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3-Acetoxyquinuclidine as Catalyst in EDA Complex-Mediated Reactions triggered by Visible Light

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3-Acetoxyquinuclidine as Catalyst in EDA Complex-Mediated Reactions triggered by Visible Light

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ABSTRACT: 3-Acetoxyquinuclidine was found to act as a catalytic electron donor species in a variety of electron donor-acceptor (EDA) complex-mediated reactions. Only substoichometric amounts (10 to 25 mol%) were needed to trigger the desired reaction. The outcome could be tuned by selecting the nature of the formed radical to perform amino- and hydro-decarboxylation, dimerization, and cyclization reactions. Importantly, no external additives were needed in this reaction.

KEYWORDS: electron donor-acceptor complex, photochemistry, 3-acetoxyquinuclidine, homogeneous catalysis, tetrachlorophthalimide.
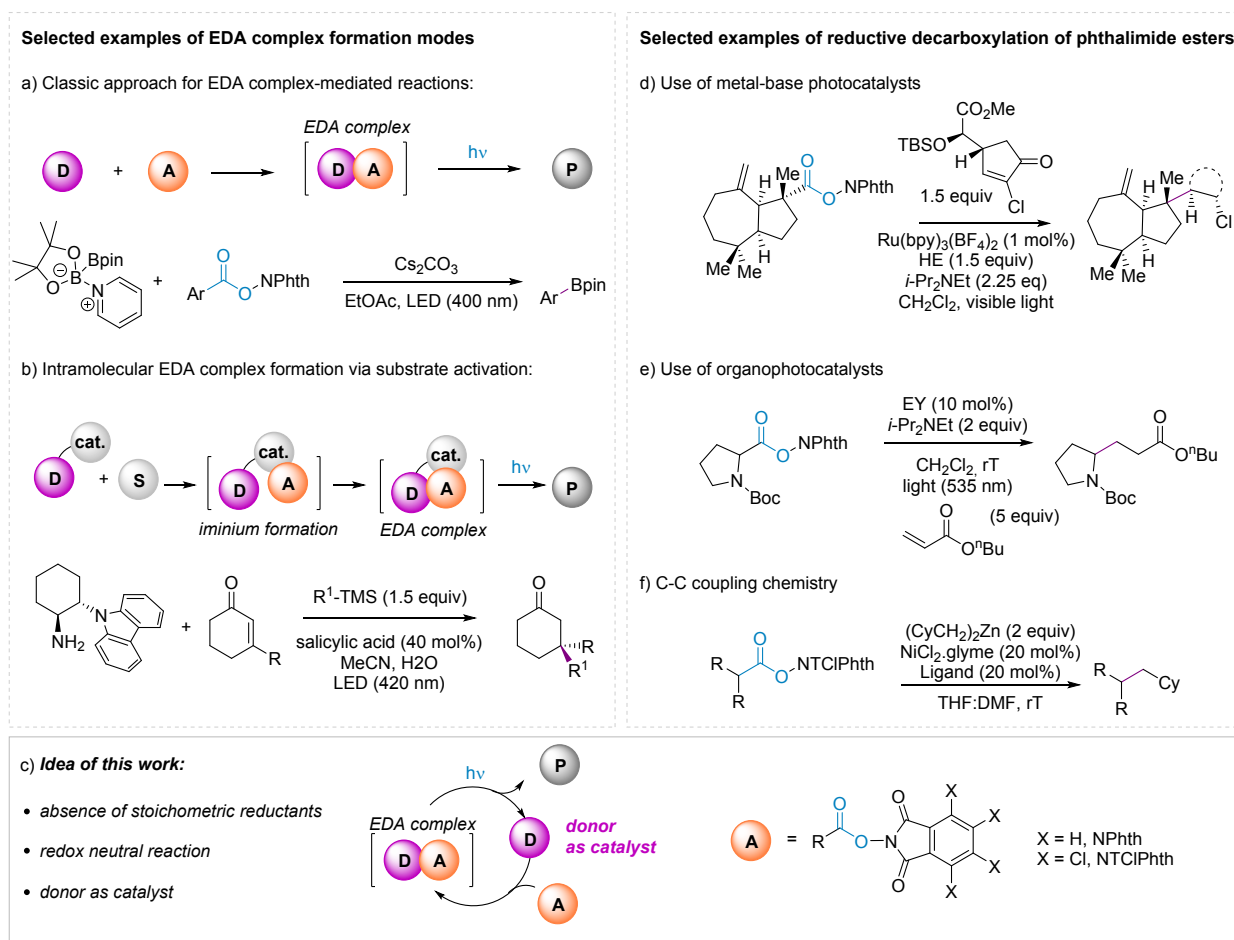
1. INTRODUCTION

