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# Visible-Light-Induced α-Amino C−H Bond Arylation Enabled by Electron Donor−Acceptor Complexes

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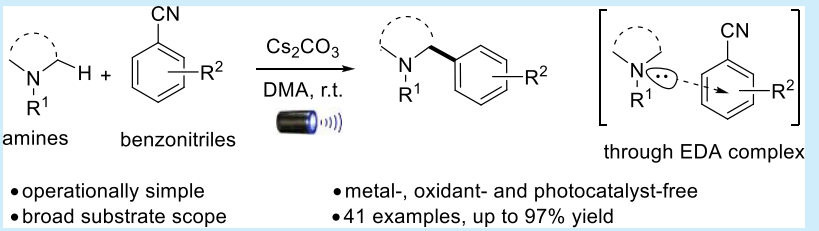


**ABSTRACT:** Enabled by electron donor−acceptor complexes, a novel visible-light-induced α-amino C−H bond arylation protocol, without a photoredox catalyst, has been disclosed. The protocol does not require any transition metal, oxidant, or exclusion of oxygen or moisture. A direct irradiation of the mixture of tertiary amines and benzonitriles with visible light in *N*,*N*-diethylethanamide in the presence of $Cs_2CO_3$ afforded α-arylated amines in good to excellent yields.



Visible light is the most green and abundant natural energy source. The utilization of visible light has been attracting the efforts of scientists to develop efficient light-harvesting technologies to promote chemical processes.[1] One of the breakthroughs is the visible-light-mediated photoredox catalysis.[2] Highlighting the unique catalytic mode and wonderful compatibility with other catalysis, it has been demonstrated as a powerful strategy since the pioneering work by MacMillian,[3] Yoon,[4] and Stephenson,[2f] enabling a number of previously inaccessible transformations with the assistance of a photocatalyst. While useful and powerful, photoredox catalysis has somewhat suffered from (i) the high cost of photocatalysts, (ii) difficulty in recovering and reusing photocatalyst from homogeneous reaction media,[5] and (iii) the need to exclude oxygen from the reaction system in many cases. The development of mechanistically novel and operationally simple protocols using the fewest reagents for challenging transformations is an ideal goal for synthetic chemists. Recently, photocatalyst-free electron donor−acceptor (EDA) complex photochemistry has emerged as a fresh and intriguing alternative.[6,7] In this new reaction mode, the ground-state in situ aggregation of an electron-donating substrate with an electron-accepting substrate forms an EDA complex, which enables the absorption of visible-light energy to trigger an intramolecular single-electron-transfer event, ultimately producing reactive radical intermediates without the assistance of any photocatalyst. Although this new reaction mode is mechanistically novel and eco-friendly, it was not until very recently that the synthetic application of EDA complexes attracted the growing attention of chemists. Representative achievements are quite limited in the contemporary literature.

Benzylic amines are ubiquitous and privileged structural motifs found among natural products, biologically active synthetic molecules, and medical agents, among which, many are simple derivatives.[8] Therefore, the assembly and elaboration of such structures through α-amino arylation have been attracting the attention of synthetic chemists. Numerous seminal methods have been established. Among them, an elegant methodology is exemplified by a decarboxylative photoredox catalysis employing α-amino acids as feedstocks.[9] However, the specific site selectivity comes at the price of having to remove the carboxylic group. Without question, the direct α-amino C−H bond arylation of amines is considered as the most efficient and straightforward approach.[10−13] In this context, mechanistically diverse protocols were disclosed through the formation of an α-amino cation,[10] an α-amino anion,[11] an α-amino radical,[12] and an α-amino C−Ru/Pd/Rh complex[13] as key intermediates (Figure 1a−d). While great advancements have been achieved, transition-metal catalysts or stoichiometric oxidants are necessary in these strategies. Recently, inspired by MacMillan's pioneer work[3b] on $Ir(ppy)_3$-catalyzed photoredox α-amino C−H bond arylation from readily available tertiary amines and cyanoaromatics (Figure 1e), Ye and co-workers[14] achieved the same transformation through a convergent paired electrolysis in

