OL | Organic Letters

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

Letter

pubs.acs.org/OrgLett

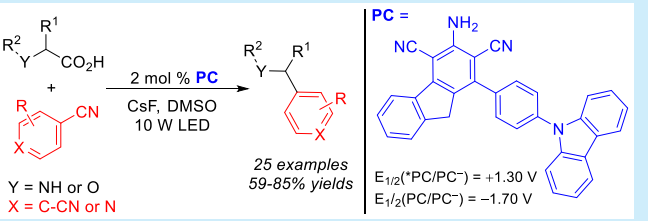
# 3-Amino-fluorene-2,4-dicarbonitriles (AFDCs) as Photocatalysts for the Decarboxylative Arylation of α-Amino Acids and α-Oxy Acids with Arylnitriles

Yiyang Chen, Ping Lu,* and Yanguang Wang*

Department of Chemistry, Zhejiang University, Hangzhou 310027, P. R. China

Supporting Information

**ABSTRACT:** 1-(4-(9*H*-Carbazol-9-yl)phenyl)-3-amino-9*H*-fluorene-2,4-dicarbonitrile as a new photocatalyst for the decarboxylative cross-coupling reaction of α-amino acids or α-oxy carboxylic acids with arylnitriles is described. This light-driven reaction enables a variety of benzylic amines and ethers to be prepared from readily available starting materials under mild conditions.






With growing environmental awareness, the past decade has witnessed tremendous advancement in the development of chemical reactions triggered by light through photocatalysis, accompanied by intensive research in the field of photocatalyst design. The light-driven reaction systems typically comprise transition-metal complexes[1] and small molecular organic dyes as molecular photocatalysts,[1a,2] both of which have been demonstrated to be efficient in homogeneous catalysis for a variety of organic photoredox reactions. Additionally, the macromolecular heterogeneous photocatalysts based on the conjugated organic dyes have also been developed for photocatalysis in metal-free alternatives.[3] Desired photophysical properties including both optimal redox windows and long-lived excited states have made polypyridyl complexes of ruthenium and iridium the most commonly used photocatalysts.[1] Small molecular organic photocatalysts have been adopted as alternatives, as they are more economical, structurally variable, and environmentally friendly.[2,4] However, a narrower redox window, photobleaching tendency, pH dependence, low solubility in common organic solvent, and a narrower redox window render most of the traditional organic photocatalysts such as fluorescein, Rose Bengal (RB), Eosin Y, and phenothiazines impractical.

Therefore, it has been our goal to develop novel and effective organic photocatalysts with easily modified molecular structures. Elegant examples for recent advances in this field include the development of a series of new acridinium salts,[4] acridones,[5] bodipy derivatives,[6] and phenoxazines,[7] bifunctional photocatalyst bearing a chiral bisoxazoline ligand,[8] and a dicyanopyrazine derived chromophore (DPZ).[9]

Recently, Zhang and co-workers reported carbazolyl dicyanobenzene (CDCB)-based donor−acceptor (D-A) fluorophores as efficient photoredox catalysts for photoredox/Ni dual catalytic decarboxylative coupling of carboxylic acids and alkyltrifluoroborates using aryl halides.[10a] Alkylation of imines were also achieved using this class of organic photocatalysts.[10b]

3-Amino-9*H*-fluorene-2,4-dicarbonitrile and derivatives (AFDCs), such as **1a**, **2a**, and **3a** (Figure 1), are a typical

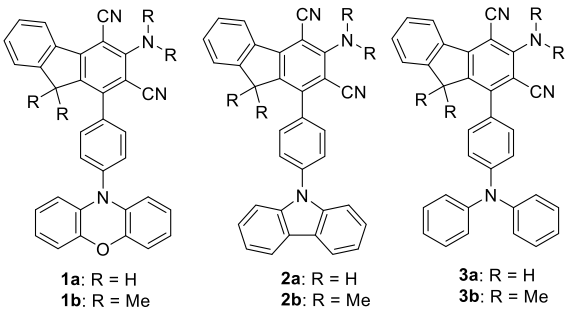



**Figure 1.** Structure of the AFDC-based photocatalysts.

class of acceptor−donor−acceptor (A−D−A) systems which have been found to exhibit strong fluorescence in our previous studies.[11] This class of stable fluorophores were measured to possess excited state redox potentials of $E_{1/2}(PC^+/PC^*)$ = −1.71 to − 1.96 V and $E_{1/2}(PC^*/PC^-)$ = +1.00 to +1.30 V vs SCE (see Supporting Information (SI), Table S1) favoring a variety of redox processes.

