Oxygen Switch in Visible-Light Photoredox Catalysis: Radical Additions and Cyclizations and Unexpected C−C-Bond Cleavage Reactions

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Ⓢ Supporting Information

ABSTRACT: Visible light photoredox catalyzed inter- and intramolecular C−H functionalization reactions of tertiary amines have been developed. Oxygen was found to act as chemical switch to trigger two different reaction pathways and to obtain two different types of products from the same starting material. In the absence of oxygen, the intermolecular addition of N,N-dimethyl-anilines to electron-deficient alkenes provided γ-amino nitriles in good to high yields. In the presence of oxygen, a radical addition/cyclization reaction occurred which resulted in the formation of tetrahydroquinoline derivatives in good yields under mild reaction conditions. The intramolecular version of the radical addition led to the unexpected formation of indole-3-carboxaldehyde derivatives. Mechanistic investigations of this reaction cascade uncovered a new photoredox catalyzed C−C bond cleavage reaction.
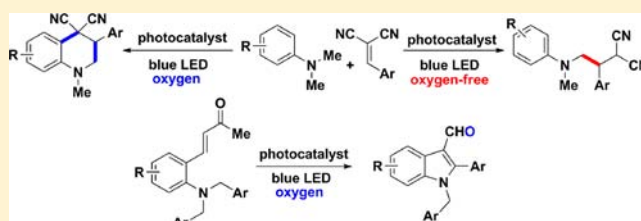
INTRODUCTION

Transformations involving the oxidative α-functionalization of amines constitute a broad area of research due to their versatility and manifold available reaction products by applying this strategy. Most of the methods developed so far involve in situ generated iminium ions as reactive intermediates. Various methods are available for the generation of iminium ions from the corresponding amines, which are subsequently trapped with an appropriate nucleophile. On one hand, metal salts and stoichiometric amounts of organic peroxides as oxidants are employed to activate the amine substrates in the reactions involving iminium ions.[1] On the other hand, the photochemical generation of iminium ions[2] through electron-transfer reactions[3] is well established and has been successfully initiated by a variety of chemical oxidants. In this context, particular attention was recently devoted to various homogeneous and heterogeneous photoredox catalyzed transformations that can effectively be conducted with low amounts of catalysts, under mild reaction conditions, by simply using visible light as energy source (Scheme 1).[4−7]

Another established way for the α-functionalization of amines takes advantage of the in situ generated α-amino alkyl radicals.[8] Different strategies for the in situ generation of nucleophilic α-amino alkyl radicals and their addition to unsaturated double bonds are described in the literature.[8] Among them, the radical addition of tertiary amines to various unsaturated systems through photoinduced electron transfer processes has been investigated by several groups.[9] Photo-induced intermolecular radical addition reactions are also reported but they are limited to cyclic and acyclic aliphatic

Scheme 1. Photoredox Catalyzed Activation of Tertiary Amines
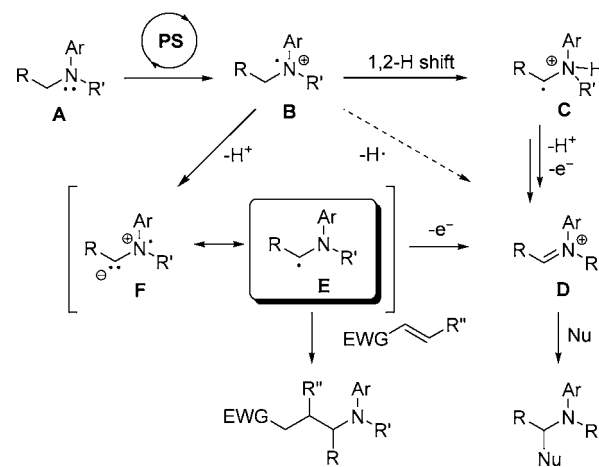
tertiary amines (e.g., N-methylpiperidine, N-methylpyrrolidine, triethylamine) and require high energy UV irradiation.[10] Intramolecular versions which have as result the formation of N-containing heterocycles have also been described.[11] However, further exploration in this area is needed in order to develop more general activation protocols applicable to different cyclic as well as acyclic amines.