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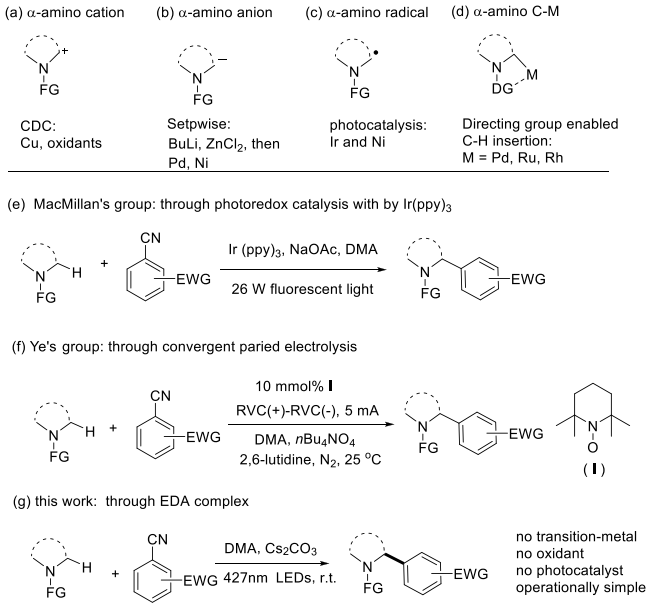
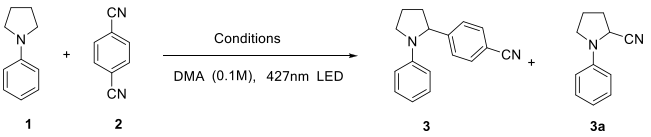



**Figure 1.** Strategies for α-amino C−H bond arylation.

the presence of a catalytic amount of 2,2,6,6-tetramethylpiperidinooxy, 2 equiv of *n*-BuNClO$_4$, and 2 equiv of 2,6-lutidine under a $N_2$ atmosphere (Figure 1f). Very soon, the same transformation was achieved by Jensen and co-workers employing microfluidic electrochemistry.[15] From the viewpoint of atom economy and environmental impact, both transition-metal and oxidant free, and operationally simple protocols are highly appealing. Herein, we report a visible-light-induced, transition-metal-free, oxidant-free, and operationally simple α-amino C−H bond arylation process through the formation of EDA complexes.

We began our investigation on the α-amino C−H arylation process by directly subjecting the *N*,*N*-diethylethanamide (DMA) solution of *N*-phenylpyrrolidine (**1**) and 1,4-dicyanobenzene (**2**) to visible-light irradiation (two Kessil 40 W 427 nm light-emitting diode lamps) for 12 h with sodium acetate (NaOAc) as the base. To our delight, the desired arylation product **3** was isolated in a 21% yield, along with cyanation byproduct **3a** in a 44% yield (Table 1, entry 1). When 1,4-dicyanobenzene was used as the limiting substrate, the product **3** was isolated in an improved yield of 37% as the major product (entry 2). We assumed that the reaction proceeded through a single-electron oxidation of *N*-phenylpyrrolidine (**1**), followed by the deprotonation of the resulting radical cation by a base to form the key α-amino radical. Thus, the base should play a crucial role for the transformation. Accordingly, a brief survey of commonly used bases, such as $K_3PO_4$, KOAc, $K_2CO_3$, CsOAc, $Cs_2CO_3$, and $Na_3PO_4{\cdot}12H_2O$, was performed (entries 3−8), indicating that $Cs_2CO_3$ was the most efficient and provided the desired arylation product **3** and the cyanation byproduct **3a** in 78% and 12% isolated yields, respectively. Increasing the amount of $Cs_2CO_3$ and *N*-phenylpyrrolidine resulted in slightly improved yields (entries 9−11). An examination of other common solvents, such as dimethyl sulfoxide (DMSO), dimethyl formamide (DMF), *N*-methylpyrrolidone (NMP), MeCN, $CH_2Cl_2$, tetrahydrofuran (THF), and DMA−$H_2O$ (4:1), showed that DMA was the superior solvent (entries 12−18). Notably, it was found by control experiments that both the light power and wavelength were of great importance. The yield of **3** was dramatically

