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Ad Hoc Adjustment of Photoredox Properties by the Late-Stage Diversification of Acridinium Photocatalysts

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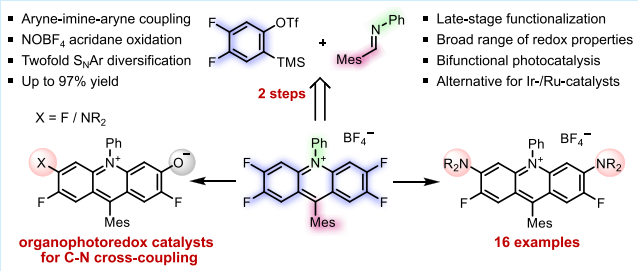
ABSTRACT: The steadily growing interest in substituting precious-metal photoredox catalysts with organic surrogates is vibrantly sustained by emerging methodologies to vary their photochemical behavior. Herein, we report an ad hoc approach for the preparation of acridinium salts with a particularly broad range of photoredox properties. The method involves an aryne−imine−aryne coupling to a linchpin tetrafluoro acridinium salt for a late-stage diversification by nucleophilic aromatic substitution reactions to form diaminoacridinium and undescribed aza-rhodol photocatalysts. The different functionalities and redox properties of the organic acridinium photocatalysts render them suitable for bifunctional photoredox catalysis and organocatalytic photochemical C−N cross-couplings.



Photoredox catalysis has markedly impacted organic chemistry as a transformative strategy for molecular functionalization.[1−3] In particular, the catalytic generation of open shell intermediates under mild reaction conditions provides a continuous impetus for conceptual advances in synthetic methodology. Due to their favorable photophysical features, ruthenium and iridium polypyridyl complexes thereby emerged as the most suitable photocatalysts (PCs).[4,5] However, their high price and the scarcity of precious metals prompt the utilization of organic photocatalysts as a sustainable alternative.[6−8] In recent findings, acridinium salts, introduced by Fukuzumi and refined by Nicewicz,[9,10] stand out as a particularly advantageous class of organic photocatalysts.[11] To access prototypical acridinium photocatalysts, addition reactions to acridones (**A**)[12−14] and Bernsthen-type reactions (**B**) are regularly applied (Scheme 1a).[15] To expand the diversity of acridinium catalysts, our group developed a route starting from esters using 1,5-bifunctional organometallic reagents (**C**)[16,17] while another recent approach implements the conversion of xanthylium salts (**D**).[18] Owing to the distinct modularity of acridinium salts, the photophysical properties can be significantly tuned by structural modifications using these catalyst preparation methodologies.[19] In particular, residues directly attached to the acridinium core (R^2 and R^3), such as amino or methoxy groups, were found to exert strong electronic effects, thereby suitably impacting the photoredox behavior of the catalysts. However, contemporary methods require the early introduction of these functionalities, necessitating multistep syntheses to alter the photoredox behavior.

We therefore envisioned that the elegant aryne−imine−aryne coupling through aza-*o*-quinone methides **II** formed from 1,2-dihydrobenzoazete **I** as reported by Yoshida et al.[20] coupled with an acridane oxidation and a versatile double late-stage diversification of tetrafluoro acridinium salts by nucleophilic aromatic substitutions (S_NAr) would enable the ad hoc adjustment of the photoredox properties of acridinium catalysts **1** (Scheme 1b). While fluorine groups at the heterocyclic core were considered ideal as leaving groups for the S_NAr diversifications, it was expected that imines with a bulky mesityl group both prevent undesired 6π-electrocyclizations[20] and photobleaching of the anticipated catalysts.[9]

To explore the feasibility of our concept, we thus started with the preparation of the tetrafluorinated acridinium salt **4**, which serves as a linchpin intermediate for the crucial late-stage diversifications (Scheme 2). Using readily available compounds **2** and **3**, we embarked on optimizing the aryne−imine−aryne coupling and the ensuing acridane oxidation to form key intermediate **4** (Table S1; see the Supporting Information for details).

