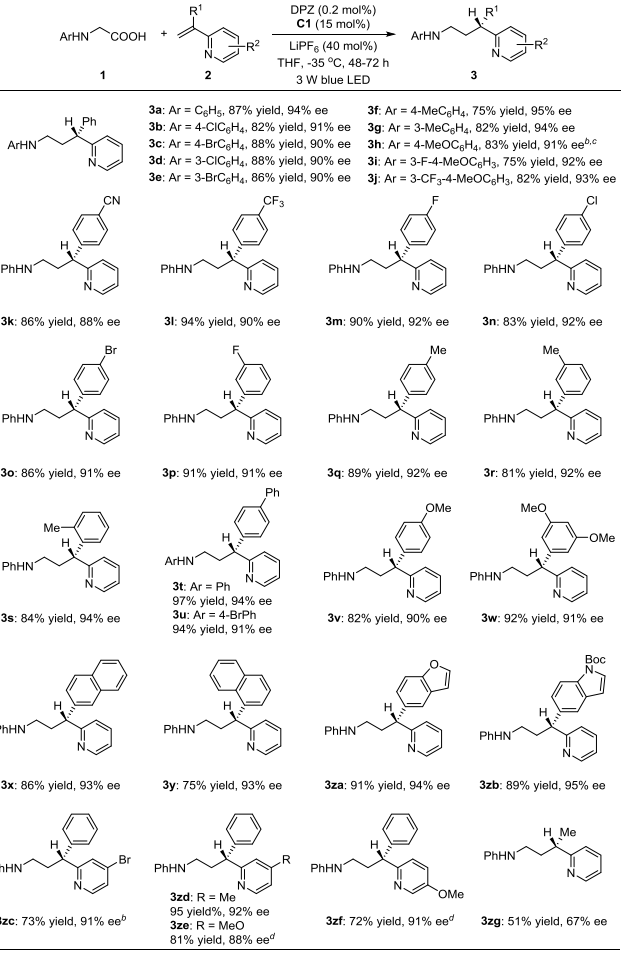
entry	Variation from standard conditions	yield (%)[b]	ee (%)[c]
1	none	90	94
2,	**C2** instead of **C1**	86	56
3	**C3** instead of **C1**	75	72
4	without $LiPF_6$	34	88
5	Rose Bengal instead of DPZ	<5	87
6	$[Ru(bpy)_3]Cl_2$ instead of DPZ	0	N.A.
7	no **C1**	0[d]	N.A.
8	no DPZ	0[d]	N.A.
9	no light	0[d]	N.A.
10	under air	0[e]	N.A.

[a] Reaction conditions: **1a** (0.05 mmol), **2a** (0.06 mmol), solvent (2.0 mL). [b] Yield of isolated product. [c] Determined by HPLC analysis on a chiral stationary phase. [d] No reaction was observed. [e] **1a** was consumed, but **3a** was not obtained.

With the optimal reaction conditions in hand, the scope of this asymmetric radical conjugate addition protocol was examined (Table 2). From the reactions of **2a** with *N*-aryl glycines **1** that feature electron-withdrawing or electron-donating substituents on the aryl ring, adducts **3a-j** were obtained in 75 to 88% yields with 90 to 95% ees. A methoxy substituent at the 4-position of the substrate (**3h**) made the reaction sluggish and lead to a decreased yield (35%, footnote *c*), but the higher temperature (0 °C) or the introduction of an additional electron-withdrawing group such as F (**3i**) and CF_3 (**3j**) at the 3-position could efficiently mitigate this drawback. With respect to the pyridine-based terminal alkene component, the reaction tolerated a wide range of α-aryl and 2-pyridine substrates regardless of their electronic properties and substitution patterns, and corresponding prod-

ucts **3k**-**3zf** were generated in 72 to 97% yields and 88 to 95% ees. The excellent chemical yields and enantioselectivities achieved with fused aromatic (**3x**-**y**) and heteroaromatic (**3za**-**zb**) rings at the α-position of the alkene underscore the generality of this catalytic system. The absolute configuration of **3u** was assigned to be *R* based on single-crystal X-ray diffraction analysis.[19] We also tested an α-methyl-substituted terminal alkene (**3zg**), and moderate yield and enantioselectivity were observed.