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




1 2 3 3a

| entry | 1:2[b] | solvent, base (eq) | 3, 3a yields (%) |
|---|---|---|---|
| 1 | 1:1.5 | DMA, NaOAc (2.9) | (21), (44) |
| 2 | 1.5:1 | DMA, NaOAc (1.5) | (37), (26) |
| 3 | 1.5:1 | DMA, $K_3PO_4$ (1.5) | 64, 16 |
| 4 | 1.5:1 | DMA, KOAc (1.5) | 56, 16 |
| 5 | 1.5:1 | DMA, $K_2CO_3$ (1.5) | 66, 22 |
| 6 | 1.5:1 | DMA, CsOAc (1.5) | 51, 24 |
| 7 | 1.5:1 | DMA, $Cs_2CO_3$ (1.5) | 81 (78), 18 (12) |
| 8 | 1.5:1 | DMA, $Na_3PO_4.12H_2O$ | 65, 28 |
| 9 | 2:1 | DMA, $Cs_2CO_3$ (2.0) | 86, 22 |
| 10 | 3:1 | DMA, $Cs_2CO_3$ (2.2) | 87 (83), 28 (24) |
| 11 | 3:1 | DMA, $Cs_2CO_3$ (3.0) | 89 (83), 28 (18) |
| 12 | 3:1 | DMSO, $Cs_2CO_3$ (2.0) | 36, 19 |
| 13 | 3:1 | DMF, $Cs_2CO_3$ (2.0) | 78, 32 |
| 14 | 3:1 | NMP, $Cs_2CO_3$ (2.0) | 77, 35 |
| 15 | 3:1 | $CH_3CN$, $Cs_2CO_3$ (2.0) | trace, trace |
| 16 | 3:1 | $CH_2Cl_2$, $Cs_2CO_3$ (2.0) | 0, 0 |
| 17 | 3:1 | THF, $Cs_2CO_3$ (2.0) | 0, 0 |
| 18 | 3:1 | DMA-$H_2O$, $Cs_2CO_3$(2.0) | 0, 0 |
| 19[c] | 1.5:1 | DMA, $Cs_2CO_3$ (1.5) | 40, 17 |
| 20[d] | 1.5:1 | DMA, $Cs_2CO_3$ (1.5) | trace, trace |
| 21[e] | 1.5:1 | DMA, $Cs_2CO_3$ (1.5) | 7, 3 |

[a]Yields were determined by $^1$H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard after workup, and the yields in brackets are isolated yields. [b]Mole ratio of *N*-phenylpyrrolidine (**1**) to 1,4-dicyanobenzene (**2**). [c]75% of light power (30 W) was used. [d]50% of light power (20 W) was used. [e]Light wavelength is 440 nm.

reduced to 40% when the light power was reduced to 75% (30 W) (entry 7 vs entry 19), and nearly no reaction took place with 50% (20 W) of the light power (entry 20). Moreover, it was revealed that the light wavelength was also crucial, as only a 7% yield of the product **3** was observed with irradiation of a longer light wavelength (440 nm). It is worth mentioning that the protocol is operationally simple, as all reactions proceed without nitrogen purging and moisture exclusion.