Encouraged by these results and inspired by Zhang's work,[10] we investigated the photocatalytic activities of AFDCs as photoredox catalysts for organic synthesis. Herein, we report our success in using AFDC-based A−D−A fluorophores as photocatalysts for the direct transformation of readily available α-amino acids, α-oxy acids, and arylnitriles into high-value benzylic amines or ethers.

AFDCs **1a**, **2a**, and **3a** as well as their derivatives **1b**, **2b**, and **3b** were synthesized according to our previous methods.[11] Their photophysical properties were measured in order to

**Received:** February 1, 2019




DOI: 10.1021/acs.orglett.9b00443
Org. Lett. XXXX, XXX, XXX−XXX

select suitable photocatalytic reaction and irradiation. Upon light excitation, the photoexcited state of these compounds shows both strong oxidative ($E_{1/2}$(PC*/PC$^-$) = +1.00 to +1.40 V vs SCE) and reductive ($E_{1/2}$(PC$^+$/PC*) = −1.67 to − 2.11 V vs SCE) capabilities that parallel or surpass those of many metal complexes and organic dyes (see SI, Table S1). Modifying the donor moieties or substituents on the 3-amino-9*H*-fluorene-2,4-dicarbonitrile core can easily afford the wide range photoredox potentials.

Since our AFDC-based photocatalysts demonstrated strong photoredox potentials, we deemed them suitable to facilitate reactions with a high energy barrier such as the decarboxylative C−C bond forming reactions. Decarboxylation is a critical step in biological systems and extremely useful in synthetic molecule construction. Discovering transformations that selectively target carboxylic acids as leaving groups is valuable for C−C bond forming reactions.[12] Elegant examples for the photocatalytic decarboxylative C−C coupling reactions of α-amino acids using iridium complex photocatalyst were reported by MacMillan and co-workers.[13] Therefore, we selected the decarboxylative aryl coupling reaction of protected α-amino acids **4** with aryl nitriles **5** to evaluate our small molecular photocatalysts.

Our work mechanism is proposed in Figure 2. First, irradiation of photocatalyst (**PC**) with light was intended to

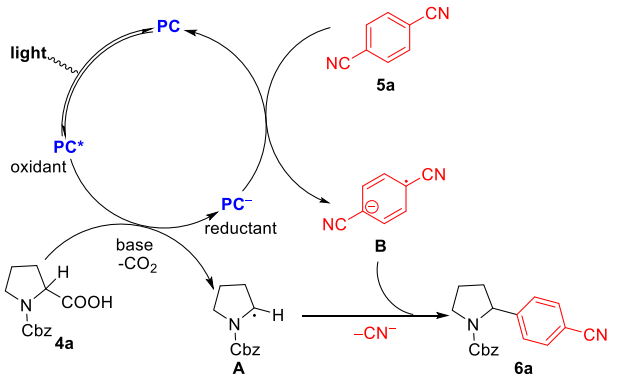
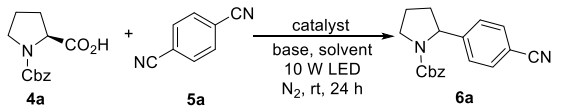



**Figure 2.** Design plan based on mechanistic considerations.

produce a photoexcited state **PC*** that is a strong oxidant (for **2a**, $E_{1/2}$(PC*/PC$^-$) = +1.30 V vs SCE). We presumed that the α-amino acid component (for Cbz-Pro-OCs, $E_{1/2}^{red}$ = +1.00 V vs SCE)[13] would be oxidized by **PC*** to form the corresponding carboxyl radical species, which should produce the α-amino radical intermediate **A** with loss of $CO_2$. Then, the reduced photocatalyst (PC$^-$) (for **2a**, $E_{1/2}$(PC/PC$^-$) = −1.70 V vs SCE) would reduce aryl nitriles such as 1,4-dicyanobenzene (**5a**) ($E_{1/2}^{red}$ = −1.53 V vs SCE)[14] via single electron transfer to form the radical anion intermediate **B**. Finally, the radical−radical coupling of **A** with **B** and subsequent aromatization with release of cyanide would deliver the benzylic amine.