The recent progress in the field of visible light mediated photoredox reactions with amines stimulated the researchers to investigate the possibility of trapping the carbon centered neutral radical intermediate **E** with electron deficient alkenes (Scheme 1). Pandey and Reiser described the application of visible light to the generation of cyclic α-amino alkyl radicals with subsequent inter- and intramolecular conjugate addition to α,β-unsaturated systems.[12] Nishibayashi reported the visible light promoted generation of α-amino alkyl radicals from tertiary amines or α-silylamines and their addition to various electron unsaturated systems.[13] MacMillan reported the photoredox catalyzed amine arylation through a process involving α-amino alkyl radicals.[14]

Herein, we present new reaction pathways in the area of photoredox catalysis including oxygen switchable radical additions and cyclizations as well as new C−C bond cleavage reactions.

■ RESULTS AND DISCUSSION

Our initial study focused on developing an intermolecular version for the addition of amines to activated alkenes. Initially,

**Table 1. Photoredox Catalyzed Radical Addition and Addition/Cyclization Reaction**
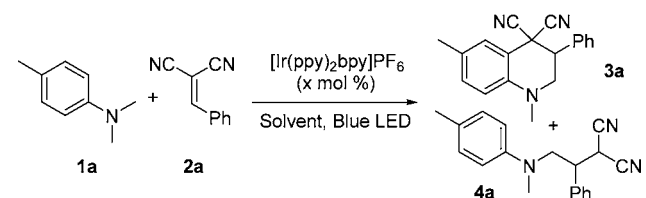
entry[a]	solvent	catalyst (x mol %)	time	3a/4a	yield (%)[b]
1	toluene	1	24		nd
2	THF	1	32		
3	DMF	1	32		
4	DMSO	1	32		
5	MeOH	1	32		
6	CH$_2$Cl$_2$	1	32	3a	42
7	CHCl$_3$	1	32	3a	46
8	DCE	1	32	3a	51
9	EtCN	1	32	3a	61
10	MeCN	1	32	3a	62
11[c]	MeCN	1	48	4a	68
12[d]	MeCN	1	48		
13[e]	MeCN		48		
14	MeCN	5	8	3a	67
15[c]	MeCN	5	20	4a	91

[a]Reaction conditions: **1a** (0.26 mmol), **2a** (0.20 mmol), catalyst (1−5 mol %), Blue LED light irradiation and solvent (1.5 mL). [b]Yield of the isolated product. [c]Reaction was carried out under argon. [d]Reaction was carried out in the dark. [e]Reaction was carried out without catalyst.

we performed the reaction of *N,N*-dimethyl-4-methylaniline (**1a**) with 2-benzylidenemalononitrile (**2a**) as electron-deficient alkene under different reaction conditions.[15] With 1 mol % of [Ir(ppy)$_2$bpy]PF$_6$ as photocatalyst various solvents were tested (Table 1, entries 1−10). In toluene we observed the formation of the addition/cyclization product **3a** together with trace amounts of the addition product **4a**. No reaction was observed in polar solvents like MeOH, THF, DMF, and DMSO. Among the chlorinated and nitrile-containing solvents tested, the best result in terms of yield (**3a**, 62%) was obtained when the

Table 2. Scope of the photoredox catalyzed radical addition/cyclization reaction
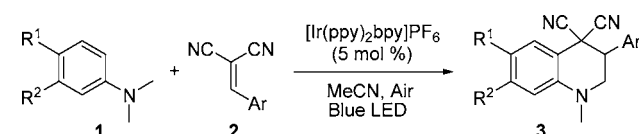
entry[a]	R^1	R^2	Ar	3	yield (%)[b]
1	Me	H	C$_6$H$_5$	3a	68
2	Me	H	4-^{t}Bu−C$_6$H$_4$	3b	71
3	Me	H	2-Me−C$_6$H$_4$	3c	57
4	Me	H	2,4-(Me)$_2$−C$_6$H$_3$	3d	62
5	Me	H	4-Br−C$_6$H$_4$	3e	61
6	Me	H	4-Me-C$_6$H$_4$	3f	60
7	^{t}Bu	H	2-Me−C$_6$H$_4$	3g	44
8	^{t}Bu	H	4-Me−C$_6$H$_4$	3h	52
9	^{t}Bu	H	2,4-(Me)$_2$−C$_6$H$_3$	3i	47
10	H	Me	4-^{t}Bu−C$_6$H$_4$	3j	40
11	H	Me	4-Br−C$_6$H$_4$	3k	41
12	H	Me	4-Me−C$_6$H$_4$	3l	53

[a]Reaction conditions: **1** (0.26 mmol), **2** (0.20 mmol), catalyst (5 mol %), Blue LED light irradiation, MeCN (1.5 mL), and reaction mixture was under air for 12 h. [b]Yield of the isolated product.

