Modulation of Acridinium Organophotoredox Catalysts Guided by Photophysical Studies

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ABSTRACT: Control over redox states and spin multiplicity of photocatalysts throughout a catalytic cycle is crucial for selective and efficient photocatalytic processes. However, the rational design of photocatalysts is often hampered by the mechanistic complexity and low modularity of catalyst structure. Herein, we demonstrate a photophysical study of diverging photocatalytic pathways that guides the design of organic acridinium catalysts to complement polypyridyl transition metal systems. A combined halogen-metal exchange / directed ortho-metalation provides reagents for a broad range of modular acridinium catalysts with fine-tuned photophysical and photochemical properties such as excited-state lifetimes, redox potentials and photostabilities poised to refine organocatalytic photoredox methodology.

KEYWORDS: acridinium salts, catalyst design, energy transfer, metalation, photoredox catalysis

INTRODUCTION

Synthetic methodology via radical intermediates has witnessed a dramatic advance by the advent of preparative visible light photoredox catalysis. A broad range of radical disconnections and mild reaction conditions allowed progressive retrosynthetic planning, expeditiously embraced by academic and industrial laboratories. The resulting versatility of visible light photoredox catalysis is reflected by numerous new reaction types developed within the last ten years. A majority of these methods rely on poly(pyridyl) transition metal complexes and in particular ruthenium and iridium catalysts. While poly(pyridyl) systems can be readily modulated by changes in the ligand structure, organic photocatalysts, which render photoredox methods sustainable and more amenable to scale up, remain limited in their tunability. However, compared to poly(pyridyl) ligand modulations, molecular scaffold variation of organic photoredox catalysts requires the development of more general synthetic methods and therefore, most transition metal complex catalyzed reactions are yet not complemented by organocatalytic methods.

For instance, the acridinium organophotoredox catalysts introduced by Fukuzumi and further developed by Nicewicz are now established as particularly valuable catalytic motifs for preparative organic synthesis, but their traditional assembly severely limits synthetic modularity. Recently, we developed a method to access acridinium salts directly from carboxylic acid esters and observed the interesting photoredox activity of diaminoacridinium salt I in a Ni-promoted cross-coupling reaction (Scheme 1, top pathway). This finding and the captivating prospect of a modular organophotocatalyst synthesis prompted us to devise a detailed understanding of the photophysical characteristics of I, guiding a versatile heterocycle synthesis towards broadly applicable acridinium catalysts. A comparative study of the novel acridinium catalysts together with prototypical organic photocatalysts furthermore underlines the significance of complementarity in photoredox catalysis.

RESULTS AND DISCUSSION

We initiated our studies with the dual catalytic decarboxylative cross coupling and an array of most commonly employed organocatalysts was compared to the acridinium system I. Notably, selectivity for the photoredox process to give A was observed exclusively for diaminoacridinium catalyst I. With a large number of other routinely used organic photocatalysts such as eosin Y, a diverging photophysical triplet-triplet energy transfer (TTET) pathway to sensitize nickel(II) species provided O-aryl ester B with up to 96% yield (Scheme 1, bottom pathway). Furthermore, with established highly oxidizing acridinium catalysts such as mesityl-2,7-dimethyl-10-phenylacridinium or the Fukuzumi catalysts, either a mixture of photoredox- and TTET products (A 16% vs. B 16%) or no product formation at all were observed. Given the unique reactivity of the diaminoacridinium system catalyzing the selective formation of decarboxylated A, comparative DFT computations of I and the Fukuzumi catalyst were performed, revealing the fundamentally different nature of lowest energetic electronic transitions in these two compounds (Figure 1).
photochemistry of mation devoid of competitive reaction discussed below.

In contrast to those highly oxidizing properties often resulting in compromised yields, excited 1 with its less energetic π-π* states is well suited for dual catalysis with nickel and compatible with the components of a complex reaction mixture.

Interestingly, a triplet energy (ET) for 1 of 1.89 eV was estimated by computation, which is identical to the triplet energy of eosin Y (1.89 eV). Since the triplet sensitization of aryl nickel carboxylates requires an ET of >1.85 eV, both photocatalysts would be thermodynamically capable of promoting ester formation via their triplet excited states. On the other hand, only the singlet states of both catalysts (ES: 2.40 eV/2.30 eV) which can both provide an excited-state reduction potential of about +1.25 V vs. SCE, would allow the oxidation of the carboxylate. We therefore envisaged that these comparable driving forces, for both triplet sensitization of the intermediate nickel complex and excited singlet state quenching by electron transfer from carboxylates, provide a suitable platform to differentiate the relative contributions and kinetics of singlet and triplet excited states.