Harnessing the power of sunlight in a productive manner has been an aim of many synthetic groups in the last decades. Different strategies such as direct excitation of molecules using UV-light, or activation via energy transfer or via electron transfer from a photocatalyst using visible light are used in order to achieve selective reactivity.[1-11] However, UV-light can be harmful, and photocatalysts are non-innocent species that might react with the product, as they are intrinsically active molecules under visible light conditions.

Electron donor-acceptor (EDA) complexes,[12] on the other hand, emerged as an alternative to the use of photocatalysts in visible light-triggered reactions.[12-16] These complexes are formed by two species, an electron donor and an electron acceptor, which show a change transfer band only when combined. When this band occurs in the visible region of the spectra, visible light can be used to induce an electron transfer from the donor to the acceptor. Thermal activation of these complexes is also possible.[17,18] Since only selected pairs of molecules form EDA complexes, there are

only few reports in the literature for selective reactivity, even though these complexes have been known for decades.[12,19] In the vast majority of the examples, after electron transfer (ET) the electron donor (ED) radical cation and the electron acceptor (EA) radical anion react with each other to form the product (Scheme 1a). Elegant work from the group of Melchiorre exploited the formation of an intramolecular EDA complex via iminium formation (Scheme 1b).[20-22] However, to the best of our knowledge, there are no reports showing the use of an electron donor or acceptor as external catalytic species for visible light-mediated reactions via EDA complex formation.

Intrigued by this lack of precedent, we sought to explore new avenues of EDA complexes, in particular, the possibility of finding a molecule easy to obtain that could act as a donor of an EDA complex, but which, at the same time, could be regenerated and used in catalytic amounts in different types of reactions (Scheme 1c). In this work, we present the synthetic possibilities of using an ED catalyst in EDA complex-mediated reactions that could greatly expand the use of this strategy in synthetic chemistry.

Selected examples of EDA complex formation modes

a) Classic approach for EDA complex-mediated reactions:

b) Intramolecular EDA complex formation via substrate activation:

Selected examples of reductive decarboxylation of phthalimide esters

d) Use of metal-base photocatalysts

e) Use of organophotocatalysts

f) C-C coupling chemistry

c) *Idea of this work:*

- *absence of stoichiometric reductants*
- *redox neutral reaction*
- *donor as catalyst*

Scheme 1. Selected literature precedents on EDA complex (top left) and reductive decarboxylative phthalimide esters chemistry (top right); Idea and advantages of this work (bottom); HE: Hantzsch ester; EY: Eosin Y.

Since phthalimide-derived esters have been largely used in borylations (Scheme 1a),[15,23,24] in photoredox catalysis (Scheme 1d-e),[25-27] or in coupling chemistry (Scheme 1f)[28-30] among others, we decided to use them as initial substrates. Most of the approaches for the reductive decarboxylation of phthalimide ester substrates are

net-reductive methods that require the use of stoichometric amounts of an external

reductant (Scheme 1d-f). In this work we propose a redox-neutral process using the

phthalimide moieties as acceptor partners of a catalytic donor to induce reactivity via

EDA complex formation.