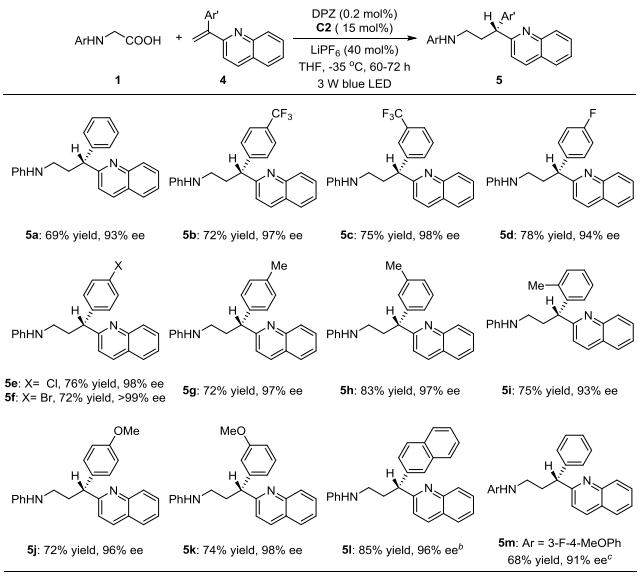
Table 2. Enantioselective Conjugate Addition–Protonation of *N*-Aryl Glycines to α-Branched 2-Vinylpyridines[a]



[a] Reaction conditions: **1** (0.1 mmol), **2** (0.12 mmol), DPZ (0.2 mol%), **C1** (15 mol%), $LiPF_6$ (40 mol%), THF (4.0 mL), –35 °C. Yield of isolated product. Ee was determined by HPLC analysis on a chiral stationary phase. [b] *T* = 0 °C. [c] When *T* = –35 °C, yield = 35%, ee = 94%. [d] 20 mol% of **C1** was used.

The success inspired us to evaluate this method in the construction of important chiral 3-(2-quinoline)-3-substituted amines[9c-d] with α-branched 2-vinylquinolines **4** as electrophiles. As shown in Table 3, under the established reaction conditions but using **C2** as the catalyst, all reactions completed within 60–72 hours, providing the desired products **5a-l** with diverse substituents on the α-aromatic ring and **5m** from *N*-(3-F-4-methoxy)-phenyl glycine in 68 to 85% yields and 91% to >99% ee. The slightly decreased yield compared to the pyridine-based products is due to a few unknown side products observed in this reaction system. Notably, the reaction proceeded very slowly for α-alkyl 2-vinylquinolines.

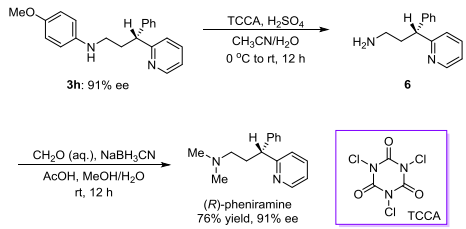
Table 3. Enantioselective Conjugate Addition–Protonation of *N*-Aryl Glycines to α-Branched 2-Vinylquinolines[a]



[a] Reaction conditions: **1** (0.1 mmol), **4** (0.12 mmol), DPZ (0.2 mol%), **C2** (15 mol%), $LiPF_6$ (40 mol%), THF (4.0 mL), –35 °C. Yield of isolated product. Ee was determined by HPLC analysis on a chiral stationary phase. [b] *T* = –20 °C. [c] 20 mol% of **C2** was used.

The products derived from these two chemical transformations are not only potentially bioactive but also excellent precursors to many drugs and bioactive compounds (Scheme 1). For example, adduct **3h** could be rapidly transformed to an enantiomerically enriched antihistamine drug i.e., (*R*)-pheniramine. As shown in Scheme 2, treatment of **3h** with *N,N',N"*-trichloroisocyanuric acid (TCAA) cleaved the *N*-protecting group. The resulting amine (**6**) was subsequently converted to pheniramine in 76% yield over two steps and without erosion of the ee via reductive amination with formaldehyde and $NaBH_3CN$. The synthetic procedure was also effective to the transformation of **3i** to (*R*)-pheniramine.[19]

Scheme 2. Preparation of Enantiomerically Pure Pheniramine.



