Letter

Enantioselective Aerobic Oxidative C(sp3)-H Olefination of Amines via Cooperative Photoredox and Asymmetric Catalysis

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Enantioselective Aerobic Oxidative C(sp^3)−H Olefination of Amines via Cooperative Photoredox and Asymmetric Catalysis

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ABSTRACT: A cooperative photoredox and asymmetric catalysis for the enantioselective aerobic oxidative C(sp^3)−H olefination of tetrahydro-*β*-carbolines (THCs) is reported. This method, which is also effective for tetrahydroisoquinolines (THIQs), features a triple-catalyst strategy, involving a dicyanopyrazine-derived chromophore (DPZ) as the metal-free photoredox catalyst, a chiral Lewis base catalyst and an inorganic salt co-catalyst. The current protocol provides straightforward access to a series of valuable α-substituted THCs and THIQs in high yields with excellent regio- and enantioselectivities (up to 95% ee).

KEYWORDS: *asymmetric cooperative catalysis, photoredox catalysis, organocatalysis, aerobic oxidative olefination, β-carbolines*

Asymmetric cooperative catalysis has long been acknowledged as a powerful tool for constructing valuable and complex chiral compounds.[1] Along with the rapid growth of the highly sustainable photochemistry,[2] in recent years, cooperative photoredox and asymmetric catalysis has attracted increasing attention of chemists.[3-5] A number of dual catalytic systems through

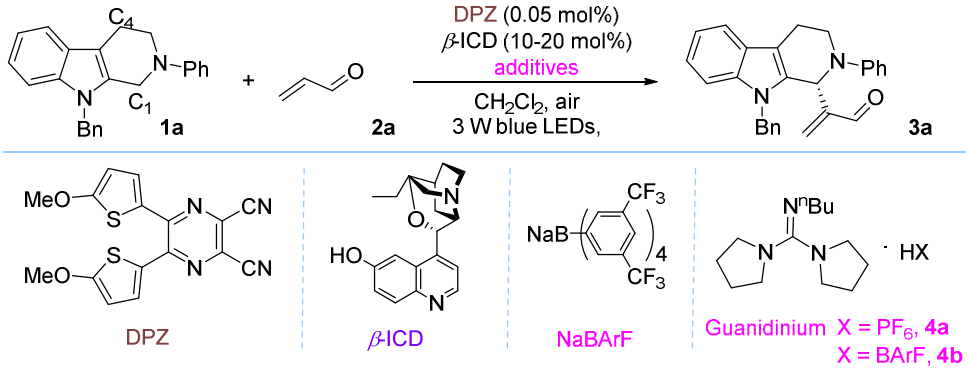
combining photoredox catalysts with chiral catalysts have been impressively established.[3-5] We recently reported a dicyanopyrazine-derived chromophore (DPZ) as a new type of metal-free photoredox catalyst that facilitated a series of achiral transformations at low catalyst loadings.[6a-b] The prominent performance of DPZ promoted us to assess its potential in the ever-growing cooperative photoredox and asymmetric catalysis. To our knowledge, rare variants using organic photoredox catalysts have been described to date.[4d]

The nucleophilic addition to iminium intermediates, which are in situ generated by photoredox catalytic oxidation of a C(sp^3)−H bond adjacent to the nitrogen atom of amines, is a straightforward approach to provide α-functionalized *N*-heterocyclic adducts.[2d,2j,2m,7] Contributed by the Rovis[4e] and Li[4l] groups, this strategy has also currently been merged with asymmetric catalysis in a cooperative manner. While these elegant works demonstrated that the cooperative catalysis involving photoreodox oxidative generation of iminium intermediates and the simultaneous enantiocontrol is viable, they still suffer from a limited substrate scope given that only THIQs have been chosen as the substrates. Tetrahydro-*β*-carbolines (THCs) with a C1-substituted stereogenic center are widely found as key structural motifs in numerous biologically important molecules.[8] However, there have been no reports on a photoredox catalytic C−H functionalization of THCs, probably due to the elusive regioselectivity between C1(sp^3)−H bond and C4(sp^3)−H bond in the oxidative process.[9] On the other hand, the current asymmetric reactions[4e,4l] are environmentally unfriendly, using excess oxidants such as *m*-DNB or $(BzO)_2$. When the more economical and green oxidant−molecular oxygen was used, poor compatibilities of these cooperative catalytic systems were encountered in view of the unsatisfactory yields.