2. RESULTS AND DISCUSSION

2.1. Selection of 3-acetoxyquinuclidine as catalyst

Our investigations started with the synthesis of the corresponding phthalimide ester

of 2-phenylbutyric acid, **1a** (Figure 1). However, no EDA complex formation was

observed when mixing **1a** with a common donor such as triethylamine (Et$_3$N). Since

the potential of the single electron reduction of phthalimide esters (E$_{1/2}$ = −1.24 to −

1.38 V vs. SCE[27]) is lower than the potential of the corresponding

tetrachlorophthalimide esters (E$_{1/2}$ = −0.70 to −0.54 V vs. SCE, see Supporting

Information) we synthetized the analogous tetrachlorophthalimide derivative. An

equimolar mixture of the tetrachlorophthalimide ester of 2-phenylbutyric acid, **2a**, with

Et$_3$N in MeCN gave a band with a maximum defined in the blue region of the spectra,

not observed for the separate components. This band was our first indication for the

formation of an EDA complex. We then decided to explore amines more stable in their

oxidized state than Et$_3$N, for instance triaryl amines such as dimethylaniline,

triphenylamine and 4-methoxytriphenylamine. Unfortunately, none of them gave an

observable band in the desired region. Even *N*-methylmorpholine, which has a higher

stability due to the orientation of the oxygen lone pairs, showed no EDA complex

formation with **2a** (See Scheme S1).

We then turned our attention to a different group of amines. In particular we focused

on quinuclidine (azabicylo[2.2.2]octane) derivatives, as we were attracted by its

peculiar tethered structure which imparts unique redox properties to this trialkylamine.

As opposed to non-cyclic trialkylamines, such as Et$_3$N, the bicyclic structure of

quinuclidine avoids its degradation after oxidation, since the fixed orientation of the C-

H bonds in α-position to the oxidized nitrogen center avoids α-deprotonation (Scheme

2a). For this reason, quinuclidine derivatives have been used by many research

groups as reductive quenchers and hydrogen atom donors (HAT) in photo-induced

processes (Scheme 2b).[31] We hypothesized that this molecule could act not only as a

single electron donor but also as an acceptor playing the role of a SET catalyst

triggered by an EDA process (Scheme 2c). To the best of our knowledge, this is the

first study of this matter in the literature.

a) Difference in stability between triethylamine and quinuclidine
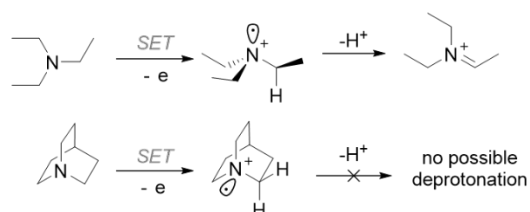
b) Quinuclidine as SET and HAT
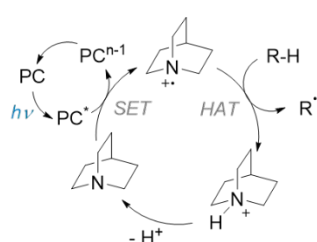
c) *New hypothesis:* ***reversible ED catalyst***
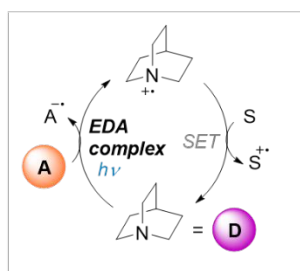
Scheme 2. Unique structure of quinuclidine. PC: photocatalyst. SET: single electron

transfer. HAT: hydrogen atom transfer. R: organic moiety. ED: electron donor. A:

molecule acting as electron acceptor. D: electron donor catalyst quinuclidine. S:

organic molecule.

2.2. Towards the aminodecarboxylation reaction

With this hypothesis in mind, 3-acetoxyquinuclidine (q-OAc) was chosen as potential

EDA catalyst for its simplicity in handling compared to the non-substituted quinuclidine.