Table 3. Scope of the Photoredox Catalyzed Radical Addition Reaction
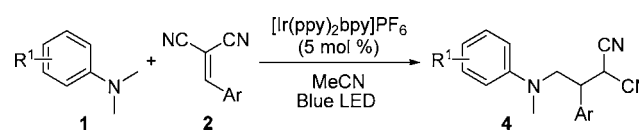
entry[a]	R^1	Ar	4	yield (%)[b]
1	4-Me	C$_6$H$_5$	4a	91
2	4-Me	4-F−C$_6$H$_4$	4b	62
3	4-Me	4-Br−C$_6$H$_4$	4c	56
4	4-Me	4-Me−C$_6$H$_4$	4d	65
5	4-Me	2-Me−C$_6$H$_4$	4e	71
6	4-Me	4-MeO−C$_6$H$_4$	4f	68
7	4-Me	4-CF$_3$−C$_6$H$_4$	4g	83
8	4-Me	4-Biphenyl	4h	82
9	4-Me	4-^{t}Bu−C$_6$H$_4$	4i	71
10	4-^{t}Bu	4-Me−C$_6$H$_4$	4j	62
11	4-^{t}Bu	2,4-(Me)$_2$−C$_6$H$_3$	4k	74
12	4-^{t}Bu	2-Me−C$_6$H$_4$	4l	78
13	4-^{t}Bu	4-^{t}Bu−C$_6$H$_4$	4m	62
14	H	C$_6$H$_5$	4n	78
15	3-Br	C$_6$H$_5$	4o	71
16	2-Me	C$_6$H$_5$	4p	72
17	3,5-(Me)$_2$	4-^{t}Bu−C$_6$H$_4$	4q	64
18	4-Br	4-CF$_3$−C$_6$H$_4$	4r	90

[a]Reaction conditions: **1** (0.26 mmol), **2** (0.20 mmol), catalyst (5 mol %), Blue LED light irradiation, MeCN (1.5 mL) and reaction mixture under argon, and reaction time: 48 h. [b]Yield of the isolated product.

reaction was performed in acetonitrile (Table 1, entry 10). In order to minimize the oxidation of **1a**, oxygen free conditions were tested and, to our surprise, the conjugate addition product **4a** was isolated as the major product in 68% yield (Table 1, entry 11). This result indicates that oxygen plays a crucial role in controlling the addition and addition/cyclization processes. This unexpected result encouraged us to optimize the reaction conditions in the presence and in the absence of oxygen, as two

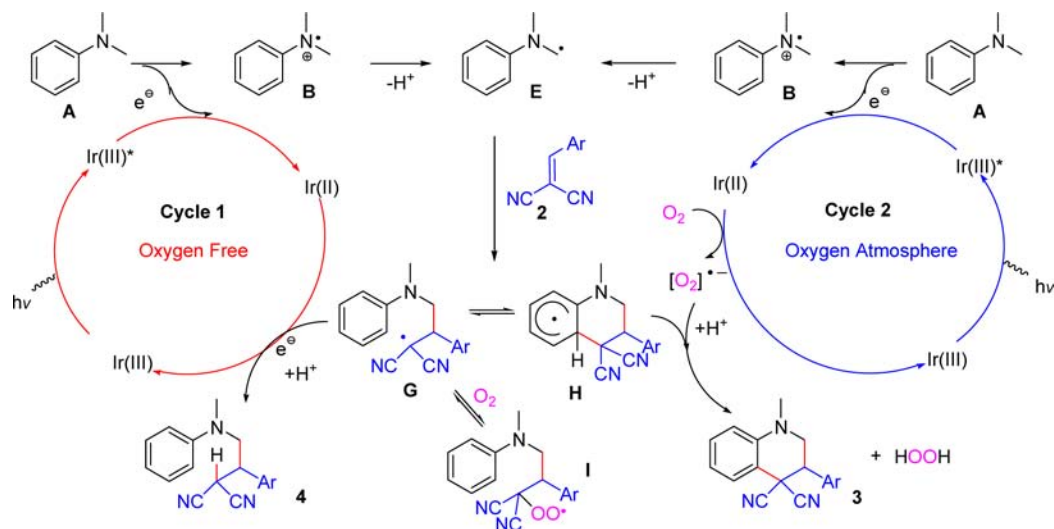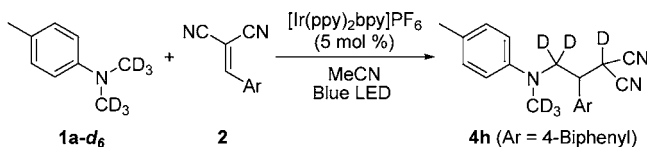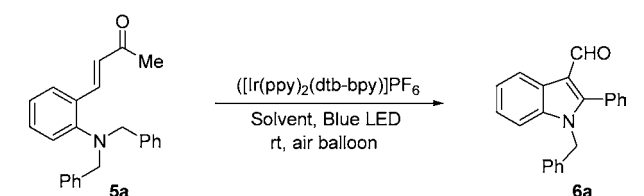**Scheme 2. Proposed Mechanism for the Photoredox Catalyzed Radical Addition and Addition/Cyclization Reactions**