Evaluation of the decarboxylative cross-coupling reaction was first investigated using Cbz-protected proline (**4a**), 1,4-dicyanobenzene (**5a**) and six AFDC-based photocatalysts **1**−**3** in the presence of $K_2HPO_4$ under irradiation from 10 W LED (390−395 nm) at room temperature (Table 1). To our delight, compounds **2a**, **2b** and **3a** could catalyze the model reaction to give a decarboxylative coupling product **6a** in 73%, 45% and 10% isolated yields, respectively (Table 1, entries 3−

**Table 1. Screening of Reaction Conditions**[a]




| entry | catalyst | light (nm) | base | solvent | yield (%) |
|---|---|---|---|---|---|
| 1 | **1a** | 390−395 | $K_2HPO_4$ | DMSO | NR |
| 2 | **1b** | 390−395 | $K_2HPO_4$ | DMSO | NR |
| 3 | **2a** | 390−395 | $K_2HPO_4$ | DMSO | 73 |
| 4 | **2b** | 390−395 | $K_2HPO_4$ | DMSO | 45 |
| 5 | **3a** | 390−395 | $K_2HPO_4$ | DMSO | 10 |
| 6 | **3b** | 390−395 | $K_2HPO_4$ | DMSO | NR |
| 7[b] | **2a** | 390−395 | $K_2HPO_4$ | DMSO | 47 |
| 8[c] | **2a** | – | $K_2HPO_4$ | DMSO | NR |
| 9[c] | – | – | $K_2HPO_4$ | DMSO | NR |
| 10 | – | 390−395 | $K_2HPO_4$ | DMSO | NR |
| 11 | **2a** | 375−380 | $K_2HPO_4$ | DMSO | 60 |
| 12 | **2a** | 385−390 | $K_2HPO_4$ | DMSO | 69 |
| 13 | **2a** | 395−400 | $K_2HPO_4$ | DMSO | 67 |
| 14 | **2a** | 390−395 | $K_2HPO_4$ | MeCN | 33 |
| 15 | **2a** | 390−395 | $K_2HPO_4$ | THF | 27 |
| 16 | **2a** | 390−395 | $K_2HPO_4$ | DMF | 68 |
| 17 | **2a** | 390−395 | $K_2HPO_4$ | DMAc | 67 |
| 18 | **2a** | 390−395 | $K_2HPO_4$ | toluene | NR |
| 19 | **2a** | 390−395 | $K_2HPO_4$ | 2,4-dioxane | NR |
| 20 | **2a** | 390−395 | $K_2HPO_4$ | acetone | NR |
| 21 | **2a** | 390−395 | CsF | DMSO | 79 |
| 22 | **2a** | 390−395 | $K_2CO_3$ | DMSO | 66 |
| 23 | **2a** | 390−395 | $Cs_2CO_3$ | DMSO | 62 |
| 24 | **2a** | 390−395 | NaOAc | DMSO | 76 |
| 25 | **2a** | 390−395 | $NaHCO_3$ | DMSO | 67 |