An equimolar mixture of **2a** and q-OAc gave a bright yellow solution, indicating the

formation of an EDA complex that was observed in the UV-visible spectra recorded

for this mixture, not observed for the separate components (Figure 1a). In order to

verify the generality of the formation of an EDA complex with q-OAc in the presence

of diverse tetrachlorophthalimide acid derivatives, we synthetized the corresponding

ester of *N*-Boc-proline **2b** which, in the presence of q-OAc, revealed a yellow solution

indicative of the formation of an EDA complex in MeCN (Figure 1b).

Based on these promising observations, we subjected the mixture of **2b** and

substoichometric amounts of q-OAc (25 mol%) in MeCN to blue LEDs irradiation (λ =

455 nm) at room temperature. A single product and complete conversion were

observed after 20 h of irradiation. The characterization of the isolated material

revealed the formation of the corresponding decarboxylated product **3b** in a 69% yield

(Figure 1c, entry 1). No starting material was recovered and no apparent formation of

any other product was detected. Control reactions in the absence of light or q-OAc

resulted in recovery of the starting material (entries 2 and 3), indicating that this is a

light-mediated reaction that proceeds via EDA-complex formation. Optimization of the

reaction conditions was performed. Change of solvent to 1,4-dioxane gave incomplete

conversion (entry 4), but the use of dimethylformamide (DMF) notably improved the

yield of this reaction, providing a 91% yield even after only 4 h of irradiation (entries 5

and 6). No conversion was observed in the absence of light but a background reaction

in the absence of catalyst gave 39% yield of **3b** (entries 7 and 8) which can be

attributed to the contribution of a radical cage mechanism explained by the absorption

at 455 nm in DMF observed in the UV-visible spectra of **2b** (see Supporting Information

for further details). The use of a higher wavelength, 470 nm, in order to minimize this

background reaction gave similar results (entries 9 and 10). Further optimization of the

catalyst revealed 10 mol% of q-OAc to be optimal, giving a yield of 89% of **3b** (entries

11 to 13. See Scheme S2).

a) UV-visible spectra of mixtures of **1a**, **2a**, Et₃N and q-OAc.

b) Qualitative observations of an EDA complex formation.

c) Optimization table.
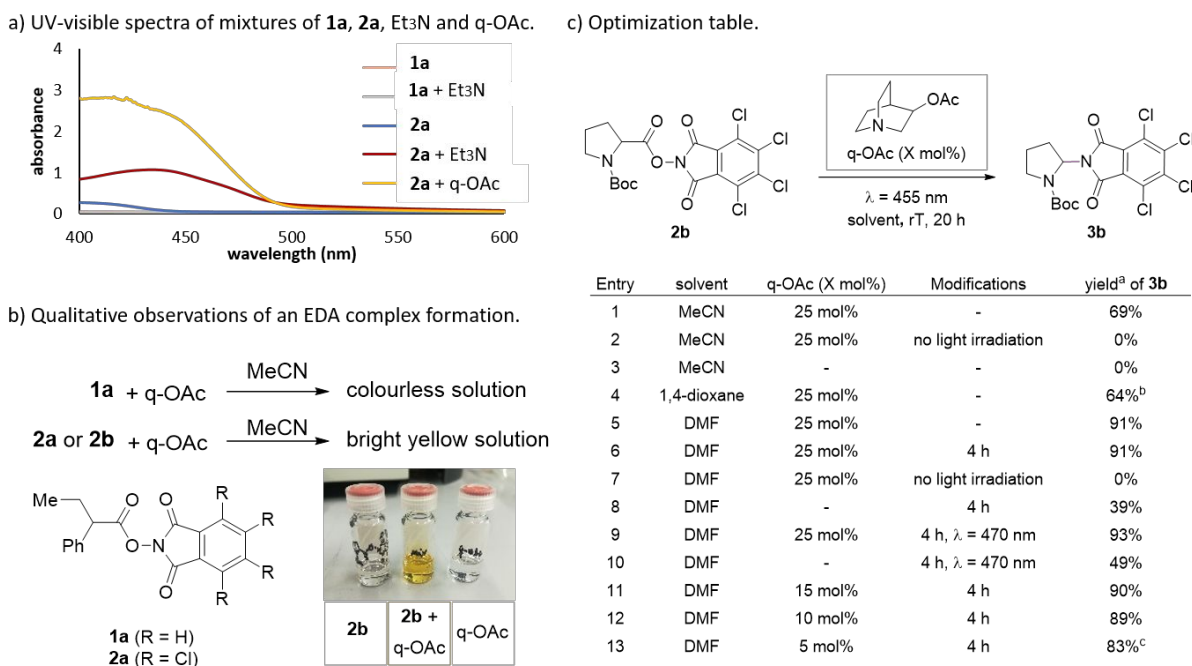
Figure 1. a) UV-visible spectra of 15 mM solutions in MeCN containing **1a**, **2a** or an equimolar mixture with the corresponding amines, path length 1 cm. b) Initial observations of an EDA complex formation; picture shows a solution of **2b** (left), q-OAc (right) and a 1:1 mixture of both (center) in MeCN. c) [a] Isolated yields. [b] 12% of **2b** was recovered, [c] 6% of **2b** was recovered.