With the optimal conditions in hand, the substrate scope was then evaluated. Later on, it was found that higher yields could be achieved by extending the reaction time from 15 to 40 h; thus, the following reactions were performed for 40 h. As shown in Scheme 1, a diverse range of substituted *N*-arylpyrrolidines were arylated with 1,4-dicyanobenzene, providing the desired arylated products **4**−**8** in moderate to good yields (50−73%). Variations of the substitutions include Me, Br, and Cl groups at the *meta* or *para* position of the phenyl ring. On the one hand, gratifyingly, the β-naphthyl analogue was also compatible in the protocol, affording the desired product **9** in a 55% yield. On the other hand, six-membered piperidine and morpholine as well as seven-membered azepane derivatives were also suitable substrates, providing the corresponding products **10**−**12** in the yields ranging from 30% to 73%. The acyclic tertiary amines *N*,*N*-dimethylaniline and *N*,*N*-diethylaniline also proceeded smoothly to afford **13** and **14** in 43% and 60% yields. The higher yield of **14** as compared to **13** might suggest the involvement of an easily formed (or a much more stable)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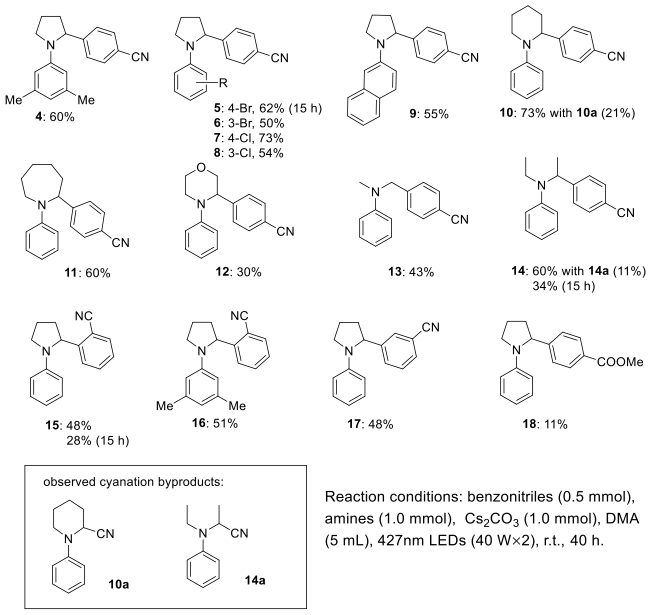
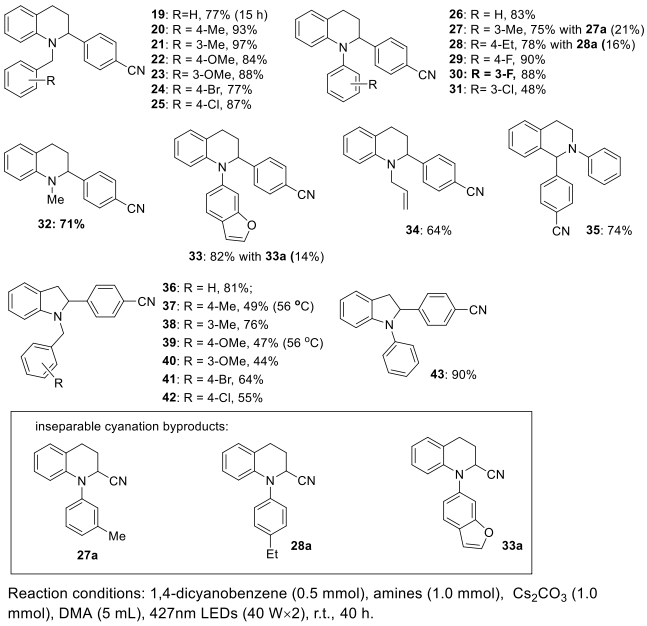
**Scheme 1. Substrate Scope Investigation**