Scheme 3. Photoredox Catalyzed Radical Addition of 1a−d_6

Table 4. Photocatalyzed Michael Addition/Aromatization/ C−C Bond Cleavage Cascade Reaction


entry[a]	catalyst (mol %)	solvent	time (h)[b]	yield (%)[c]
1	5	CH_3CN	40	48
2	10	CH_3CN	22	51
3		CH_3CN	40	E:Z isomerization
4[d]	10	CH_3CN	40	starting material
5	10	CH_3NO_2	20	56
6	10	DCM	24	15
7	10	toluene	36	E:Z isomerization
8	10	CHCl_3	20	63
9	10	THF	24	
10	10	dioxane	24	E:Z isomerization
11	10	MeOH	24	
12	10	DMF	24	

[a]Reaction conditions: 0.1 mmol substrate 10 mol % catalyst, 1 mL solvent, Blue LED light irradiation. [b]Refers to the time until all starting material is consumed. [c]Yield of the isolated product. [d]No light source.

different classes of compounds can be obtained from the same starting materials by simply switching the reaction conditions.

In search for more efficient catalysts for the photoredox catalyzed radical reactions, a series of Ir(III) and Ru(II) poly pyridyl based complexes were evaluated as photoredox catalysts. In general, all tested Ir(III) and Ru(II) photocatalysts gave the addition/cyclization reaction product **3a** in the presence of air (Supporting Information, SI, Table S1, entries

Table 5. Scope of the Photoredox Catalyzed Cascade Reaction
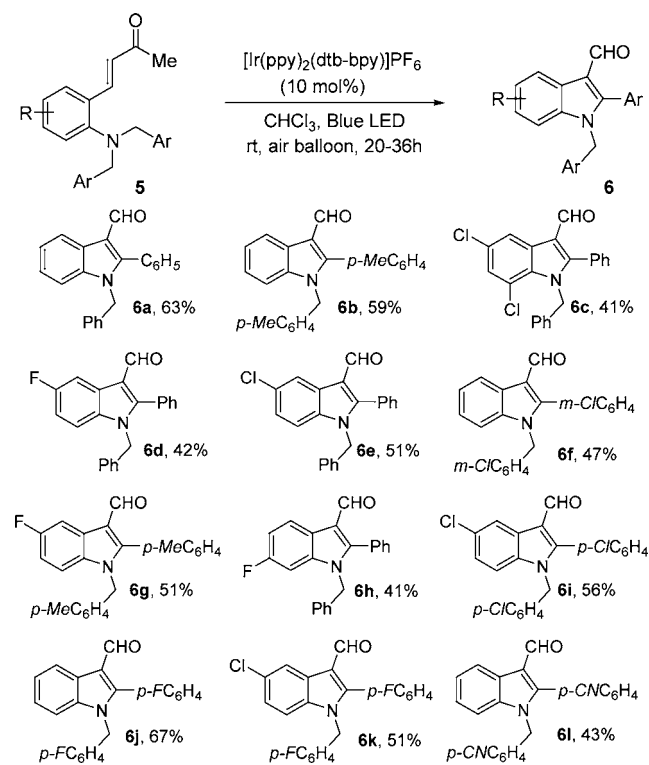
1−7). However, [Ir(ppy)_2bpy]PF_6 complex turned out to be the catalyst of choice to evaluate the catalyst loading for this reaction. A slight improvement in the yield of the addition/ cyclization product **3a** was observed with 5 mol % [Ir-(ppy)_2bpy]PF_6 (Table 1, entry 14). Notably, no reaction occurred in the absence of a photocatalyst or light (Table 1, entries 12 and 13). The addition product **4a** was isolated in 91% yield when 5 mol % [Ir(ppy)_2bpy]PF_6 was used under oxygen free conditions (Table 1, entry 15).