Based on the previous reports[11,17a-b,g] and product structure, the conjugate addition of α-amino radicals derived from *N*-aryl glycines to terminal alkenes is feasible. Nota-

bly, the subsequently yielded α-carbon radical variants of azaarenes could undergo two possible C–H bond forming pathways, namely, protonation after catalyst turnover enables the second single-electron reduction[11d] and direct hydrogen atom transfer (HAT)[11a-c] with another *N*-aryl glycine molecule via radical chain propagation.[20] We thus performed control experiments to elucidate this crucial stereocenter-forming process (Figure 1A). We first attempted the reaction of *N*-Boc-protected glycine **7** with alkene **2a** in the presence of 2 mol% DPZ and 20 mol% Cs_2CO_3 in THF at 25 °C. As expected, no reaction was observed as photo-induced DPZ (*DPZ, $E^t(S^*/S^{\bullet-})$ = +0.91 V vs a saturated calomel electrode (SCE) in CH_2Cl_2)[13] cannot oxidize carboxylate via a single-electron process (carboxylate ions, $E^{red}_{1/2}$ ≈ +1.10 vs SCE in CH_3CN).[17c-f] The photoredox catalyst Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$ oxidizes these ions due to its strongly oxidizing excited state (Ir(III)*/Ir(II) = +1.21 vs SCE in CH_3CN).[17c-f] Therefore, the reaction was tested with this Ir catalyst, and product **8** was obtained in 95% yield within 12 hours. The results demonstrate the viability and rather high reactivity of the *N*-Boc-based α-amino radical in this conjugate addition. A mixture of **1a** (0.5 equiv), **7** (10 equiv), **2a** (1.0 equiv) and DPZ (2 mol%) in THF at 25 °C was then stirred for 24 hours. If a HAT mechanism is operative, it may be possible to detect adduct **8**; however, only *rac*-**3a** was obtained (93% yield). This result was consistent with the reaction performed under the established asymmetric reaction conditions.[21] Therefore, the protonation is an important step in the construction of the tertiary carbon center.

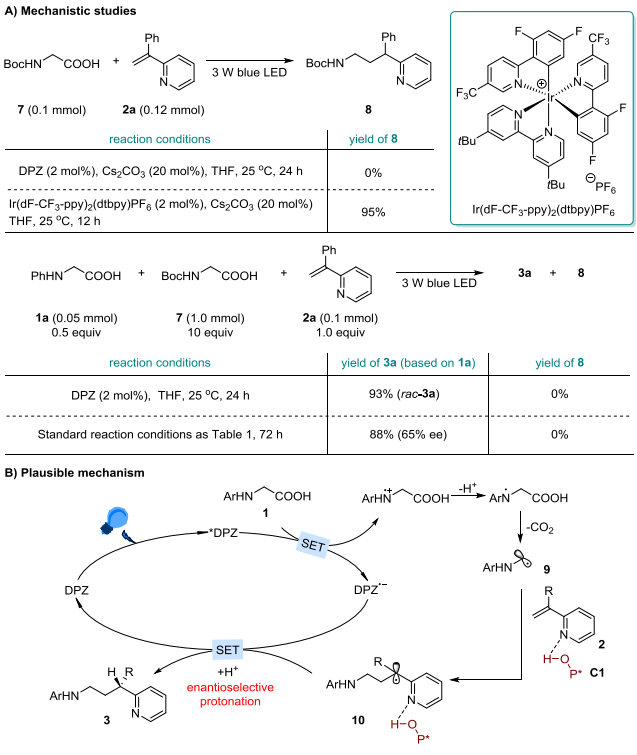


Figure 1. Evidence for protonation and the proposed mechanism.