The highest yields for the aryne−imine−aryne coupling were achieved with cesium fluoride in acetonitrile, whereas nitrosonium tetrafluoroborate proved to be the most efficient reagent for the oxidation step. Interestingly, only a few examples of the application of nitrosonium salts for acridane oxidations are described in the literature,[21] while the treatment

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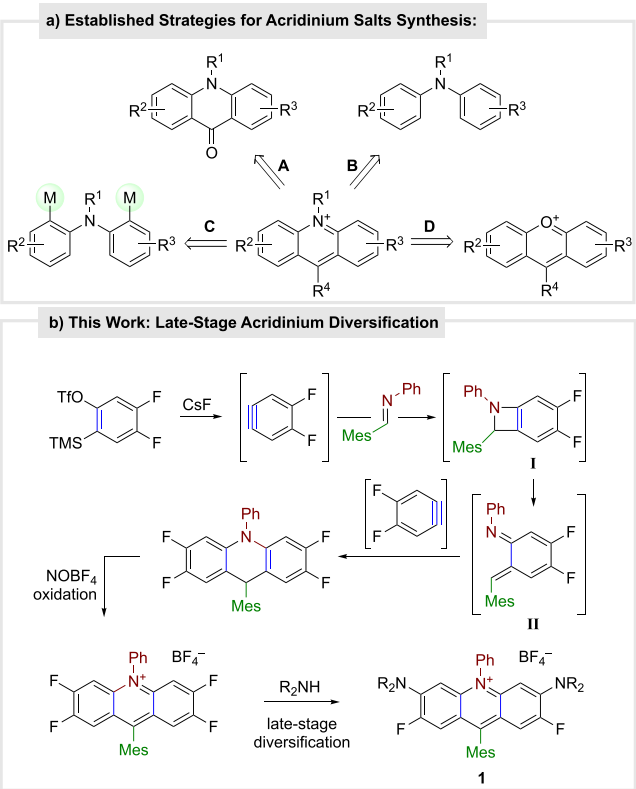
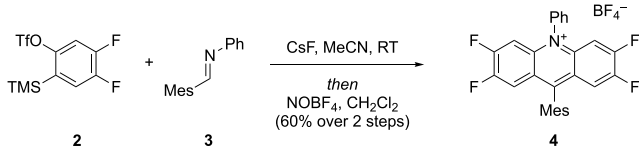
Scheme 1. Background and Acridinium Diversification