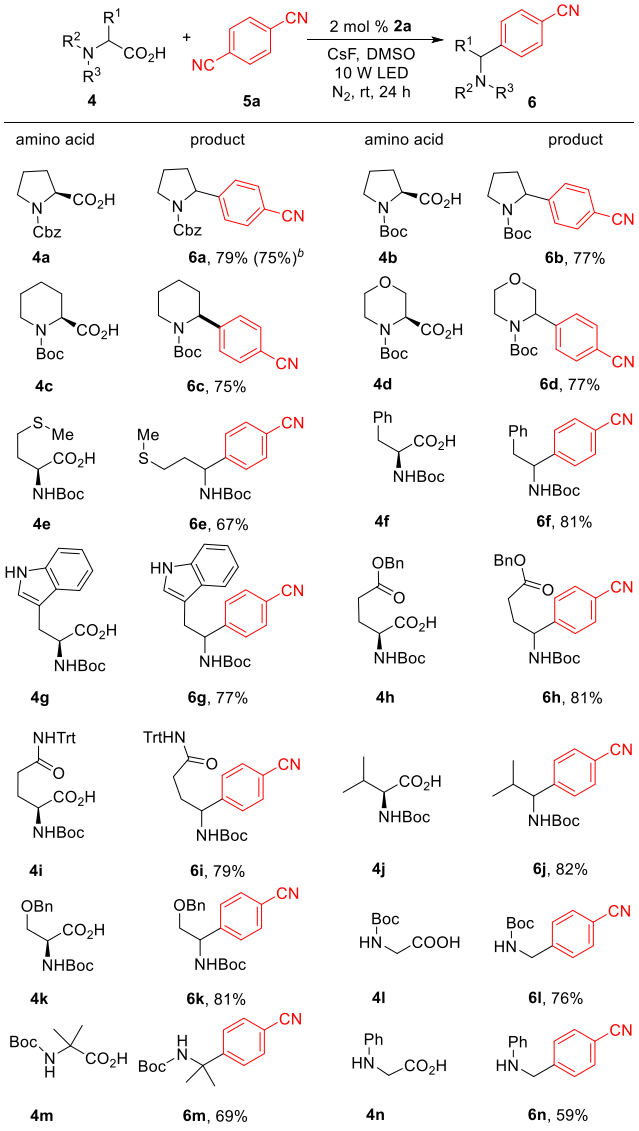
[a]Reaction conditions: **4a** (0.4 mmol), **5a** (0.2 mmol), catalyst (2 mol %), base (0.4 mmol), irradiation from 10 W LED, $N_2$ atmosphere, room temperature, 24 h; isolated yield. [b]Under an air atmosphere. [c]At 90 °C.

5). However, no reaction was observed when **1a**, **1b**, and **3b** were used as catalysts (Table 1, entries 1, 2, and 6). When the reaction was performed under an air atmosphere, a lower yield was obtained (Table 1, entry 7). Control experiments demonstrated that both the photocatalyst and light were all indispensable ingredients to achieve a successful coupling reaction (Table 1, entries 8−10). Then, we fixed **2a** as the catalyst to screen other reaction conditions. Both decreasing and increasing the light wave led to a reduction in the yield (Table 1, entries 11−13). Changing the solvent from DMSO to acetonitrile, THF, DMF, or DMAc did not further improve the reaction (Table 1, entries 14−17), while the reaction did not take place when toluene, 2,4-dioxane, and acetone were used as solvent (Table 1, entries 18−20). Finally, several other bases, such as CsF, $K_2CO_3$, $Cs_2CO_3$, NaOAc, and $NaHCO_3$, were screened (Table 1, entries 21−25), and the optimal result was obtained when CsF was used as the base (Table 1, entry 21).

After establishing the optimal reaction conditions, we next investigated the scope of amino acids for their reaction with 1,4-dicyanobenzene (**5a**). As shown in Scheme 1, all amino acid derivatives **4a**−**n** reacted smoothly with **5a** to give the corresponding products **6a**−**n** in good to high yields (59−82%). The protecting groups, such as Cbz (product **6a**), Boc (products **6b**−**l**), trityl (product **6i**), and benzyl (products **6k** and **6h**), could tolerate the reaction conditions. The α-carbon