Employing laser flash photolysis (LFP) studies, we first observed a long-lived (τ: 330 μs) species after green laser excitation of 1 (Figure 2); its TTET reactivity towards aromatic hydrocarbons such as anthracene (as opposed to the Fukuzumi catalyst, which undergoes electron transfer) allowed us to identify that species as the triplet state of 1 (see SI page S5 for details). Quantitative LFP experiments on the sensitized "anthracene formation with 1 as energy donor gave an ISC (triplet) quantum yield for 1 of about 7%. A kinetic analysis of our TTET experiments finally yielded the experimental triplet energy of the acridinium dye 1 (1.91 eV), which is very close to the calculated value (see above). Compared to eosin Y (triplet quantum yield of 80%) whose triplet is usually considered as photoactive species, the importance of the excited singlet state of acridinium photoredox catalysts can be further substantiated in agreement with the studies by Nicewicz as discussed below. Nevertheless, in a photochemical transformation devoid of competitive reaction pathways, the triplet photochemistry of 1 remains operative for a classical stilbene photoisomerisation giving the cis isomer in 71% yield. This conclusion is borne out by LFP studies on the TTET reaction between 3* and pyrene, which has almost the same triplet energy as trans-stilbene, and the fact that singlet excited 1 cannot oxidize stilbene for thermodynamic reasons.

Based on these photochemical considerations, we conclude that in comparison to eosin Y, both the lower triplet quantum yield of 1 and the higher kinetic reactivity of its excited singlet state for carboxylate oxidation give rise to the divergent pho-
tocatalytic reaction pathways illustrated in Scheme 1. Guided by the notable photophysical differences between the aminoa
cridinium system 1 and the established Fukuzumi and Nicewicz
catalysts, we set out to explore the generality of these charac
teristics with an entirely modular acridinium core structure
assembly, providing a wide range of redox properties akin to
Ir- and Ru-catalysts. In contrast to our double X-M exchange\textsuperscript{ab} reactions to 3,6-diamino- and the double directed ortho-
metalation methods (dDoM) giving 1,8-dimethoxy-acridinium
salts,\textsuperscript{abc} we investigated an integrated synthesis of amino- and
methoxy-acridinium salts by combining X-M exchange and
DoM processes (Table 1).

**Table 1: Modular synthesis of amino- and methoxy-
acridinium salts\textsuperscript{a}\**

<table>
<thead>
<tr>
<th>Product \textsuperscript{b}</th>
<th>Product \textsuperscript{b}</th>
<th>Product \textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="" /> 4a, 98%</td>
<td><img src="image2" alt="" /> 4e, 71%</td>
<td><img src="image3" alt="" /> 4i, 78%</td>
</tr>
<tr>
<td><img src="image4" alt="" /> 4b, 53%</td>
<td><img src="image5" alt="" /> 4f, 74%</td>
<td><img src="image6" alt="" /> 4j, 95%</td>
</tr>
<tr>
<td><img src="image7" alt="" /> 4c, 78%</td>
<td><img src="image8" alt="" /> 4g, 91%</td>
<td><img src="image9" alt="" /> 4k, 78%</td>
</tr>
<tr>
<td><img src="image10" alt="" /> 4d, 71%</td>
<td><img src="image11" alt="" /> 4h, 76%</td>
<td><img src="image12" alt="" /> 4l, 94%</td>
</tr>
</tbody>
</table>

\textsuperscript{a} The combined DoM/Br-Li exchange was carried out with 2a-e (160 µmol) in a mixture of Et\textsubscript{2}O (200 µL) and n-hexane (2.0 mL) with n-BuLi at 65°C for 6 h. Ester substrates (100 µmol) were treated with resulting reagents 3a-e at a temperature of -20°C and for 12 h at RT followed by aqueous work-up with HBr.

\textsuperscript{b} Isolated yields.

Di- or triaryl amines 2a-e bearing a directing group and bro
mide with or without amino substituents at distinct positions are readily accessible, rendering this method particularly ver
satile.\textsuperscript{10} Gratifyingly, the combined X-M exchange/DoM
double metalation with n-BuLi at 65°C afforded 1,5-dilithium
organyls 3a-e, that convert various esters into a broad range of
unsymmetric acridinium salts 4a-l.