With the best reaction conditions for the radical addition and radical addition/cyclization reactions established, the generality of this novel oxygen manipulative visible-light photoredox catalyzed reactions was investigated.

Scheme 4. Identification of the Reactive Intermediates
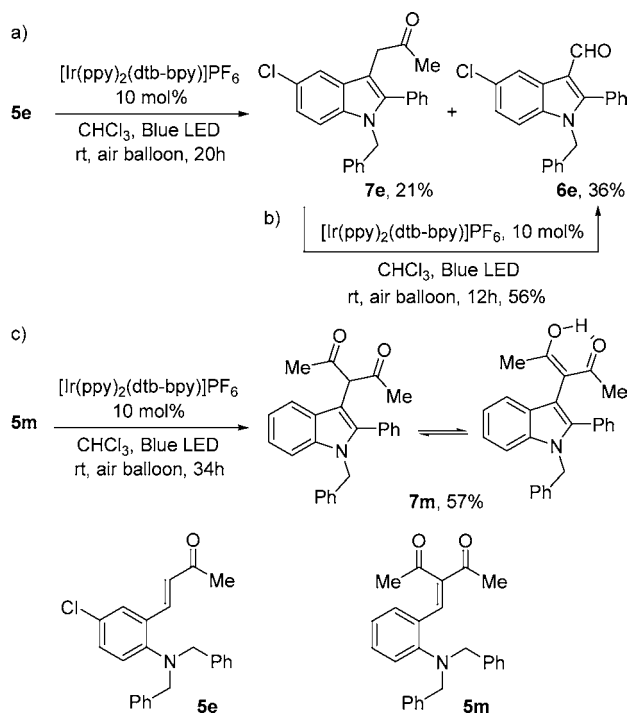
Scheme 5. Isotope Incorporation Experiments
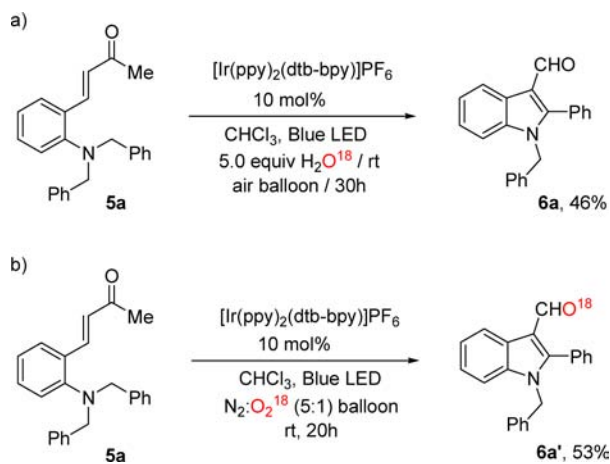
Different anilines **1** and electron-deficient alkenes **2** were subjected to the optimal reaction conditions. In the presence of oxygen, a variety of *N*-alkyl-tetrahydroquinolines **3a–l** was obtained in moderate to good yields. Electron-deficient alkenes **2** bearing aromatic groups with different electronic and steric properties were tested in reaction with 3- and 4-substituted dimethylanilines and the corresponding addition/cyclization sequence products **3b–l** could be obtained under mild conditions (Table 2, entries 2–12). In the case of 3-Me substituted dimethylaniline, the cyclization occurred exclusively at the ortho position to *N* and para to the methyl substituent (Table 2, entries 10–12). The radical addition/cyclization reaction with ortho substituted dimethylanilines proceeded sluggishly, most likely due to electronic and steric effects.