A plausible mechanism was proposed based on this evidence (Figure 1B). *DPZ first undergoes a single-electron transfer (SET) reductive quenching by the N atom of **1**, which was verified by our Stern-Volmer experiments and analysis of the electrochemical properties (carboxylate ion of **1a**, *E*p = +0.52 [for the N moiety] and +1.09 V [for the COO^- moiety] vs Ag/AgCl in CH_3CN).[19] After a cascade reaction process[16b] involving a deprotonation, HAT and decarboxylation, generated α-amino radical **9** undergoes conjugate addition to CPA (**C1**)-activated alkene **2** to produce intermediate radical **10**. The presence of this H-bonding interaction is clearly demonstrated by the results shown in entry 7, Table 1 and that *rac*-**3a** with a poor 12% yield was obtained after 72% hours when with **C1**-derived chiral lithium phosphate **C29** as the catalyst (See entry 63, Table S1).[22] The strength of this mutual effect would be further enhanced by using $LiPF_6$ as an additive to increase the acidity of **C1**, thus improving yield and enantioselectivity (entries 1 and 4, Table 1). Following the single-electron reduction, the pivotal H-bonding induction from **C1** provides a stereocontrol for the protonation of the prochiral carbanion intermediate, leading to chiral adducts **3** in high enantioselectivities.[19] Such an embedded proton would come from the free proton in the reaction system such as the secondary amine and carboxylic acid of *N*-aryl glycines **1** and **C1** on the basis of the deuterium labelling experiments.[19]

CONCLUSIONS

In summary, we have developed redox-neutral, enantioselective, radical conjugate addition–protonation reactions of α-aryl glycines to α-branched 2-vinylpyridines and 2-vinylquinolines via visible-light-driven cooperative photoredox and chiral H-bonding catalysis. The current organocatalytic method provides access to a range of pharmaceutically and biologically important enantioenriched 3-(2-pyridine/quinoline)-3-substituted amines in high yields and ees. This work demonstrates a new application of an enantioselective protonation and opens an unexplored avenue for the synthesis of chiral α-tertiary azaarenes. Furthermore, this is the first highly enantioselective synthesis of chiral azaarenes via the direct exploitation of azaarenes to trigger transformations in asymmetric photoredox catalysis. We anticipate that this result will inspire the pursuit of asymmetric protonation reactions and other valuable transformations for the synthesis of useful chiral azaarenes through this versatile, radical-based dual catalysis platform.

ASSOCIATED CONTENT

Supporting Information Available: [General information, general procedures, mechanistic studies, characterization data, determination of the absolute configurations, plausible transition states, and HPLC and NMR spectra.] This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

¶These authors contributed equally.

Notes

The authors declare no competing financial interests.

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REFERENCES

(1) For a selected review, see: (a) Mohr, J. T.; Hong, A. Y.; Stoltz, B. M. *Nat. Chem.* **2009**, *1*, 359. For selected recent examples, see: (b) Dai, X.; Nakai, T.; Romero, J. A. C.; Fu, G. C. *Angew. Chem., Int. Ed.* **2007**, *46*, 4367. (c) Uraguchi, D.; Kinoshita, N.; Ooi, T. *J. Am. Chem. Soc.* **2010**, *132*, 12240. (d) Claraz, A.; Leroy, J.; Oudeyer, S.; Levacher, V. *J. Org. Chem.* **2011**, *76*, 6457. (e) Xiao, X.; Xie, Y.; Sun, C.; Liu, M.; Shi, Y. *J. Am. Chem. Soc.* **2011**, *133*, 12914. (f) Lee, J.-W.; List, B. *J. Am. Chem. Soc.* **2012**, *134*, 18245. (f) Wu, Y.; Deng, L. *J. Am. Chem. Soc.* **2012**, *134*, 14334. (g) Lee, J. H.; Deng, L. *J. Am. Chem. Soc.* **2012**, *134*, 18209. (h) Repka, L. M.; Ni, J.; Reisman, S. E. *J. Am. Chem. Soc.* **2010**, *132*, 14418. (i) Li, X.; Luo, S.; Chen, J.-P. *Chem. Eur. J.* **2010**, *16*, 14290. (j) Duan, S.-W.; An, J.; Chen, J.-R.; Xiao, W.-J. *Org. Lett.* **2011**, *13*, 2290. (k) Kieffer, M. E.; Repka, L. M.; Reisman, S. E. *J. Am. Chem. Soc.* **2012**, *134*, 5131. (l) Zhu, B.; Lee, R.; Li, J.; Ye, X.; Hong, S.-N.; Qiu, S.; Coote, M. L.; Jiang, Z. *Angew. Chem., Int. Ed.* **2016**, 55, 1299. (m) Hong, S.; Liu, Y.; Lee, R.; Jiang, Z. *Chem. Commun.* **2017**, 53, 7493. (n) Paladhi, S.; Liu, Y.; Kumar, B. S.; Jung, M.-J.; Park, S. Y.; Yan, H.; Song, C. E. *Org. Lett.* **2017**, *19*, 3279.