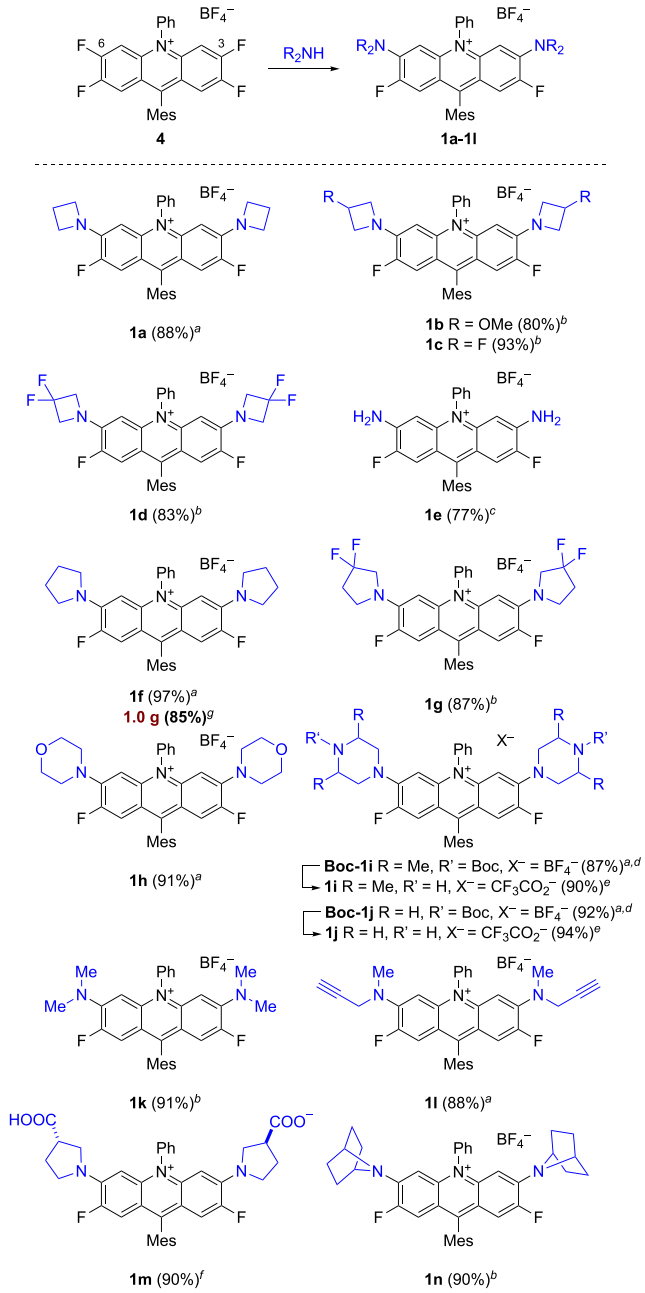
Scheme 2. Substrate Synthesis



of the acridane with chloranil, air, MnO_2, and Bobbitt's salt resulted in either decomposition or unreacted starting material. After optimization, the two steps allowed short reaction times, an unproblematic isolation, and thus an operationally simple synthetic protocol toward the tetrafluoroacridinium salt **4** (Scheme 2).

Having acridinium intermediate **4** in hand, we focused our attention on the pivotal acridinium late-stage functionalization reactions. To test our notion of the disposition of the fluorinated acridinium core to nucleophilic attack, enabling the ad hoc preparation of photophysically distinct acridinium derivatives, we began with substitution reactions using azetidine (Scheme 3). Gratifyingly, an efficient 2-fold S_NAr at the most electrophilic positions (C3 and C6) was observed within 1 hour at ambient temperature, yielding desired diazetidine product **1a** in 88% yield. Interestingly, neither reduced amounts of amine nor substantial dilution led to monosubstitution. To determine the scope of this method, various amines were next subjected to the reaction. To our delight, the reactions proceeded smoothly, giving rise to the desired acridinium photocatalysts in excellent yields. Azetidines with fluorine and methoxy groups, which considerably alter the electronic properties, were readily introduced (**1a**−**d**). Furthermore, free amino groups were also installed by using ammonia in dioxane (**1e**). Nonetheless, all attempts to add

Scheme 3. Substrate Scope



[a−g]Yields of isolated products. Conditions: [a]**4** (47.0 μmol), R_2NH (188 μmol), CH_2Cl_2 (1.4 mL), rt; [b]**4** (47.0 μmol), $R_2NH{\cdot}HCl$ (470 μmol), Cs_2CO_3 (470 μmol), CH_3CN (3.3 mL), rt; [c]**4** (47.0 μmol), NH_3 (188 μmol, 0.5 M, dioxane), THF (1.5 mL); [d]**4** (90.0 μmol), R_2NH (360 μmol); [e]Boc-**1i** or Boc-**1j** (20 μmol), TFA (2.0 mL), CH_2Cl_2 (0.5 mL); [f]**4** (47.0 μmol), R_2NH (188 μmol), NEt_3 (94.0 μmol), CH_2Cl_2 (6.0 mL)/THF (2.0 mL), rt; [g]**4** (1.9 mmol).

arylamines resulted in undetectable conversions. On the contrary, selective reactions were observed for the 2-fold addition of pyrrolidines to provide **1f** or **1g** and also a gram-scale synthesis of diaminoacridinium catalyst **1f** was feasible (85% yield). The nucleophilic aromatic substitution with morpholine and Boc-piperazine led to a yield of ≥90%, and Boc deprotection reactions were readily achieved. Acyclic amines were also efficiently introduced (**1k**, 91%) even with propargylic moieties (**1l**, 88%), and the double substitutions of