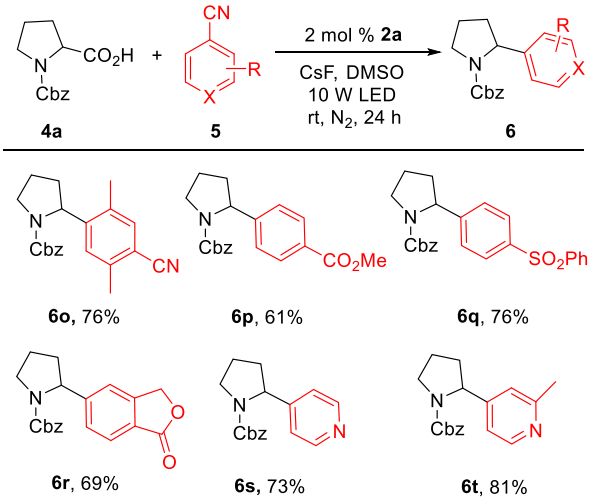

DOI: 10.1021/acs.orglett.9b00443
Org. Lett. XXXX, XXX, XXX−XXX

**Scheme 1. Scope of Amino Acids 4**[a]



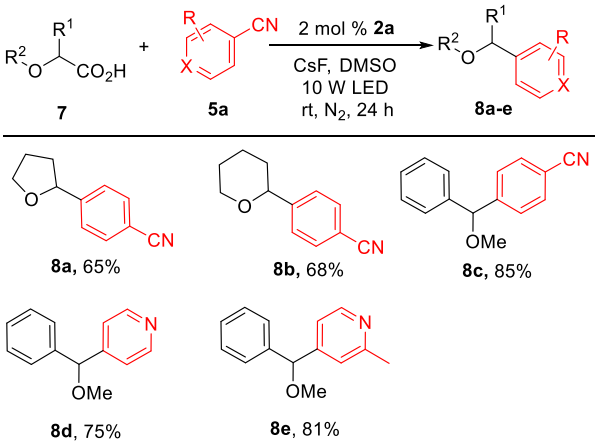

[a]Reaction conditions: **4** (0.4 mmol), **5a** (0.2 mmol), **2a** (2 mol %), CsF (0.4 mmol), DMSO (2 mL), irradiation from 10 W LED (390−395 nm), room temperature, $N_2$, 24 h; isolated yield. [b]Reaction was conducted at 1 mmol scale.

**Scheme 2. Scope of Aryl Nitriles 5**[a]




[a]Reaction conditions: **4a** (0.4 mmol), **5** (0.2 mmol), **2a** (2 mol %), CsF (0.4 mmol), DMSO (2 mL), irradiation from 10 W LED (390−395 nm), room temperature, $N_2$, 24 h; isolated yield.

**Scheme 3. Direct Arylation with α-Oxy Carboxylic Acids 7**[a]




[a]Reaction conditions: **7** (0.4 mmol), **5a** (0.2 mmol), **2a** (2 mol %), CsF (0.4 mmol), DMSO (2 mL), 10 W LED (390−395 nm), room temperature, $N_2$, 24 h; isolated yield.

of the amino acid derivative could bear two methyl groups (product **6m**) and the nitrogen atom of the α-amino could be substituted by a phenyl (product **6n**), although a relatively lower yield (59%) was obtained in the last case. It is noteworthy that this reaction could be scaled up as demonstrated by the preparation of **6a** at 1 mmol scale (75% isolated yield).

Subsequently, we examined the scope of arylnitriles under established conditions. As shown in Scheme 2, 2,5-dimethylterephthalonitrile (**5b**), methyl 4-cyanobenzoate (**5c**), 4-(phenylsulfonyl)benzonitrile (**5d**), 1-oxo-1,3-dihydroisobenzofuran-5-carbonitrile (**5e**), 4-cyanopyridine (**5f**), and 4-cyano-2-methylpyridine (**5g**) smoothly reacted with **4a** to give the corresponding products **6o−t** in 61−81% yields.

As an extension of our method, the established procedure was used for the direct arylation with α-oxy carboxylic acids **7** (Scheme 3). The reaction of tetrahydrofuran-2-carboxylic acid (**7a**), tetrahydro-2*H*-pyran-2-carboxylic acid (**7b**), and 2-methoxy-2-phenylacetic acid (**7c**) with **5a** provided the corresponding products **8a−c** in 65−85% yields. Moreover, treatment of **7c** with 4-cyanopyridines **5f** and **5g** under the standard conditions led to the desired products **8d** and **8e** with higher levels of efficiency, respectively.

We next explored the mechanism of this decarboxylative cross-coupling reaction. The Stern−Volmer experiments showed no measurable luminescence quenching of PC* (**2a**) by 1,4-dicyanobenzene (**5a**). However, cesium salt of **4a** could significantly quench the emission of PC* (see Supporting Information, Figure 7). This result supports the proposed photocatalytic cycle that is triggered from a single-electron-transfer reduction of PC* by carboxylate (Scheme 1).