(2) For selected reviews, see: (a) Poulsen, T. B.; Jørgensen, K. A. *Chem. Rev.* **2008**, *108*, 2903. (b) Deutsch, C.; Krause, N. *Chem. Rev.* **2008**, *108*, 2916. (c) Klumpp, D. A. *Synlett* **2012**, *23*, 1590. (d) Best, D.; Lam, H. W. *J. Org. Chem.* **2014**, *79*, 831.

(3) For selected examples of building α-tertiary azaarenes, see: (a) Botteghi, C.; Del Ponte, G.; Marchetti, C. *J. Mol. Catal.* **1993**, *83*, L1. (b) Marchetti, M.; Alberico, E.; Bertucci, C.; Botteghi, C.; Del Ponte, G. *J. Mol. Catal A: Chemical* **1997**, *125*, 109. (c) Zupančič, B.; Mohar, B.; Stephan, M. *Org. Lett.* **2010**, *12*, 1296. (d) Yang, H.; Wang, E.; Yang, P.; Lv, H.; Zhang, X. *Org. Lett.* **2017**, *19*, 5062. (e) Yu, S.; Sang, H. L.; Ge, S. *Angew. Chem., Int. Ed.* **2017**, *56*, 15896.

(4) For selected examples of building α-quaternary azaarenes, see: Izquierdo, J.; Landa, A.; Bastida, I.; López, R.; Oiarbide, M.; Palomo, C. *J. Am. Chem. Soc.* **2016**, *138*, 3282.

(5) For selected examples of building α-tertiary-β-tertiary azaarenes, see: (a) Trost, B.; Thaisrivongs, D. A. *J. Am. Chem. Soc.* **2009**, *131*, 12056. (b) Saxena, A.; Choi, B.; Lam, H. W. *J. Am. Chem. Soc.* **2012**, *134*, 8428. (c) Best, D.; Kujawa, S.; Lam, H. W. *J. Am. Chem. Soc.* **2012**, *134*, 18193. (d) Fallan, C.; Lam, H. W. *Chem. Eur. J.* **2012**, *18*, 11214. (e) Meazza, M.; Tur, F.; Hammer, N.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2017**, *56*, 1634.

(6) For selected examples of building β-tertiary azaarenes, see: (a) Trost, B. M.; Thaisrivongs, D. A. *J. Am. Chem. Soc.* **2008**, *130*, 14092. (b) Rupnicki, L.; Saxena, A.; Lam. H. W. *J. Am. Chem. Soc.* **2009**, *131*, 10386. (c) Pattison, G.; Piraux, G.; Lam, H. W. *J. Am. Chem. Soc.* **2010**, *132*, 14373. (d) Saxena, A.; Lam, H. W. *Chem. Sci.* **2011**, *2*, 2326. (e) Trost, B. M.; Thaisrivongs, D. A.; Hartwig, J. *J. Am. Chem. Soc.* **2011**, *133*, 12439. (f) Li, T.; Zhu, J.; Wu, D.; Li, X.; Wang, S.; Li, H.; Li, J.; Wang, W. *Chem. Eur. J.* **2013**, *19*, 9147. (g) Roy, I. D.; Burns, A. R.; Pattison, G.; Michel, B.; Parker, A. J.; Lam, H. W. *Chem. Commun.* **2014**, 50, 2865. (h) Wang, Y.-Y.; Kanomata, K.; Korenaga, T.; Terada, M. *Angew. Chem., Int. Ed.* **2016**, 55, 927.

(7) For an example of building γ-tertiary azaarenes, see: Wang, S.; Li, X.; Liu, H.; Xu, L.; Zhuang, J.; Li, J.; Li, H.; Wang, W. *J. Am. Chem. Soc.* **2015**, *137*, 2303.

(8) For an example of building δ-quaternary azaarenes, see: Bai, X.; Zeng, G.; Shao, T.; Jiang, Z. *Angew. Chem., Int. Ed.* **2017**, *56*, 3684.