To our delight, the reagent from the combined X-M ex
change/DoM double metalation gave the phenyl acridinium
product 4a in an excellent yield of 98% and also the sterically
demanding mesityl and vic.-m-xylyl substituted products were
reliably obtained (4e, 4i). Interestingly, both the dimethyla
mino- and the triarylamino substitution further improved the
reaction outcome (4a vs. 4b and 4c vs. 4h) and even provided
atropisomeric\textsuperscript{10,16} 1-naphthyl substituted acridinium products
in high yields (4f, 4j, 4l). We next investigated the photophy
sical and electrochemical properties of the products. The sin
glet-excited states of all catalysts possess lifetimes of a few
nanoseconds, which is long enough for bimolecular substrate
activations. Notably, we observed catalyst tunability in terms
of oxidative character in their excited state (Table 2). In
agreement with an adjustable π-π* transition character be
tween the frontier orbitals of the catalysts (as in Figure 1), the
novel acridinium dyes 4a-l span a wide range of triplet ener
gies (ET) and excited state reduction potentials from E_{1/2}(P*/P) = +1.81 V (4b) over E_{1/2}(P*/P) = +1.40 V (4h and 4j) simi
lar to Ru(bpz)\textsubscript{2}\textsuperscript{2+}, to E_{1/2}(P*/P) = +1.19 V vs. SCE (4l) with an
even lower E_{1/2}(P*/P) than Ir[dF(CF\textsubscript{3})ppy\textsubscript{2}(dtbbpy)] (E_{1/2}(P*/P) = +1.21 V).

**Table 2: Photophysical and electrochemical properties of the catalysts**

<table>
<thead>
<tr>
<th>Dye</th>
<th>E\textsubscript{1/2} \textsuperscript{+} [eV]</th>
<th>E\textsubscript{1/2} \textsuperscript{–} [eV]</th>
<th>E\textsubscript{1/2}(P*/P) \textsuperscript{+} [V]</th>
<th>E\textsubscript{1/2}(P*/P) \textsuperscript{–} [V]</th>
<th>τ \textsuperscript{+} [ns]</th>
<th>HOMO-LUMO transition \textsuperscript{a}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1\textsuperscript{aa}</td>
<td>2.40</td>
<td>1.89</td>
<td>-1.15</td>
<td>+1.25</td>
<td>2.2</td>
<td>π-π*</td>
</tr>
<tr>
<td>4a</td>
<td>2.30</td>
<td>1.91</td>
<td>-0.83</td>
<td>+1.47</td>
<td>0.9, 4.4</td>
<td>π-π*</td>
</tr>
<tr>
<td>4b</td>
<td>2.29</td>
<td>1.76</td>
<td>-0.48</td>
<td>+1.81</td>
<td>1.0, 3.0, 17.3</td>
<td>π-π*</td>
</tr>
<tr>
<td>4c</td>
<td>2.23</td>
<td>1.75</td>
<td>-0.54</td>
<td>+1.69</td>
<td>1.0, 9.9</td>
<td>π-π*</td>
</tr>
<tr>
<td>4d</td>
<td>2.25</td>
<td>1.76</td>
<td>-0.57</td>
<td>+1.68</td>
<td>1.4, 12.1</td>
<td>mixed</td>
</tr>
<tr>
<td>4e</td>
<td>2.25</td>
<td>1.75</td>
<td>-0.56</td>
<td>+1.69</td>
<td>1.2, 3.3, 16.8</td>
<td>mixed</td>
</tr>
<tr>
<td>4f</td>
<td>2.26</td>
<td>1.74</td>
<td>-0.53</td>
<td>+1.73</td>
<td>1.0, 4.5</td>
<td>CT</td>
</tr>
<tr>
<td>4g</td>
<td>2.29</td>
<td>1.90</td>
<td>-0.89</td>
<td>+1.40</td>
<td>1.0, 6.9</td>
<td>π-π*</td>
</tr>
<tr>
<td>4h</td>
<td>2.29</td>
<td>1.91</td>
<td>-0.89</td>
<td>+1.40</td>
<td>1.1, 6.8</td>
<td>π-π*</td>
</tr>
<tr>
<td>4i</td>
<td>2.29</td>
<td>1.91</td>
<td>-0.90</td>
<td>+1.39</td>
<td>1.1, 7.2</td>
<td>π-π*</td>
</tr>
<tr>
<td>4j</td>
<td>2.27</td>
<td>1.88</td>
<td>-0.87</td>
<td>+1.40</td>
<td>1.0, 6.2</td>
<td>mixed</td>
</tr>
<tr>
<td>4k</td>
<td>1.94</td>
<td>1.17</td>
<td>-0.71</td>
<td>+1.23</td>
<td>1.5, 5.3</td>
<td>π-π*</td>
</tr>
<tr>
<td>4l</td>
<td>1.87</td>
<td>1.14</td>
<td>-0.68</td>
<td>+1.19</td>
<td>0.9, 5.0</td>
<td>π-π*</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Measured in MeCN (15 µmolL\textsuperscript{–}1). \textsuperscript{b} DFT calculation, experimental ET for 1: 1.91 eV. \textsuperscript{c} Measured in 0.1 µmolL\textsuperscript{–}1 n-BuNPF\textsubscript{6} in degassed, dry MeCN against SCE. \textsuperscript{d} Details are described in the SI.\textsuperscript{10}
As a rule of thumb, the introduction of NMe₂ substituents lowers the E₁/₂(P*/P) by 0.3–0.4 V and OMe groups by 0.1–0.2 V, while differences in substitution patterns show an expected strong influence on the redox behavior.