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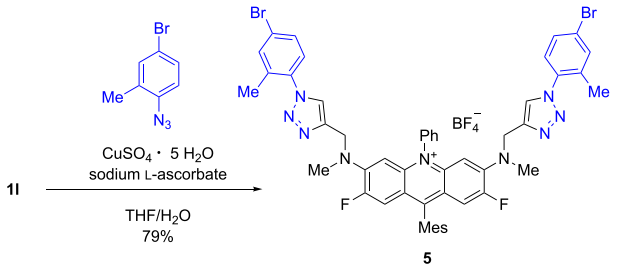
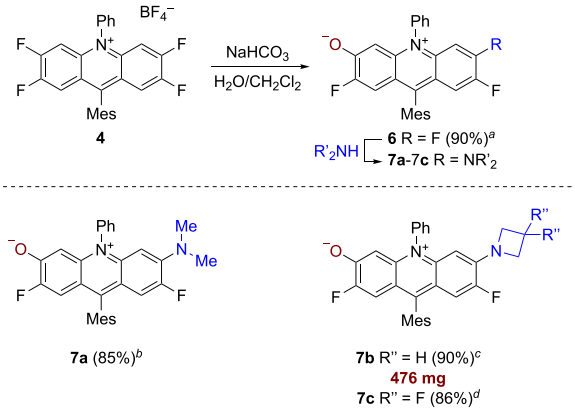
L-β-proline and 7-azabicyclo[2.2.1]heptane both proceeded with 90% isolated yield. Notably, compounds **1l** and **1m** comprise reactive functional groups that allow further manipulations, giving access to an even broader scope of applications. Indeed, acridinium salt **1l** could be effortlessly coupled by an azide−alkyne click reaction under standard conditions (Scheme 4).[22] No other side products were observed after the 2-fold copper-catalyzed cycloaddition, and the desired bis-triazole acridinium compound **5** was isolated in 79% yield.

Scheme 4. Double Click Reaction with an Acridinium Salt



Captivatingly, aza-rhodols, a novel class of acridinium photoredox catalysts, could be prepared likewise by the late-stage functionalization strategy. A remarkable monohydrolysis of the linchpin tetrafluoro acridinium intermediate **4** was observed with aqueous sodium bicarbonate [**6**, 90% (Scheme 5)]. This oxygenation of the heterocycle combined with amine

Scheme 5. Synthesis of Aza-Rhodol Photoredox Catalysts



[a−d]Yields of isolated products. [b−d]Yield over two steps. Reaction conditions: [a]**4** (47.0 μmol), CH_2Cl_2 (2.0 mL)/$NaHCO_3$ (2.0 mL), rt, 18 h; [b]**6** (30.0 μmol), R_2NH (6.00 mmol), THF (4.0 mL), 24 h; [c]**4** (1.10 mmol), CH_2Cl_2 (50 mL)/$NaHCO_3$ (100 mL), rt, 18 h, then CH_2Cl_2 (50 mL), R_2NH (15.7 mmol), 1 h, rt; [d]**6** (30.0 μmol), $R_2NH\cdot HCl$ (3.00 mmol), Cs_2CO_3, CH_3CN (4.0 mL).

S_NAr reactions gave rise to aza-rhodols **7a−7c** in high overall yields. Moreover, the efficacy of this methodology was confirmed by the preparation of **7b** on a 1.1 mmol scale (90% yield).

We next examined the photophysical and electrochemical properties of acridinium salts **1a−1n**, **4**, **6**, and **7a−7c** (Table 1; see Table S4 for full details). With time-correlated single-photon counting, we were pleased to observe fluorescence lifetimes that were sufficient for photoredox catalysis for all aminoacridinium salts. Remarkably, the unique diversity of the

Table 1. Spectrophotometric and Electrochemical Data

PC[a]	$E_{0,0}$ (eV)	$E_{1/2}$(PC/PC$^-$) (V)[b]	$E_{1/2}$(PC*/PC$^-$) (V)	τ(^{1}PC) (ns)
1a	2.40	−0.98	+1.42	3.7
1b	2.42	−0.94	+1.48	3.4
1c	2.45	−0.89	+1.56	3.4
1d	2.50	−0.80	+1.70	3.2
1e	2.63	−0.99	+1.64	3.9
1f	2.37	−0.97	+1.40	0.6 (89%)
1g	2.48	−0.85	+1.61	5.1 (54%)
1h	2.38	−0.73	+1.65	5.4 (96%)
Boc-1i	2.37	−0.73	+1.64	4.7 (56%)
Boc-1j	2.38	−0.73	+1.65	4.3 (59%)
1k	2.39	−0.89	+1.50	3.1 (89%)
1l	2.46	−0.75	+1.71	4.4 (64%)
1m	2.37	−1.06[c]	+1.31	1.4 (48%)
1n	2.40	−0.81	+1.59	4.2
4	2.35	−0.33	+2.02	5.9 (76%)
6	2.35	−1.20	+1.15	5.4
7a	2.40	−1.36	+1.03	5.02
7b	2.42	−1.41	+1.01	4.8
7c	2.40	−1.36	+1.03	5.4 (95%)