In conclusion, we have demonstrated that 1-(4-(9*H*-carbazol-9-yl)phenyl)-3-amino-9*H*-fluorene-2,4-dicarbonitrile, one of AFDC-based fluorophores, is a novel and efficient photocatalyst that promotes the decarboxylative aryl coupling reaction of α-amino acids or α-oxy carboxylic acids with arylnitriles. The reaction is general for a remarkable range of



DOI: 10.1021/acs.orglett.9b00443
Org. Lett. XXXX, XXX, XXX−XXX

carboxylic acid and arylnitrile substrates. Furthermore, this method enables a plethora of benzylic amines and ethers to be prepared from easily available $\alpha$-amino acid or $\alpha$-hydroxy acid precursors.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00443.

Experimental procedures and characterization data for all new compounds (PDF)

## ■ AUTHOR INFORMATION


### Corresponding Authors

*E-mail: pinglu@zju.edu.cn.
*E-mail: orgwyg@zju.edu.cn.

### ORCID

Ping Lu: 0000-0002-3221-3647
Yanguang Wang: 0000-0002-5096-7450


### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

This work was supported by National Natural Science Foundation of China Grants Nos. 21871229 and 21632003 to P.L. and Y.G.W. The authors thank Jiarui Wang for language editing.

## ■ REFERENCES


(1) For recent reviews on the use of transition-metal complexes in photoredox catalysis, see: (a) Zhou, Q. Q.; Zou, Y. Q.; Lu, L. Q.; Xiao, W.-J. *Angew. Chem., Int. Ed.* **2018**, *57*, 2. (b) Marzo, L.; Pagire, S. K.; Reiser, O.; König, B. *Angew. Chem., Int. Ed.* **2018**, *57*, 10034. (c) Matsui, J. K.; Lang, S. B.; Heitz, D. R.; Molander, G. A. *ACS Catal.* **2017**, *7*, 2563. (d) Chatterjee, T.; Iqbal, N.; You, Y.; Cho, E. J. *Acc. Chem. Res.* **2016**, *49*, 2284. (e) Koike, T.; Akita, M. *Acc. Chem. Res.* **2016**, *49*, 1937. (f) Skubi, K. L.; Blum, T. R.; Yoon, T. P. *Chem. Rev.* **2016**, *116*, 10035. (g) Chen, J. R.; Hu, X. Q.; Lu, L. Q.; Xiao, W. J. *Acc. Chem. Res.* **2016**, *49*, 1911. (h) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. *Chem. Rev.* **2013**, *113*, 5322.

(2) For recent reviews on the usage of organic dyes in photoredox catalysis, see: (a) Romero, N. A.; Nicewicz, D. A. *Chem. Rev.* **2016**, *116*, 10075. (b) Majek, M.; Wangelin, A. J. *Acc. Chem. Res.* **2016**, *49*, 2316. (c) Nicewicz, D. A.; Nguyen, T. M. *ACS Catal.* **2014**, *4*, 355. For selected examples, see: (d) Hamilton, D. S.; Nicewicz, D. A. *J. Am. Chem. Soc.* **2012**, *134*, 18577. (e) Nguyen, T. M.; Nicewicz, D. A. *J. Am. Chem. Soc.* **2013**, *135*, 9588. (f) Perkowski, A. J.; Nicewicz, D. A. *J. Am. Chem. Soc.* **2013**, *135*, 10334. (g) Nguyen, T. M.; Manohar, N.; Nicewicz, D. A. *Angew. Chem., Int. Ed.* **2014**, *53*, 6198. (h) Romero, N. A.; Nicewicz, D. A. *J. Am. Chem. Soc.* **2014**, *136*, 17024. (i) Yajima, T.; Shigenaga, S. *Org. Lett.* **2019**, *21*, 138.

(3) For a review, see: Li, R.; Byun, J.; Huang, W.; Ayed, C.; Wang, L.; Zhang, K. A. I. *ACS Catal.* **2018**, *8*, 4735.