In the absence of oxygen, the reaction of different anilines **1** was performed with electron-deficient alkenes **2** and a variety of radical addition products (**4a–r**) was obtained in good to high yields (56–91%, Table 3). Anilines and alkenes bearing

substituents with different electronic properties were evaluated and they are well tolerated under the developed conditions.

On the basis of these results, a plausible mechanism is proposed in Scheme 2. Upon irradiation, Ir(III) is excited providing Ir(III)*, which is then reductively quenched by **A** to produce Ir(II) and amine radical cation **B** via single electron transfer oxidation. The amine radical cation **B** can be deprotonated yielding the tertiary α-amino carbon radical **E**,[16] which can easily react with highly reactive alkene **2** to produce the alkyl radical **G**. At this stage, a radical chain process in which the alkyl radical **G** reacts with the tertiary amine **A** to give product **4** and the regenerated radical **E** might be feasible. However, a long radical chain process may be negligible in our system as the reaction does not proceed further upon switching off the light. This observation is also in agreement with recent studies by Nishibayashi which appeared during our investigations.[13] Hence we propose that radical **G** is involved in regenerating the Ir catalyst through oxidation, and deprotonation of the amine radical cation **B** to yield the corresponding radical addition product **4** and the α-amino alkyl radical **E**. This route is supported by the fact that reaction of **1a**-d_6 with **2** (Ar = 4-Biphenyl) resulted in the corresponding product **4h** fully enriched at the α-amine protons and at the activated methine group (Scheme 3).

On the other hand, radical **G** could undergo intramolecular radical arylation[17,18] to furnish cyclohexadienyl radical **H**. However, in the absence of oxygen this pathway is reversible[17] as the species present in the reaction mixture can oxidize **H** only to a small extent. In the presence of oxygen, electron transfer from Ir(II) to the molecular oxygen yields the superoxide anion radical $O_2^{\cdot-}$. Proton and electron transfer from cyclohexadienyl radical **H** to $O_2^{\bullet-}$ yields the cyclization product **3** and HOO⁻. The HOO⁻ will be subsequently protonated to yield H_2O_2(Cycle 2). In addition radical **G** can react with oxygen to give **I**. However, this is a reversible reaction[19] and still a H abstractor, such as $O_2^{\bullet-}$ or the hydroxyl anion, is essential for the cyclization sequence to proceed.

Next we became interested in performing the photoredox mediated radical addition in an intramolecular fashion. For this purpose we prepared (E)-4-(2-(dibenzylamino)phenyl)but-3-en-2-one **5a**[20] and evaluated it under different reaction conditions with various ruthenium and iridium based photocatalysts. Irradiation of the test substrate **5a** in the presence of catalytic amounts of [Ir(ppy)$_2$(dtb-bpy)]PF$_6$ (5 mol %) in acetonitrile under air resulted in the unexpected formation of indole-3-carbaldehyde **6a** in 48% yield (Table 4, entry 1). This type of compounds has received particular attention as indole-3-carbaldehydes are important precursors for many biologically and medicinally active compounds. Increasing the catalyst loading resulted in a better yield for **6a** (51%, 22 h).

Further iridium and ruthenium based photocatalysts were tested but did not show improved activity in this transformation (see SI). Furthermore, no product formation was observed in the absence of light or photocatalyst (Table 4, entries 3 and 4). The molecular structure of 1-benzyl-2-phenyl-1*H*-indole-3-carbaldehyde **6a** was unambiguously determined by X-ray crystal structure analysis (see SI). Owing to the synthetic and mechanistic interest of this visible-light induced catalytic reaction, we further examined its scope by applying the optimized condition to various substrates **5b–l** which were easily prepared by Heck coupling of the corresponding *N,N*-dibenzyl-2-iodoaniline. Several functional groups on the aromatic moieties are well tolerated under the reaction