Remarkably, this reaction failed when common photocatalysts as Ru(bpy)$_3$Cl$_2$ or Eosin Y were used under the same reaction conditions (Scheme 3). For comparison, substrate **2b'** was selected since the control reaction in the absence of catalyst gave no product formation. The reduction potentials of the excited states of these two photocatalysts suggest that both should be capable of reducing the tetrachlorophthalimide

moiety. On the other hand, a second SET event needs to occur for the turnover of the photocatalyst to its ground state, which might not be the case for these catalysts. In any case, our catalyst q-OAc fulfils both requirements and it is capable of reducing the tetrachlorophthalimide moiety via EDA-complex formation and closing the catalytic cycle for a redox-neutral process without the need of any external additives. Furthermore, the formation of this aminodecarboxylated product would not be possible by using other EDA complex-mediated approaches due to the following reasons: (1) the use of stoichiometric amounts of a non-tethered amine, such as Et_3N, gave minimal or no product formation when substrates **2b'** (Scheme 3) or **2b** (see Scheme S6) where used, probably due to the degradation of the oxidized amine, which avoids the second SET from taking place; (2) there was no EDA complex formation observed between tetrachlorophthalimide and *N*-Boc-pyrrolidine; nor (3) between **2b** and **3b** (see Scheme S10); and (4) no concentration dependency of absorption spectrum of **2b** was observed (see Scheme S10) which excludes the possibility of intramolecular SET.
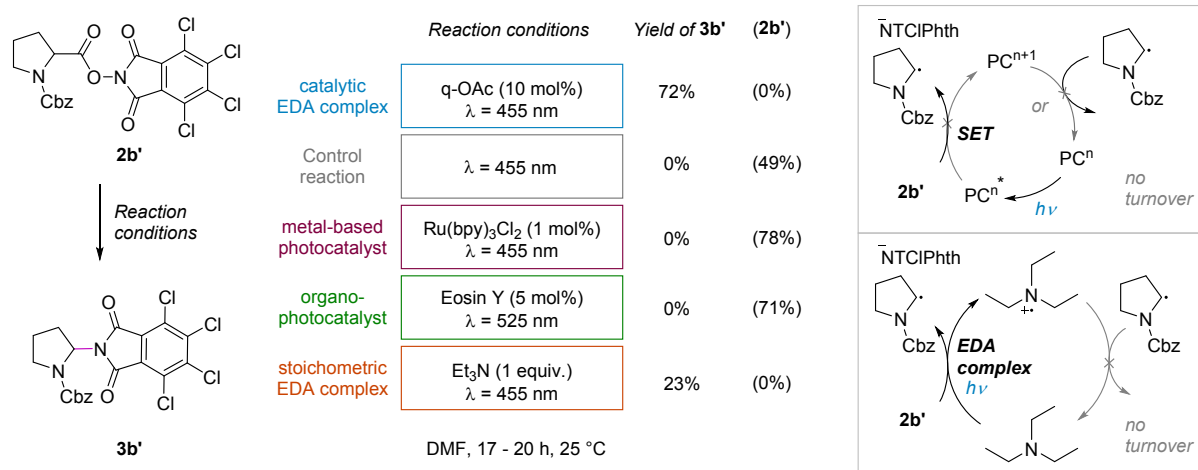
Scheme 3: Comparison of the method described in this work using q-OAc vs the use of other photocatalysts or stoichiometric EDA complex conditions in the synthesis of compound **3b'** from substrate **2b'**. Isolated yields given. Yields of recovered starting material **2b'** are given in parenthesis.