(9) (a) Goetz, A. E.; Garg, N. K. *Nat. Chem.* **2013**, 5, 54. (b) Kleemann, A. *Chem. Zeit*. **1977**, *9*, 389. (c) Andersen, H. S.; Madsen, P.; Jakobsen, P. *PCT Int. Appl.*, WO 2002038559 A1 20020516, 2002. (d) Iyer, P.; Lucas, M. C.; Schoenfeld, R. C.; Villa, M.; Weikert, R. J. *U.S. Pat. Appl. Publ.*, US 20070123527 A1 20070531, 2007. (e) Remiszewski, S.; Koyuncu, E.; Sun, Q.; Chiang, L. *PCT Int. Appl.*, WO 2016077240 A2 20160519, 2016.

(10) For selected reviews, see: (a) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. *Chem. Rev.* **2013**, *113*, 5322. (b) Schultz, D. M.; Yoon, T. P. *Science* **2014**, *343*, 985; (c) Beatty, J. W.; Stephenson, C. R. J. *Acc. Chem. Res.* **2015**, *48*, 1474. (d) Shaw, M. H.; Twilton, J.; MacMillan, D. W. C. *J. Org. Chem.* **2016**, *81*, 6898. (e) Romero, N. A.; Nicewicz, D. A. *Chem. Rev.* **2016**, *116*, 10075.

(11) (a) Nakajima, M.; Lefebvre, Q.; Rueping, M. *Chem. Commun.* **2014**, 50, 3619. (b) Lee, K. N.; Lei, Z.; Ngai, M.-Y. *J. Am. Chem. Soc.* **2017**, *139*, 5003. (c) Capaldo, L.; Fagnoni, M.; Ravelli, D. *Chem. Eur. J.* **2017**, *23*, 6527. (d) Lima, F.; Sharma, U. K.; Grunenberg, L.; Saha, D.; Johannsen, S.; Sedelmeier, J.; Van der Eychen, E. V.; Ley, S. V. *Angew. Chem., Int. Ed.* **2017**, *56*, 15136.

(12) Hepburn, H. B.; Melchiorre, P. *Chem. Commun.* **2016**, 52, 3520.

(13) (a) Lin, L.; Bai, X.; Ye, X.; Zhao, X.; Tan, C.-H.; Jiang, Z. *Angew. Chem., Int. Ed.* **2017**, *56*, 13842. (b) Liu, X.; Ye, X.; Bureš, F.; Liu, H.; Jiang, Z. *Angew. Chem., Int. Ed.* **2015**, *54*, 11443. (c) Wei, G.; Zhang, C.; Bureš, F.; Ye, X.; Tan, C.-H.; Jiang, Z. *ACS Catal.* **2016**, *6*, 3708. (d) Liu, Y.; Li, J.; Ye, X.; Zhao, X.; Jiang, Z. *Chem. Commun.* **2016**, 52, 13955.

(14) Rono, L. J.; Yayla, H. G.; Wang, D. Y.; Armstrong, M. F.; Knowles, R. R. *J. Am. Chem. Soc.* **2013**, *135*, 17735.