With respect to the synthesis of chiral C1-functionalized THCs, huge efforts have been made in several elegant catalytic asymmetric tactics, including Pictet−Spengler reaction of tryptamines[10] and transformations[11] of the preformed stable THC-imines. Liu and co-workers[12] established the possibility of generating iminium intermediates of THCs by regioselective C1(sp^3)−H oxidation using stoichiometric DDQ as the oxidant, wherein a highly enantioselective catalytic oxidative alkenylation of *N*-carbamoyl THCs with boronates was addressed. However, the oxidative coupling reaction between THCs and activated alkenes has never been achieved.[13,14] Herein, we report a highly enantioselective aerobic oxidative C1(sp^3)−H olefination of THCs through developing a novel cooperative catalytic system with DPZ as the photocatalyst.

Our study was initiated by exploring the model reaction between *N*-phenyl-9-benzyl THC (**1a**) and acrolein **2a**, utilizing 0.05 mol% of DPZ in CH_2Cl_2 under irradiation from 3 W blue LEDs (λ = 450−455 nm) (Table 1).[15] After the evaluation of distinct chiral Lewis bases, *β*-ICD was proved to be the best, affording **3a** with 19% ee (entry 1). 4Å Molecular sieves (MS) were tested as additives to prevent the nucleophilic addition of water; although the conversion of **1a** was sluggish, the chemoselectivity could be improved, affording **3a** in 56% yield with 53% ee after 48 hours (entry 2). When salts with weak coordinating anions[16] were used as co-catalysts, the ee value of **3a** was effectively increased (entries 3−6). With NaBArF as salt additive, further improved chemo- and enantioselectivity were observed at lower temperature (entry 7). When the amount of *β*-ICD was increased to 20 mol%, the ee value of **3a** was enhanced to 87% (entry 8). While the lithium salt of *β*-ICD (*β*-ICD-Li) displayed similar efficiency as *β*-ICD (entry 9), a sharp decrease in enantioselectivity was observed when it was used in the absence of NaBArF co-catalyst (entry 10), indicating the crucial role of the coordinating anion ($BArF^-$). Finally, **3a** was obtained with best results using guanidinium **4a** as another additive (81% yield, 90% ee, entry 11). When guanidinium **4b** was used without adding additional NaBArF, the ee value dropped to 70% (entry 12), thus implying the importance of metal cations (Na^+ or Li^+) for the chiral induction. Noteworthy is that slightly decreased yield and enantioselectivity were observed when in the absence of 4 Å MS (entry 13). Moreover, no reaction occurred when the reaction was performed without irradiation (entry 14). When in the absence of DPZ, only trace amounts of **3a** was observed even after 72 hours, indicating the crucial participation of photocatalyst DPZ in the oxidation process (entry 15).

Table 1. Optimization of the Reaction Conditions.[a]



entry	conditions	yield (%)[b]	ee (%)[c]