These results are in agreement with the hypothesized behavior of q-OAc in its role as reversible SET catalyst. We envisioned that the formation of the EDA complex **2b**/q-OAc and light irradiation of this complex would result in SET from the catalyst (q-OAc) to the tetrachlorophthalimide moiety. Decarboxylation to form the corresponding α-amino radical intermediate would be followed by its oxidation with q-OAc$^{+\bullet}$, regenerating the initial q-OAc in this process, to presumably form an iminium ion that would be trapped by the previously liberated tetrachlorophthalimide anion, delivering

the observed product **3b** (Scheme 4a). The quantum yield of this reaction was found

to be 0.02 (See Supporting Information), suggesting that propagative pathways can

be ruled out of the mechanism. We believe that the close proximity of the generated

q-OAc⁺• to the α-amino radical species after SET promotes a fast back SET and avoids

any HAT pathway from being productive. The formation of this α-amino radical

intermediate was proved when the reaction was run in the presence of 2 equiv. of

TEMPO as radical trapping agent. Starting material **2b** was recovered in 66% yield

and product **3b** was observed only in trace amounts. The product formed as

consequence of TEMPO trapping the α-amino radical (m/z = 327 [M+H⁺]) was

observed by mass-spectrometry (MS) (see Scheme S5).

a) Proposed mechanism for the use of q-OAc as reversible SET catalyst
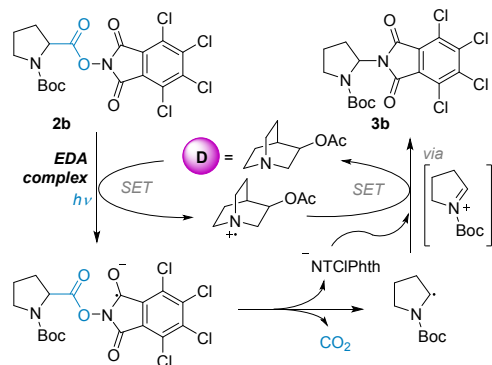
b) Proposed mechanism for the use of q-OAc as SET/HAT catalyst
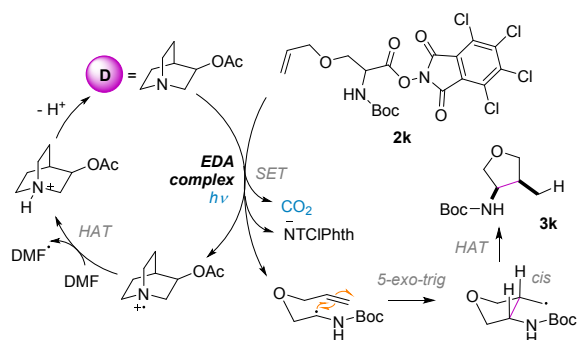
Scheme 4. Mechanistic proposal.