(15) For selected reviews, see: (a) Wang, C.; Lu, Z. *Org. Chem. Front.* **2015**, *2*, 179. (b) Brimioulle, R.; Lenhart, D.; Maturi, M. M.; Bach, T. *Angew. Chem., Int. Ed.* **2015**, *54*, 3872. (c) Meggers, E. *Chem. Commun.* **2015**, *51*, 3290. (d) Poplata, S.; Tröster, A.; Zou, Y.-Q.; Bach, T. *Chem. Rev.* **2016**, *116*, 9748. For selected recent examples, see: (e) Espelt, L. R.; McPherson, I. S.; Wiensch, E. M.; Yoon, T. P. *J. Am. Chem. Soc.* **2015**, *137*, 2452. (f) Gutierrez, O.; Tellis, J. C.; Primer, D. N.; Molander, G. A.; Kozlowski, M. C. *J. Am. Chem. Soc.* **2015**, *137*, 4896. (g) Uraguchi, D.; Kinoshita, N.; Kizu, T.; Ooi, T. *J. Am. Chem. Soc.* **2015**, *137*, 13768. (h) Zuo, Z.; Cong, H.; Li, W.; Choi, J.; Fu, G. C.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2016**, *138*, 1832. (i) Amador, A. G.; Sherbrook, E. M.; Yoon, T. P. *J. Am. Chem. Soc.* **2016**, *138*, 4722. (j) Wang, C.; Harms, K.; Meggers, E. *Angew. Chem., Int. Ed.* **2016**, *55*, 13495. (k) Huang, X.; Webster, R. D.; Harms, K.; Meggers, E. *J. Am. Chem. Soc.* **2016**, *138*, 12636. (l) Murphy, J. J.; Bastida, D.; Paria, S.; Fagnoni, M.; Melchiorre, P. *Nature* **2016**, 532, 218. (m) Yang, Q.; Zhang, L.; Ye, C.; Luo, S.; Wu, L.-Z.; Tung, C.-H. *Angew. Chem., Int. Ed.* **2017**, *56*, 3694. (n) Capacci, A. G.; Malinowski, J. T.; McAlpine, N. J.; Kuhne, J.; MacMillan, D. W. C. *Nat. Chem.* **2017**, *9*, 1073. (o) Ma, J.; Rosales, A. R.; Huang, X.; Harms, K.; Riedel, R.; Wiest, O.; Meggers, E. *J. Am. Chem. Soc.* **2017**, *139*, 17245. (p) Nacsa, E. D.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2018**, *140*, 3322.

(16) Xiang, J.-C.; Wang, Z.-X.; Cheng, Y.; Xia, S.-Q.; Wang, M.; Tang, B.-C.; Wu, Y.-D.; Wu, A.-X. *J. Org. Chem.* **2017**, *82*, 9210.

(17) (a) Rajesh, C. S.; Thanulingam, T. L.; Das, S. *Tetrahedron* **1997**, *53*, 16817. (b) Chen, L.; Chao, C. S.; Pan, Y.; Dong, S.; Teo, Y. C.; Wang, J.; Tan, C.-H. *Org. Biomol. Chem.* **2013**, *11*, 5922. (c) Zuo, Z.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2014**, *136*, 5257. (d) Chu, L.; Ohta, C.; Zuo, Z.; MacMillan D. W. C. *J. Am. Chem. Soc.* **2014**, *136*, 10886. (e) Zhou, Q.-Q.; Guo, W.; Ding, W.; Wu, X.; Chen, X.; Lu, L.-Q.; Xiao, W.-J. *Angew. Chem., Int. Ed.* **2015**, *54*, 11196. (f) Johnston, C. P.; Smith, R. T.; Allmendinger, S.; MacMillan, D. W. C. *Nature* **2016**, *536*, 333. (g) Millet, A.; Lefebvre, Q.; Rueping, M. *Chem. Eur. J.* **2016**, *22*, 13464.

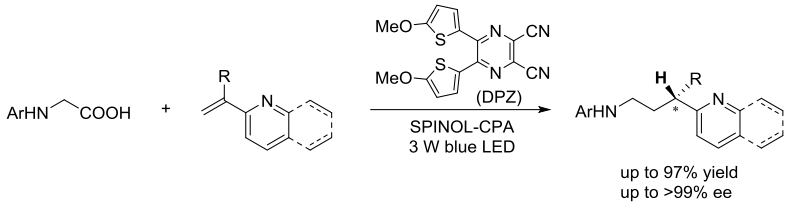
(18) Čorić, I.; Müller, S.; List, B. *J. Am. Chem. Soc.* **2010**, *132*, 17370.

(19) See the Supporting Information for the details.

(20) Cismesia, M. A.; Yoon, T. P. *Chem. Sci.* **2015**, *6*, 5426.

(21) When 1.0 equiv of **1a** was used, **3a** was obtained in 91% yield with 80% ee. The decreased enantioselectivity could be due to the H-bonding interference from the excess *N*-Boc glycine **7**.

(22) Hatano, M.; Moriyama, K.; Maki, T.; Ishihara, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 3823.


ArHN
COOH
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(DPZ)
SPINOL-CPA
3 W blue LED
ArHN
H
R
*
N
up to 97% yield
up to >99% ee