Scheme 6. Proposed Reaction Mechanism for the Photoredox Catalyzed Addition/Aromatization/C−C Bond Cleavage Cascade Reaction
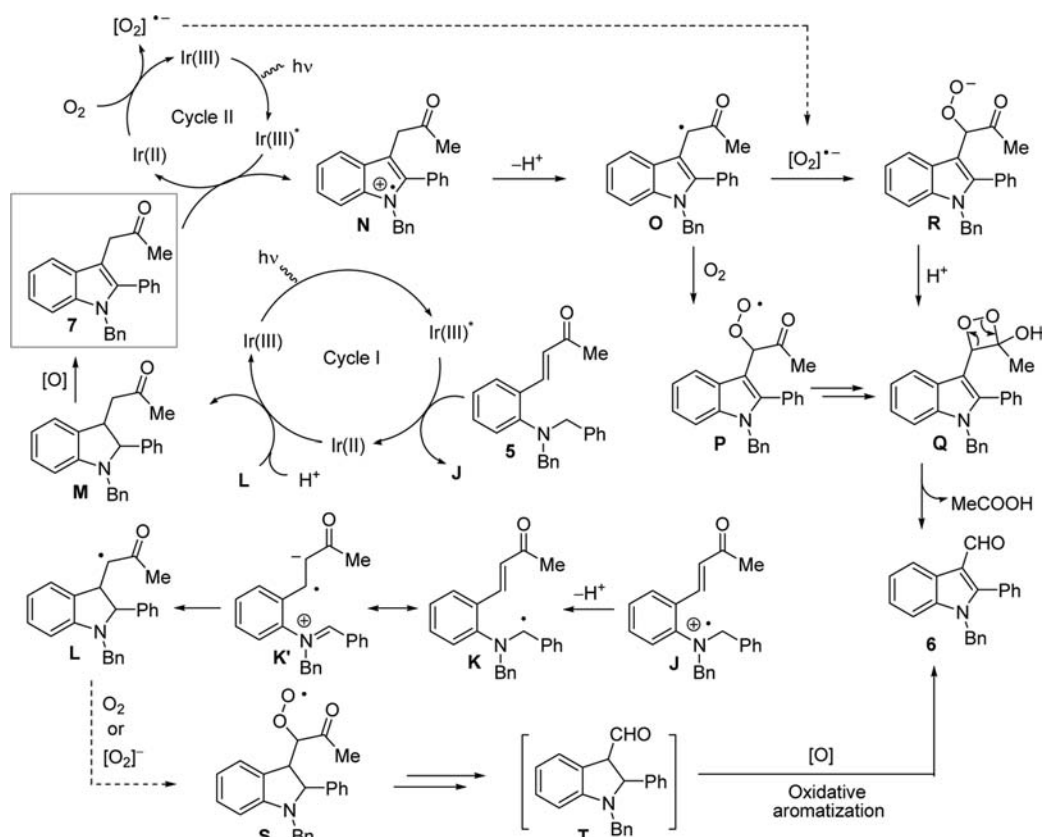
condition, affording indole-3-carbaldehydes **6b−l** in moderate to good yields (Table 5).

To understand the mechanism of this transformation, we have conducted several control experiments (Scheme 4). Subjection of compound **5e** to the reaction conditions for a period of 20 h gave a separable mixture of indole-3-carbaldehyde **6e** (36%) together with the Michael addition product **7e** (21%, Scheme 4a). In a further experiment **7e** was subjected to the same reaction conditions and led to **6e** (Scheme 4b), suggesting that **7e** is the reactive intermediate for the final oxidative cleavage reaction. We have prepared 3-(2-(dibenzylamino) benzylidene)pentane-2,4-dione **5m**, which gave addition product **7m** as a mixture of keto−enol tautomer without further oxidative cleavage under the catalytic condition (Scheme 4c). From this observation, we conclude that for further oxidative cleavage a free hydrogen atom α to the keto functionality is necessary.

To reveal the source of aldehyde oxygen, we have first performed the photoredox reaction of **5a** in the presence of H_2O^{18} (5.0 equiv.) which gave 1-benzyl-2-phenyl-1H-indole-3-carbaldehyde **6a** without any ^{18}O enriched at its aldehyde oxygen (Scheme 5a). Subsequently, we have performed the photoredox reaction in the presence of $^{18}O_2$ gas (20% in N_2) which afforded ^{18}O enriched 1-benzyl-2-phenyl-1H-indole-3-carbaldehyde **6a** as confirmed by mass spectroscopy measurements (Scheme 5b). These experiments indicate that the aldehyde oxygen originates from the superoxide anion radical $O_2^{•-}$ generated by the reaction of dissolved oxygen with Ir(II) and results in Ir(III) via electron transfer. The presence of singlet oxygen as active species in our reaction has been excluded as no reaction took place in the presence of TPP

(tetraphenylporphyrin) and Rose Bengal, which are well-known sensitizers for the generation of singlet oxygen. A plausible mechanistic scenario based on the control experiments is depicted in Scheme 6. During control experiments it was proven that the reaction does not proceed further if the light source is switched off.