A variety of tetrachlorophthalimide esters derived form α-amino acids (**2b** to **2f**) as well as α-hydroxy acid derivatives (**2g** to **2j**) were synthesized and submitted to the optimized catalytic conditions. In order to achieve full conversion of the starting material in all cases, irradiation times were established to be 17 to 20 h. Cyclic and acyclic amines and ethers gave stable aminals (**3b** – **3f**) and hemiaminals (**3g** – **3j**, through the corresponding oxonium ion) in yields up to 89% yield using only 10 mol%

of q-OAc. Olefinic double bonds in **3c**, **3e** and **3h** were tolerated as well as the NH

group of products **3d** and **3f**. Interestingly, product **3d** bearing a sensitive sulfinyl group

was obtained in a 76% yield. Aromatic ethers with substituents in meta- and para-

positions **3i** and **3j** were obtained in 78% and 70% respectively, with special interest

in **3j** due to the formation of a quaternary hemiaminal center (Scheme 5).

2.3. Cyclization reaction

Intrigued by the high efficiency of these reaction conditions, we wondered whether we

could tune the outcome of this reaction by selecting the molecular structure of the

starting material. As observed in examples **3c** and **3h**, products derived from the

corresponding 6-exo-trig or 7-*exo-trig* cyclization were not observed. However, the

irradiation of the tetrachlorophthalimide derivative of *O*-allyl-*N*-Boc-serine (**2k**) in the

presence of an optimized 25 mol% of q-OAc (see Scheme S3 for optimization

conditions) induced the 5-exo-trig cyclization to form the tetrahydrofuran derivative **3k**

in 59% yield. The use of other photocatalysts as Eosin Y failed to give the product

(See Scheme S9). Importantly, control reactions in the absence of light or q-OAc gave

no product formation and led to recovery of **2k**, highlighting the essential role of the q-

OAc in the formation of the EDA complex for this reaction to proceed under blue LEDs.

Two-dimensional NMR analysis revealed the formation of a 4:1 diasteromeric *cis:trans*

mixture (See Supporting Information). According to the proposed mechanism, radical

cyclization would be followed by the oxidation of the primary radical to the primary

carbocation (from the q-OAc$^{+\bullet}$), which is a highly energetically uphill process, and

proton elimination to form a double bond. However, this behavior was not observed.

In order to better understand the mechanism we attempted to use DMF-d$_7$ as solvent

which resulted in the formation of **3k** in trace amounts and degradation of the starting

material **2k** (See Scheme S7). These results suggest that DMF has a crucial role in

this cyclization, probably as a terminal hydrogen atom transfer (HAT) species (Scheme

4b), which is precedented in the literature[32,33] (See Supporting Information for more

details). This is in agreement with the absence of product formation when the reaction

was performed in MeCN (see Scheme S3). Comparing bond dissociation energies

(BDE) of a primary alkyl radical (BDE [C1-H in propane] = 100 kcal/mol[34]) and DMF

(BDE [H-CH$_2$N(Me)CHO or Me$_2$NC(O)-H] = 89 – 90 kcal/mol[32]), HAT is feasible.

Furthermore, the submission of esters **2l** and **2m** to the reaction conditions resulted in