(4) Joshi-Pangu, A.; Lévesque, F.; Roth, H. G.; Oliver, S. F.; Campeau, L. C.; Nicewicz, D.; DiRocco, D. A. *J. Org. Chem.* **2016**, *81*, 7244.

(5) Xie, H. Y.; Han, L. S.; Huang, S.; Lei, X.; Cheng, Y.; Zhao, W. F.; Sun, H. B.; Wen, X. A.; Xu, Q. L. *J. Org. Chem.* **2017**, *82*, 5236.

(6) Huang, L.; Zhao, J. Z.; Guo, S.; Zhang, C. S.; Ma, J. *J. Org. Chem.* **2013**, *78*, 5627.

(7) Pearson, R. M.; Lim, C.-H.; McCarthy, B. G.; Musgrave, C. B.; Miyake, G. M. *J. Am. Chem. Soc.* **2016**, *138*, 11399.

(8) Ding, W.; Lu, L. Q.; Zhou, Q. Q.; Wei, Y.; Chen, J. R.; Xiao, W. J. *J. Am. Chem. Soc.* **2017**, *139*, 63.

(9) (a) Zhao, Y.; Zhang, C.; Chin, K.; Pytela, O.; Wei, G.; Liu, H.; Bureš, F.; Jiang, Z. *RSC Adv.* **2014**, *4*, 30062. (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. (e) Zhang, C.; Li, S.; Bureš, F.; Lee, R.; Ye, X.; Jiang, Z. *ACS Catal.* **2016**, *6*, 6853. (f) Lin, L.; Bai, X.; Ye, X.; Zhao, X.; Tan, C. H.; Jiang, Z. *Angew. Chem., Int. Ed.* **2017**, *56*, 13842. (g) Yin, Y.; Dai, Y.; Jia, H.; Li, J.; Bu, L.; Qiao, B.; Zhao, X.; Jiang, Z. *J. Am. Chem. Soc.* **2018**, *140*, 6083. (h) Shao, T.; Yin, Y.; Lee, R.; Zhao, X.; Chai, G.; Jiang, Z. *Adv. Synth. Catal.* **2018**, *360*, 1754. (i) Li, J.; Kong, M.; Qiao, B.; Lee, R.; Zhao, X.; Jiang, Z. *Nat. Commun.* **2018**, *9*, 2445. (j) Liu, Y.; Liu, X.; Li, J.; Zhao, X.; Qiao, B.; Jiang, Z. *Chem. Sci.* **2018**, *9*, 8094.

(10) (a) Luo, J.; Zhang, J. *ACS Catal.* **2016**, *6*, 873. (b) Patel, N. R.; Kelly, C. B.; Siegenfeld, A. P.; Molander, G. A. *ACS Catal.* **2017**, *7*, 1766.

(11) (a) Chen, Y. Y.; Peng, Z. X.; Tao, Y. H.; Wang, Z. B.; Lu, P.; Wang, Y. G. *Dyes Pigm.* **2019**, *161*, 44. (b) Chen, X. H.; Zhao, Z.; Liu, Y.; Lu, P.; Wang, Y. G. *Chem. Lett.* **2008**, *37*, 570. (c) Cui, S. L.; Lin, X. F.; Wang, Y. G. *J. Org. Chem.* **2005**, *70*, 2866.

(12) For a review on decarboxylations, see: Gooßen, L. J.; Gooßen, K.; Rodríguez, N.; Blanchot, M.; Linder, C.; Zimmermann, B. *Pure Appl. Chem.* **2008**, *80*, 1725.

(13) The reduction potential of Cbz-Pro-OCs was measured in THF following the methods in: (a) Andrieux, C. P.; Gonzalez, F.; Saveant, J. *J. Electrochem. Soc.* **2001**, *498*, 171. (b) Galicia, M.; Gonzalez, F. J. *J. Electrochem. Soc.* **2002**, *149*, D46.

(14) The reduction potential of 1,4-dicyanobenzene was measured in THF following the methods in: Mori, Y.; Sakaguchi, W.; Hayashi, H. *J. Phys. Chem. A* **2000**, *104*, 4896.




DOI: 10.1021/acs.orglett.9b00443
*Org. Lett.* XXXX, XXX, XXX−XXX