[a]λ_{max}(abs) from 458 to 513 nm; λ_{max}(em) from 494 to 551 nm; ε_{max} from 1.5×10^3 to 7.2×10^4 L mol^{-1} cm^{-1}. See the Supporting Information for the full photophysical data of the catalysts. [b]Measured in 0.1 mol L^{-1} n-Bu_4NPF_6 in degassed, dry MeCN against SCE. [c]Measured in 0.1 mol L^{-1} n-Bu_4NPF_6 in degassed, dry CH_3OH against SCE.

catalysts is significantly reflected by the exceptionally broad range of excited state redox potentials from an $E_{1/2}$(PC*/P$^-$) of +1.01 V (**7b**) to an $E_{1/2}$(PC*/PC$^-$) of +2.02 V (**4**). While diamino-substituted (**1a−1n**) and unsymmetric acridinium catalysts (**6** and **7a−7c**) possess redox potentials similar to those of the transition-metal-based photocatalysts [Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)]PF$_6$ [$E_{1/2}$(PC/PC$^-$) = −1.37 V; $E_{1/2}$(PC*/PC$^-$) = +1.21 V vs SCE],[6] compound **4** shows redox potentials close to that of the Fukuzumi system [MesMeAcr$^+$BF$_4^-$; $E_{1/2}$(PC/PC$^-$) = −0.57 V; $E_{1/2}$(PC*/PC$^-$) = +2.06 V vs SCE].[15] It is thus worth pointing out that an increase in the electron-withdrawing nature of the substituents at the amine moiety generally leads to a stronger oxidative character of the excited photocatalysts, as observed for compounds **1a**, **1c**, and **1d** (Table 1). On the other hand, aza-rhodols **7a−7c** possess $E_{1/2}$(PC*/PC$^-$) and $E_{1/2}$(PC/PC$^-$) values considerably lower than those of prior diaminoacridinium dyes,[16,19] making them suitable for transformations that were unfeasible with preceding acridinium photocatalysts.

Since the diversification enabled the preparation of acridinium photocatalysts containing a variety of functional groups, including free amines (**1i** and **1j**), we explored the feasibility of an unprecedented bifunctional photocatalysis approach. Inspired by the elegant work of Akita and co-workers,[23] we thus studied the α-oxyamination of aldehydes previously utilizing a combination of amine and photoredox catalysts. To investigate bifunctional amine/acridinium catalysis (Table 2),[24] the activity of **1i** was compared to that of **1f** in combination with secondary amines. However, the methyl groups in **1i** and 2,6-dimethylpiperidine strongly hampered conversion. In contrast, **1f** together with morpholine as well as bifunctional aminoacridinium catalyst **1j** showed excellent catalytic activity. Under optimized conditions, full conversion

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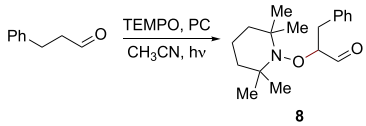
Table 2. Catalytic α-Oxyamination of Aldehydes



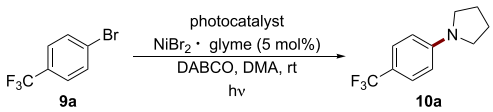
entry[a]	PC	amine	conversion[b] (%)
2	**1i** (8%)	–	25
3	**1f** (8%)	2,6-dimethylpiperidine (16%)	28
4	**1f** (5%)	morpholine (5%)	100
5	**1j** (5%)	–	83
6[c]	**1j** (6%)	–	100 (84)[d]

[a]*hν*, Kessil LED A160WE, 40 W (λ_{max} = 464 nm). Reaction conditions: aldehyde (50.0 μmol), TEMPO (100 μmol), CH_3CN (0.5 mL), Ar, 18 h. [b]Determined by NMR. [c]At 24 h; *hν*, SynLED parallel photoreactor (λ = 465−470 nm). [d]Isolated yield.

and an isolated yield of 84% were conclusively obtained, confirming the aptitude of acridinium **1i** to serve as a bifunctional catalyst.