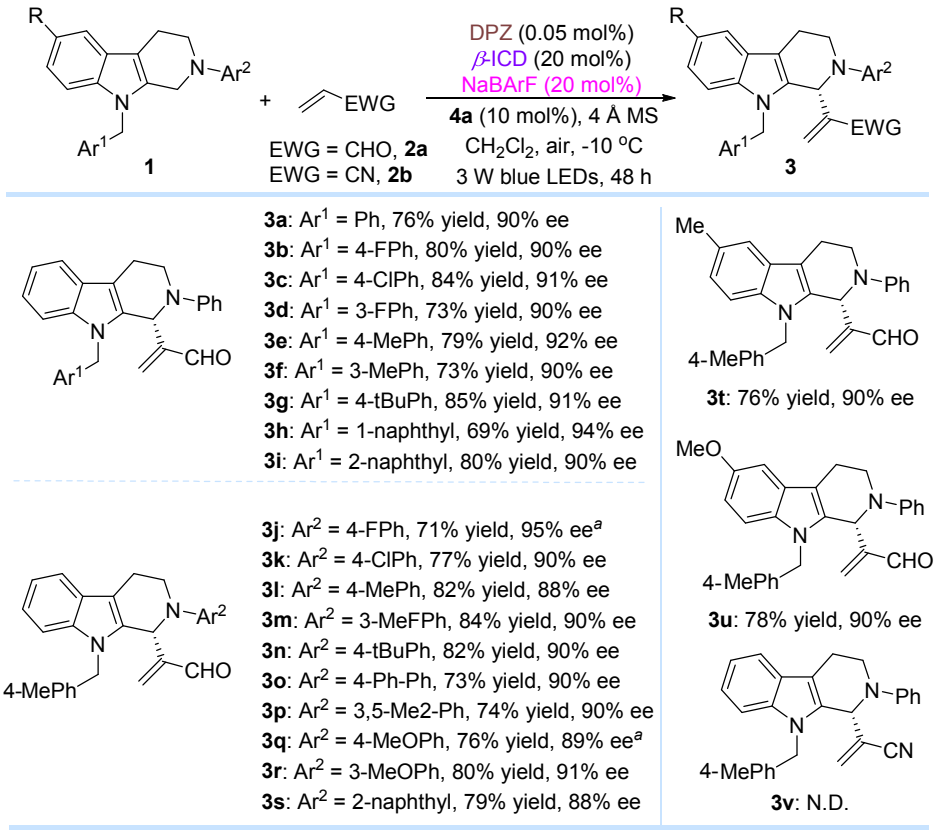
1	25 °C, 24 h	30	19
2	4 Å MS, 25 °C, 48 h	56	53
3	4 Å MS, $LiBF_4$, 25 °C, 48 h	57	64
4	4 Å MS, $NaPF_6$, 25 °C, 48 h	52	67
5	4 Å MS, NaBArF, 25 °C, 48 h	53	70
6	4 Å MS, LiBArF, 25 °C, 48 h	55	70
7	4 Å MS, NaBArF, −10 °C, 48 h	84	83
8	4 Å MS, NaBArF, −10 °C, 48 h	85	87
9[d]	4 Å MS, NaBArF, −10 °C, 48 h	80	85
10[d]	4 Å MS, −10 °C, 48 h	80	34
11	4 Å MS, NaBArF, **4a**, −10 °C, 48 h	81	90
12	4 Å MS, **4b**, −10 °C, 48 h	80	70
13	NaBArF, **4a**, −10 °C, 48 h	63	83
14	4 Å MS, NaBArF, **4a**, −10 °C, ***no light***, 48 h	N.R.	N.A.
15	***No DPZ***, 4 Å MS, NaBArF, **4a**, −10 °C, 72 h	15	87

[a] The reaction was performed on a 0.025 mmol scale. 4 Å MS (20 mg), NaBArF (20 mol%), guanidinium **4a**/**4b** (10 mol%). In entries 1−7, 10 mol% of *β*-ICD was used; in entries 8−15, 20 mol% of *β*-ICD was used. [b] Yield of isolated product. [c] Determined by HPLC on chiral stationary phase. [d] *β*-ICD-Li instead of *β*-ICD was used. *β*-ICD = *β*-isocupreidine, MS = molecular sieves, N.R. = no reaction, N.A. = not available.