**Scheme 2. Substrate Scope Investigation**



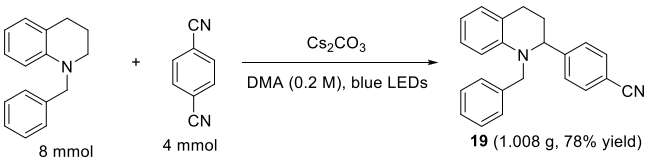

intermediate in the reaction. Moreover, 1,2-dicyanobenzene and 1,3-dicyanobenzene readily underwent the same reaction with *N*-arylpyrrolidines to afford the products **15**−**17** in 48−51% yields. To our delight, methyl 4-cyanobenzoate was also an amenable substrate to form **18**, albeit with a low yield of 11%. We reasoned that, in some cases, the relatively low yields should be attributed to the formation of $\alpha$-cyanation byproducts, which formed through the addition of $CN^-$ to an iminium ion intermediate. For example, $\alpha$-cyanation byproducts **10a** and **14a** were detected in 21% and 11% yields, respectively.

Tetrahydroquinolines, tetrahydroisoquinolines, and indolines are privileged heteroaromatics commonly found in pharmaceuticals and biologically active compounds. The derivatization of these heteroaromatics further highlights the synthetic utility of this operationally simple and green protocol. The arylation of tetrahydroquinoline derivatives was first performed (Scheme 2). A variety of *N*-arylmethylated tetrahydroquinolines, including benzyl, *p*-/*m*-methylbenzyl, *p*-/*m*-methoxybenzyl, and *p*-bromo-/*p*-chlorobenzyl, were suitable substrates, and good to excellent yields (77−97%) of the products **19**−**25** were achieved under the optimal conditions. Similarly, *N*-arylated tetrahydroquinolines possessing phenyl, *p*-/*m*-alkylphenyl, and *p*-/*m*-fluorophenyl substituents furnished the products **26**−**30** in 75−90% yields, although the arylation of *N*-(3-chlorophenyl)-1,2,3,4-tetrahydroquinoline with 1,4-dicyanobenzene afforded product **31** in a moderate yield (48%). The results demonstrated that both electron-donating (Me, OMe) and electron-withdrawing (Br, Cl, F) substitutions on the *N*-arylmethyl and *N*-aryl groups were tolerated. It was found that *N*-methyl-1,2,3,4-tetrahydroquinoline demonstrated good reactivity in the arylation reaction to give the product **32** in 71% yield. Notably, for *N*-benzyl-substituted tetrahydroquinolines, there is a specific preference for the arylation at the ring position as opposed to the acyclic benzylic site, and no regioisomers were detected. The regioselectivity was consistent with the findings made by MacMillan group's.[3b] Delightedly, *N*-(benzofuran-6-yl)-1,2,3,4-tetrahydroquinoline was amenable via the arylation protocol, affording the desired product **33** in an 82% yield, along with an inseparable $\alpha$-cyanation byproduct **33a** in a 14% yield. Two other inseparable $\alpha$-cyanation byproducts **27a** and **28a** were also detected in 21% and 16% yields, and their structures were confirmed by a gas chromatography-mass spectrometry (GC-MS) analysis. Moreover, *N*-allyl-1,2,3,4-tetrahydroquinoline was also arylated smoothly on the ring site with 1,4-dicyanobenzene to afford product **34** in 64% yield, leaving both the double bond and allylic position intact. It was interesting to observe that *N*-phenyl-1,2,3,4-tetrahydroisoquinoline produced the product **35** (74%) in favor of arylation at the benzylic position on the ring. Moreover, *N*-arylmethyl and *N*-phenyl indolines were also amenable to this $\alpha$-arylation strategy, albeit with a little bit lower yields than those of the corresponding tetrahydroquinoline counterparts. A variation of the substitutions, including *p*-/*m*-methylbenzyl, *p*-/*m*-methoxybenzyl, and *p*-bromo/*p*-chlorobenzyl, was tolerated with excellent regioselectivity on the ring, affording the arylated indolines **36**−**42** in 44−81% yields. Delightedly, the reaction of *N*-phenylindoline could proceed smoothly, and the desired arylated product **43** was isolated in an excellent yield (90%).