To test the performance of the modular acridinium catalysts, we comparatively investigated the decarboxylative fluorination of substrates 5a and 5b (Scheme 2). Gratifyingly, the diaminoacridinium catalyst 1 allowed to reduce the reaction time to convert 5a from 60 h to 6 h and to halve the catalyst loading to 2.5 mol% with respect to previous organocatalytic methods,²⁶ approaching the efficiency of optimized polypyridyl Ir-catalysts (1 mol%).²⁶ Interestingly, the complementarity to known acridinium catalysts (47–52%)¹⁰ and donor-acceptor cyanophenyl photocatalysts was particularly evident (4CzIPN, 65%).¹⁷ Cognizant of the complex interplay of the numerous catalyst properties impacting their performance, tentative correlations indicate the merits of a library based on an identical core structure. The yield was found to increase from 58% with catalyst 4e (E₁/₂(P/P⁺) = -0.56 V; E₁/₂ (P*/P) = +1.69 V), 75% with 6-aminoacridinium 4h (E₁/₂(P/P⁺) = -0.89 V; E₁/₂ (P*/P⁺) = +1.40 V) to 80% with catalyst 1 (E₁/₂(P/P⁺) = -1.15 V; E₁/₂ (P*/P⁺) = +1.25 V), whereas the Fukuzumi catalyst, 4d and 4e appear as too strongly oxidizing for this multicomponent system.

Table 3: Impact of modularity for acridinium-catalyzed cross couplings

<table>
<thead>
<tr>
<th>Dye</th>
<th>A (%)</th>
<th>B (%)</th>
<th>Dye</th>
<th>A (%)</th>
<th>B (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>86%</td>
<td>-</td>
<td>4h</td>
<td>57%</td>
<td>5%</td>
</tr>
<tr>
<td>4d</td>
<td>-</td>
<td>3%</td>
<td>4i</td>
<td>75%</td>
<td>6%</td>
</tr>
<tr>
<td>4e</td>
<td>-</td>
<td>9%</td>
<td>4k</td>
<td>-</td>
<td>8%</td>
</tr>
</tbody>
</table>

² Dual catalytic cross coupling as shown in Scheme 1.

Notably the differences of 1 and the Fukuzumi catalyst observed in the photophysical study were also confirmed in stilbene isomerization reactions using 4a-4i and a dimethylacridinium catalyst,¹⁴ resulting in significant variation of the isomerization efficiency (17–84%) yield for cis-stilbene, Table 4).¹⁰ While the distinction between TTET (triplet mechanism)⁹ and electron transfer driven (radical cation mechanism)²⁰ stilbene isomerization remains tentative, the most highly oxidizing acridinium catalysts with CT excited states were found to result in low cis isomer yields (4c, (E₁/₂(P/P⁺) = -0.56 V; E₁/₂ (P*/P⁺) = +1.69 V, 16%). In contrast, low excited-state reduction potentials, π–π* states and high triplet energies appear as promising catalyst properties for accumulating the thermodynamically less stable cis-stilbene isomer (4k, (E₁/₂(P/P⁺) = -0.71 V; E₁/₂ (P*/P⁺) = +1.23 V, 84%).