With the newly developed DPZ/*β*-ICD/NaBArF catalytic system, the scope of substrates for the asymmetric aerobic oxidative C1(sp^3)−H olefination of THCs with activated terminal alkenes (**2**) was studied (Table 2). For the reaction with acrolein **2a**, a series of THCs **1** having various

substituents on the aromatic rings of 9-*N*-benzyls (**1a-1i**,) and 2-*N*-aryls (**1j-1s**) as well as at C6-positions (**1t-1u**) were examined. It was observed that all reactions were complete within 48 hours, and both electron-rich and -deficient THCs were well tolerated, thus affording the desired products **3a-u** in 69−85% yields and 88−95% ee. Acrylonitrile **2b** has also been attempted in the reaction, exhibiting unfortunately rather poor chemoselectivity in view of the failed delivery of **3v**.

Table 2. Investigation towards Tetrahydro-*β*-carbolines 1.

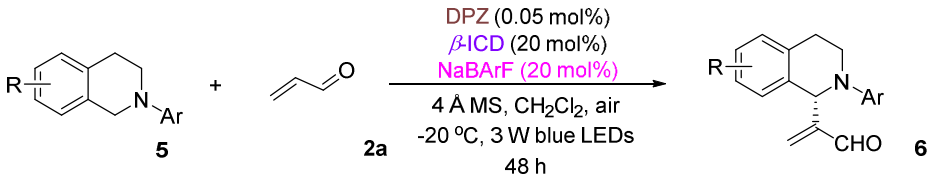


[a] The reaction was performed at −15 °C. N.D. = not determined.

To demonstrate the versatility of this cooperative catalytic strategy, we were next engaged in the C−H functionalization of *N*-aryl THIQs **5** (Table 3).[14] Under slightly modified reaction conditions (at −20 °C and in the absence of guanidinium **4a**), a broad array of THIQs with various substituents on *N*-aryls were first evaluated. The reactions often completed within 48 hours, affording the desired products **6a-h** in 74−90% yields with 84−95% ee. THIQs with

methoxy on the 6-position (**5i**) or on the 6, 7-positions (**5j**) also gave good yields and good to excellent enantioselectivities (entries 9−10).

Table 3. Investigation towards *N*-Aryl-tetrahydroisoquinolines 5.



entry	**5** (R, Ar)	**6**	yield (%)[a]	ee (%)[b]
1	**5a** (H, Ph)	**6a**	81	94
2	**5b** (H, 4-FPh)	**6b**	80	94
3	**5c** (H, 4-ClPh)	**6c**	85	95
4	**5d** (H, 4-MePh)	**6d**	90	94
5	**5e** (H, 3-MePh)	**6e**	85	93
6	**5f** (H, 4-*t*BuPh)	**6f**	80	92
7	**5g** (H, 4-MeOPh)	**6g**	82	93
8	**5h** (H, 2-MeOPh)	**6h**	74	84
9	**5i** (6-OMe, Ph)	**6i**	83	82
10	**5j** (6,7-$(MeO)_2$, Ph)	**6j**	85	90

[a] Yield of isolated product. [b] Determined by HPLC on chiral stationary phase.

A plausible reaction pathway of our triple-catalysis oxidative olefination is described in Figure 1. It has been well established that tertiary amines (**1**/**5**) can be transformed to iminiums **7** through a photoredox catalytic C1(sp^3)−H oxidation (see the photoredox catalytic cycle).[7] The asymmetric catalytic cycle includes the nucleophilc addition of *β*-ICD as a Lewis base to acrolein **2a** generating the intermediate **8** and the Mannich-type reaction of **7** with **8** affording adducts **3** or **6**. The inorganic salt NaBArF, which is known to have good affinities for

carboxylate and carbonyl oxygens,[16] is likely involved in activating carbonyl group of acrolein to benefit the addition of *β*-ICD, stabilizing iminiums **7**, and bridging the nucleophilic intermediate **8** and iminiums **7** into the transition states **9** via multisite coordination. The forming intermediates **10** could also be stabilized by NaBArF. The aforementioned coordination would conceivably lower the activation energy of this transformation effectively, and thus increase the reaction rate with improved chemoselectivity and amplified chiral induction by *β*-ICD.