Under irradiation Ir(III) is excited to Ir(III)* which is then reductively quenched via a single electron transfer from substrate **5**, forming Ir(II) and the radical cation **J** (Scheme 6, cycle I). Radical cation **J** undergoes facile deprotonation to give α-amino alkyl radical **K**. Intramolecular addition gives intermediate **L**. On the other hand, one can consider intermediate **K** as iminium ion intermediate **K′**[21] which will give the same intermediate **L** via subsequent addition reaction.

Single electron reduction of intermediate **L** followed by protonation results in intermediate **M** and regenerates Ir(III) to continue the catalytic cycle. Intermediate **M** undergoes oxidative aromatization[4d] under the same reaction conditions to give 1-(1-benzyl-2-phenyl-1H-indol-3-yl)propan-2-one **7**. The intermediacy of **7** has been confirmed by the isolation of its analogous derivative **7e** and its subsequent oxidation to indole 3-carbaldehyde **6e** (Scheme 4a) under the same reaction conditions, which supports this reaction pathway. One electron oxidation of **7** gives **N** which in turn may give rise to the captodative α-radical carbonyl intermediate **O**. Subsequent reaction with oxygen results in **P** which upon electron transfer and carbon−carbon bond cleavage results in product **6**. Alternatively, but less likely addition of superoxide anion radical $O_2^{•-}$ to the α-radical carbonyl intermediate **O** results in the formation of **R**. The following reaction with the keto functional group gives cyclic peroxide intermediate **Q** which

undergoes cleavage of the carbon−carbon bond[22] to form 1-benzyl-2-phenyl-1H-indole-3-carbaldehyde **6** and acetic acid. These pathways are supported by the fact that **7e** can be converted into **6e** (Scheme 4). Alternatively, one may consider addition of O_2 to the intermediate **L** which gives aldehyde **T** upon oxidative cleavage of **S**. The subsequent oxidative aromatization would result in product **6**. However, the unexpected finding that compound **7** can be isolated and independently transferred to product **6** not only strongly supports the upper reaction pathway (Scheme 6) but additionally opens up new opportunities for developing further photoredox catalyzed C−C bond cleavage reactions.

CONCLUSIONS

We have developed a direct intermolecular and intramolecular C−H functionalization of tertiary amines by employing visible light photoredox catalysis. Notably, oxygen can be used as a chemical switch to trigger two different reaction pathways and to obtain two different types of products from the same staring material. On one hand, γ-amino nitriles were obtained in good to high yields in the absence of oxygen via an intermolecular addition of N,N-dimethyl-anilines to benzylidene malononitriles. On the other hand, in the presence of oxygen, a radical addition/cyclization reaction sequence occurred, leading to the corresponding tetrahydroquinoline derivatives in good yields, under mild reaction conditions.

In addition, an intramolecular version has been developed. In this case, a photoredox catalyzed domino reaction involving C−C bond formation, aromatization, and carbon−carbon bond cleavage took place and afforded biologically and medicinally important precursor indole-3-carbaldehyde derivatives via the formation of α-amino alkyl radical intermediates. Mechanistic investigations have been performed to elucidate the reactive intermediates and to propose a plausible reaction pathway for the photoredox catalyzed addition/aromatization/C−C bond cleavage cascade reaction. Importantly, a new photoredox catalyzed C−C bond cleavage of indolylpropanones into the corresponding indolecarbaldehydes has been uncovered which in its more elaborated way holds great potential in organic synthesis. This catalysis is mechanistically new and can be further explored to design new transformations in the field of photoredox catalysis.

ASSOCIATED CONTENT

Ⓢ Supporting Information

Full characterization of the products and spectra are available as ESI. 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. This manuscript was written through contributions of all authors.
Notes
The authors declare no competing financial interest.

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