Table 4: Acridinium stilbene isomerization

<table>
<thead>
<tr>
<th>Dye</th>
<th>cis-stilbene</th>
<th>Dye</th>
<th>cis-stilbene</th>
<th>Dye</th>
<th>cis-stilbene</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>78%</td>
<td>4e</td>
<td>16%</td>
<td>4j</td>
<td>54%</td>
</tr>
<tr>
<td>4a</td>
<td>47%</td>
<td>4f</td>
<td>45%</td>
<td>4k</td>
<td>84%</td>
</tr>
<tr>
<td>4b</td>
<td>17%</td>
<td>4g</td>
<td>41%</td>
<td>4l</td>
<td>77%</td>
</tr>
<tr>
<td>4c</td>
<td>37%</td>
<td>4h</td>
<td>72%</td>
<td>dimethylacridinium¹⁴</td>
<td>28%</td>
</tr>
<tr>
<td>4d</td>
<td>36%</td>
<td>4i</td>
<td>70%</td>
<td>Fukuzumi catalyst</td>
<td>18%</td>
</tr>
</tbody>
</table>

Scheme 2. Comparative acridinium catalyzed decarboxylative fluorination.¹⁰

These findings were substantiated by an unprecedented organophotocatalytic variant of Yoon's [3+2]-cycloaddition induced by the oxidation of phenol 7 to form 2,3-dihydrobenzofuran (±)-9 (Scheme 3).¹⁸ The aminoacridinium catalyst 4h provided (±)-9 with a suitably low catalyst loading of 2.5 mol%, thus representing an efficient organophotocatalytic alternative for this oxidative cycloaddition.¹⁰ While subtle effects likely also impact the performance of this reaction, the aminomethoxyacridinium catalysts, which are readily accessible by the described synthetic approach (Table 1) and characterized by reduction potentials of around (E₁/₂(P/P⁺) = -0.89 V; E₁/₂ (P*/P⁺) = +1.40 V), appear as optimal catalysts. Highly oxidizing photocatalysts (4d, 4e) might also oxidize the olefinic co-substrate, reducing the overall yield of the transformation.
The combined effects of the numerous catalyst properties, such as excited-state energies, redox potentials, excited-state lifetimes, extinction coefficients, catalyst stabilities and the photoactivities of degradation products, underline the value of tunability within a class of photocatalysts for the design and optimization of photocatalytic reactions. Moreover, photostable catalysts significantly reduce further uncertainties, which prompted us to investigate the inherent photostabilities of the prepared acridinium dyes. Good to excellent intrinsic catalyst stabilities that compare favorably to Ru(bpy)$_2^{2+}$ were observed in the photostability assay (see SI page 538 for details).

CONCLUSIONS

In conclusion, divergent organophotocatalytic reaction pathways investigated in detail by photophysical studies revealed the hallmarks of aminoacridinium catalysts and the contributions of singlet and triplet excited state kinetics. Moreover, the modularity of organophotocatalysts to complement tunable polypyridyl transition metal complexes was emphasized by a versatile acridinium synthesis using bifunctional organodilithium reagents from the combination of X-M exchange and directed ortho-metalation. Twelve novel acridinium catalysts with charge transfer or π-π*: lowest-energy electronic transitions, high inherent photostabilities, adjustable triplet energies and a broad range of excited state reduction potentials were prepared. The virtues of modular organophotocatalysts were evident by optimal catalytic features to refine photocatalysis methodology. With the growing scope of complementary families of organophotocatalysts, significant contributions to reaction discovery, sustainable synthesis and scale-up can be anticipated. Our current studies focus on the applications of the novel organophotocatalysts and the design of particularly photostable aminoacridinium catalysts.

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Author Contributions

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Notes

The authors declare no conflict of interest. Compounds 4a-l are part of a filed patent (C. Fischer, C. Sparr. EP 17/188,288) licensed to Solvias. The catalysts will be commercially available.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, compound characterization, divergent pathways, DFT calculations, photophysical properties, quenching studies, emission lifetime determinations, benchmarking reactions and inherent photostability studies (PDF)

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(10) See Supporting Information for details.