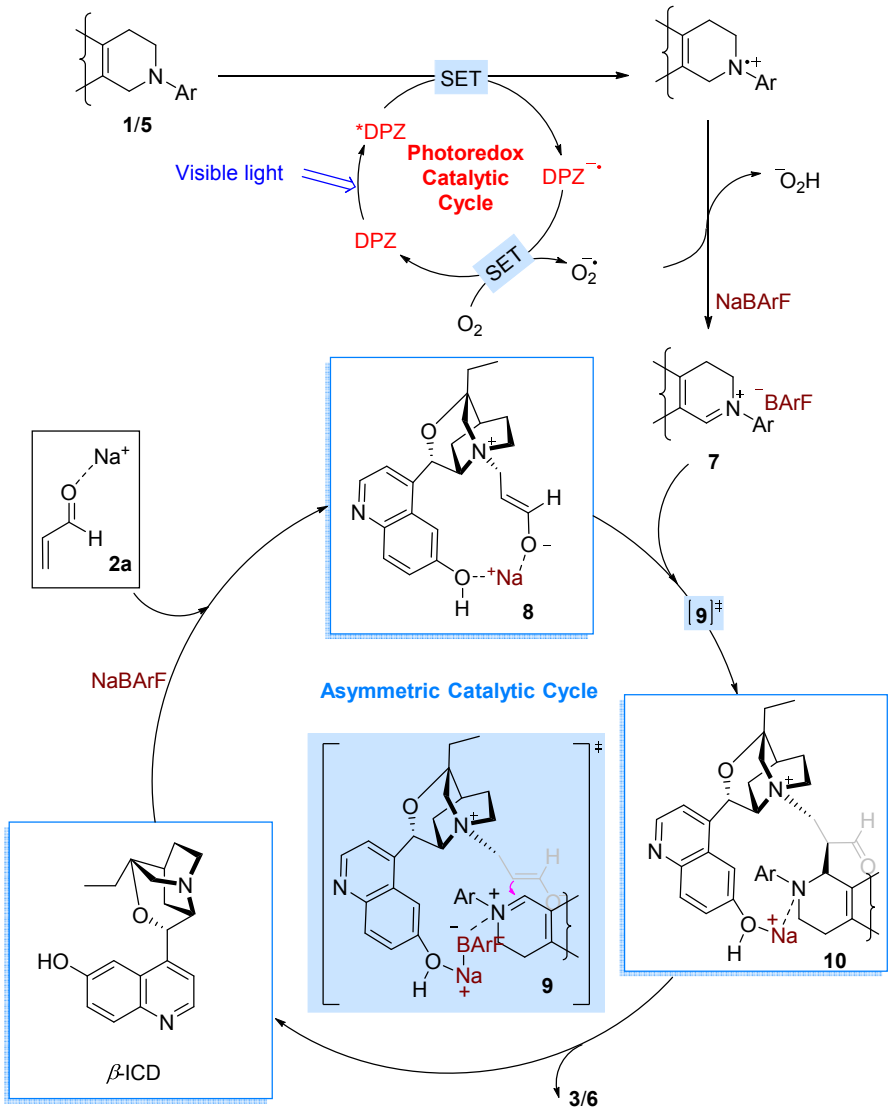
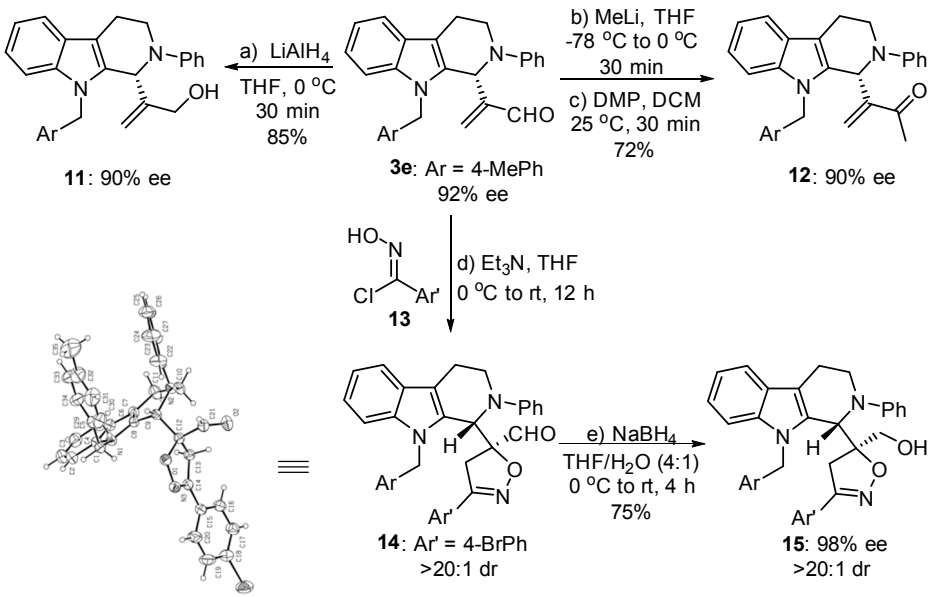