Owing to the suitably low $E_{1/2}(PC^*/PC^-)$ of aza-rhodol photocatalysts **7a**−**7c**, the scope for acridinium photocatalysis was distinctly expanded. These favorable properties are deemed advantageous for various catalytic applications, such as the photoredox catalytic C−N cross-coupling requiring sufficiently reducing photocatalysts [$E_{1/2}(PC/PC^-) \leq -1.26$ V] for precatalyst reduction [$E_i(Ni^{II}/Ni^{I}) = -1.43$ V].[25−27] As benign alternatives to Ir and Ru catalysts,[28] aza-rhodols **7a**−**7c** with suitable redox properties were investigated (Table 3; see

Table 3. Comparison of Photoredox C−N Cross-Couplings



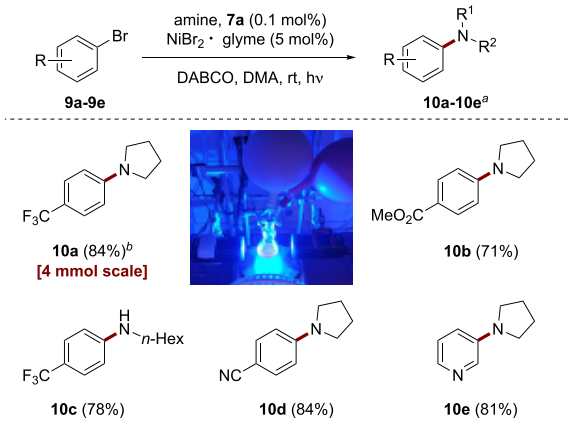
entry[a]	PC	yield[b] (%)
1	di-*t*Bu-Mes-Acr$^+BF_4^-$ (0.1%)	8
2	$Ir[dF(CF_3)ppy)]_2(dtbpy)PF_6$ (0.02%)	85
3	**7a** (0.02%)	75
4	**7a** (0.1%)	98
5	**1f** (0.1%)	15

[a]*hν*, SynLED parallel photoreactor (λ = 465−470 nm). Reaction conditions: **9a** (200 μmol), pyrrolidine (600 μmol), $NiBr_2$·glyme (10.0 μmol), DABCO (360 μmol), DMA (1.0 mL), Ar, rt, 36 h. [b]Determined by NMR using durene as the standard.

Table S3 for details). In the reaction of aryl bromide **9a** with pyrrolidine, a comparison of photocatalyst (di-*t*Bu-Mes-Acr$^+BF_4^-$),[3] $Ir[dF(CF_3)ppy]_2(dtbpy)PF_6$, aza-rhodol **7a**, and diaminoacridinium **1f** indicated the suitabilty of **7a** to serve as an alternative to precious metallaphotoredox catalysts.

With optimized conditions in hand, we explored the practicality and generality of aza-rhodol catalysis using different substrates (Scheme 6). We were pleased to observe that products **10a**−**10e** were obtained with good to excellent yields and that the robustness was confirmed by the synthesis of compound **10a** on a 4.0 mmol scale. Because oxygen and amino substituents are readily introduced during the final step, we envisage that precisely adjusted acridinium photoredox catalysts allow applications for a captivating variety of photoredox reactions.

Scheme 6. Organophotoredox C−N Cross-Coupling



Reaction conditions: aryl halide (200 μmol), pyrrolidine (600 μmol), $NiBr_2$·glyme (10.0 μmol), DABCO (360 μmol), **7a** (0.20 μmol), DMA (1.0 mL), Ar, rt, 36 h; *hν*, SynLED Parallel Photoreactor (λ = 465−470 nm). [a]Isolated yields. [b]On a 4 mmol scale; *hν*, two Kessil LED A160WE, 40 W, λ_{max} = 464 nm.

In summary, we have developed a late-stage diversification strategy toward acridinium salts involving an aryne−imine−aryne coupling, acridane oxidation, and a versatile nucleophilic aromatic substitution reaction. The approach thereby provided 20 acridinium catalysts with a particularly broad range of redox potentials. Because of the mild reaction conditions, various functional groups were tolerated and high yields were obtained. The novel route to acridinium salts allowed the synthesis of bifunctional catalysts to efficiently merge amine and photoredox catalysis. Furthermore, the late-stage diversification approach opened access to aza-rhodol photocatalysts with uniquely low $E_{1/2}(PC/PC^-)$ values, enabling the replacement of precious-metal complexes in photoredox C−N cross-couplings.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01673.

Experimental details and characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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