Finally, with the employment of 4 mmol of 1,4-dicyanobenzene as the limiting substrate, a gram-scale synthesis of the product **19** was performed, and a comparable yield was achieved (1.008 g, 78% vs 77%), indicating the wonderful potential for the practical utility of the protocol (Scheme 3).

To get insight into the reaction mechanism, UV−vis absorption spectra of *N*-phenylpyrrolidine (**1**), 1,4-dicyanobenzene (**2**), the mixture of **1** and **2**, and the combination of **1**,

**Scheme 3. A Gram-Scale Synthesis of the Product 19**





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2, and $Cs_2CO_3$ were recorded in DMA (see the Supporting Information). A bathochromic shift of the mixture of **1** and **2** was observed, indicating the formation of an EDA complex. The results are consistent with the obvious color change from colorless to yellowish when **1** and **2** were mixed. Meanwhile, only a trace amount of **3** was detected when a radical scavenger (2,2,6,6-tetramethylpiperidine-1-oxy radical (TEMPO)) was added to the reaction mixture of **1** and **2**, indicating the probable formation of radical intermediates. On the basis of the above observations and literature reports, a plausible mechanistic explanation was proposed in Figure 2. The

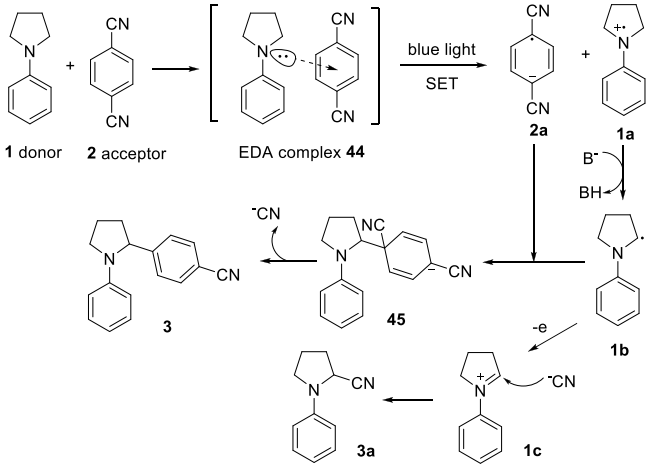


**Figure 2.** Proposed mechanistic pathway.

mixture of tertiary amine **1** (electron-donor) and benzonitrile **2** (electron-acceptor) in DMA forms the EDA complex **44**. Upon irradiation with visible light, a direct single-electron transfer event from electron-rich amine **1** to electron-deficient benzonitrile **2** took place, generating the arene radical anion **2a** and amino radical cation **1a** simultaneously. **1a** then underwent deprotonation (the C−H bond adjacent to nitrogen atom) by a base to afford the key $\alpha$-amino radical **1b**. The coupling of $\alpha$-amino radical **1b** with arene anion radical **2a** generates the key intermediate **45**, which undergoes the subsequent elimination of $^-$CN to then form the aromatized benzylic amine product **3**. Meanwhile, the $\alpha$-amino radical **1b** processed a further single-electron oxidation to afford iminium ion **1c**, which was then attacked by $^-$CN to form the $\alpha$-cyanation byproduct **3a**.

In conclusion, we have developed a novel visible-light-induced, transition-metal-free, and oxidant-free protocol for $\alpha$-amino C−H bond arylation under extremely mild and simple conditions. The mechanistically different, eco-friendly protocol highlights the formation of a new kind of electron donor−acceptor complex from readily available tertiary amines and benzonitriles. Without the exclusion of moisture and oxygen, the direct irradiation of the mixture of a tertiary amine and a benzonitrile in DMA in the presence of $Cs_2CO_3$ afforded benzylic amines in good to excellent yields with good substrate scope and functional group tolerance. The protocol constitutes the most operationally simple and the least reagent-used alternative for $\alpha$-amino C−H bond arylation, showing great potential for practical application.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00984.

Experimental procedures, compound characterization, and NMR spetra for all compounds (PDF)

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### Notes

The authors declare no competing financial interest.

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