Figure 1. Proposed Mechanism.

The synthetic value of this work was evaluated through performing a series of transformations from the olefination products (Scheme 1). A THC-derived chiral alcohol **11** could be obtained

from the reduction of **3e** by $LiAlH_4$ in 85% yield with 90% ee. Through a sequence of addition of MeLi and Dess-Martin oxidation, **3e** was readily transformed to the chiral ketone **12** with good yield and without compromising ee value. The THCs featuring a C1-substituted oxa-containing five-membered ring were found having potential bioactivity for the treatment of severe acute respiratory syndrome (SARS).[8e] We were thus engaged in conducting a 1,3-dipolar cycloaddition between **3e** and nitrile *N*-oxide, generated *in situ* from **13**; after 12 hours, the desired product **14** with vicinal quaternary−tertiary chiral centers was obtained with a high diastereoselectivity. The subsequent reduction of **14** by utilizing $NaBH_4$ could conveniently provide the alcohol **15**, which was easily recrystallized to 98% enantiomeric excess. The absolute configurations of the oxidative olefination products were assigned on the basis of X-ray crystallographic analysis of a single crystal of **14**.



Scheme 1. Synthetic Transformations.

In summary, we have developed the first enantioselective aerobic oxidative cross-coupling reaction between THCs and acrolein for building C_{sp2}−C_{sp3} bonds through a novel cooperative photoredox and asymmetric catalysis. The triple catalytic system comprises DPZ as a metal-free photoredox catalyst at a low loading of 0.05 mol%, a chiral Lewis base catalyst (*β*-ICD) and an inorganic salt co-catalyst (NaBArF). With the assistance of 4 Å MS, the reaction proceeded smoothly, providing structurally and electronically diverse chiral C1-olefinated THCs with excellent regio- and enantioselectivity (up to 95% ee). Significantly, it represents an

unprecedented report on visible-light photoredox catalytic C−H functionalization of THCs. Being equally applicable to THIQs, this mild strategy represents the first successful example of using molecular oxygen as the sustainable oxidant to address oxidative coupling reactions of amines in asymmetric photocatalysis. Further investigations into the extension of DPZ as a photoredox catalyst in asymmetric cooperative catalysis, and the bioactivities of these chiral N-heterocycles are in progress in our laboratory.

ASSOCIATED CONTENT

Supporting Information.

Supporting Information Available: [General information, optimization results, general procedures, characterization data, determination of the absolute configuration and spectra.] This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript. ‡These authors contributed equally.

Notes

The authors declare no competing financial interest.

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Graphical Abstract