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4 the isolation of product **3l** in slightly lower yield (49%), and detection of product **3m**
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7 only in traces (Scheme 5).
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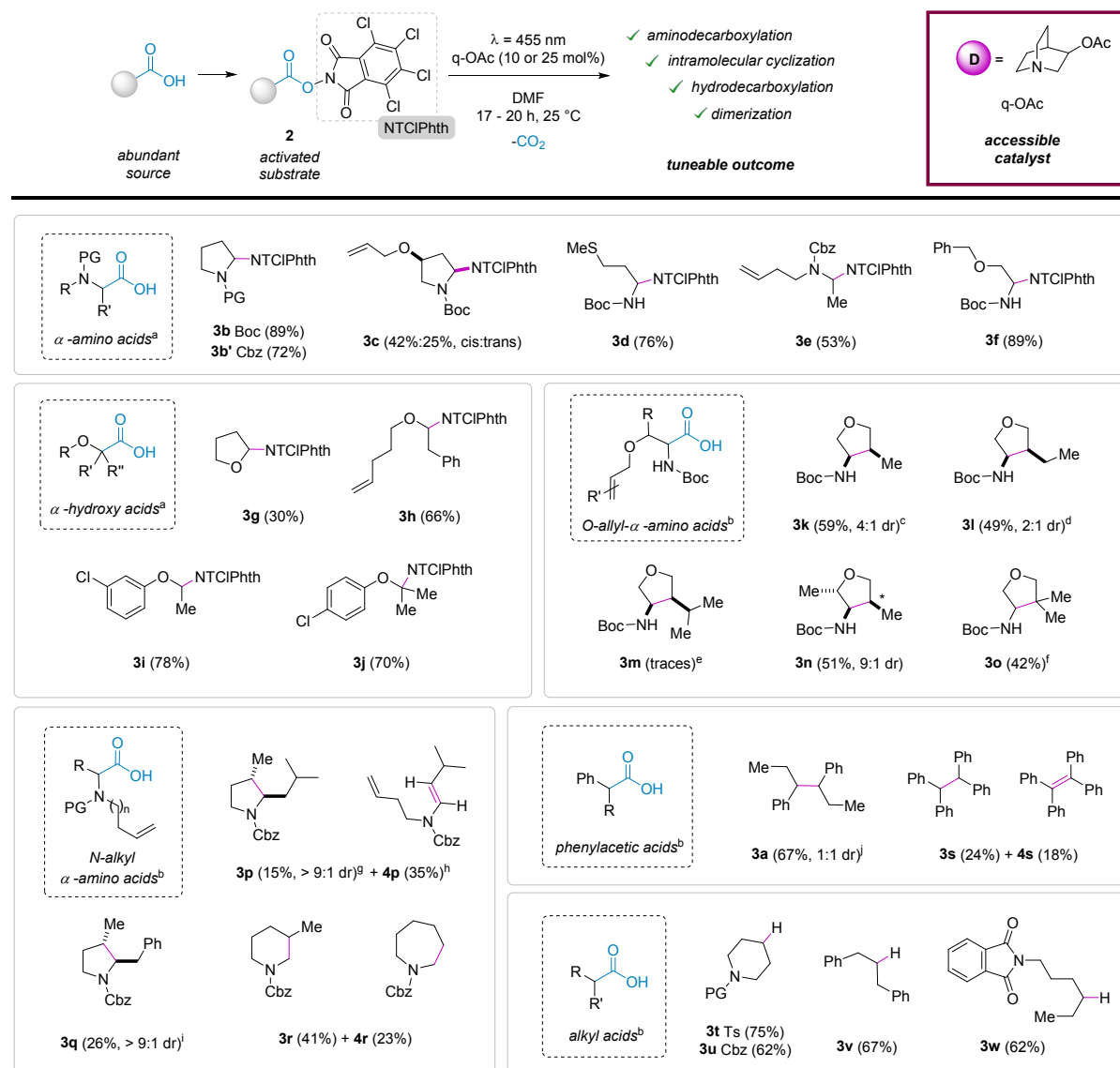
Scheme 5. Products isolated from the photocatalytic reaction. [a] 10 mol% of q-OAc was

used. [b] 25 mol% of q-OAc was used. [c] 8% of product **4k** was also isolated. [d] Isolated

as an inseparable 88:12 mixture of **3l** and **4l**. [e] Not isolated. [f] 8% of product **4o** was

also isolated. [g] 14% of product **5p** was also isolated. [h] Only the *trans*-configurated

product was observed. [i] 25% of an unidentified product was also isolated. [j] 3% of

product **4a** was also isolated. *Indicates the center to which the dr refers to. NTClPhth:

tetrachlorophthalimide moiety. PG: protecting group. For cyclic voltammograms (CVs)

and UV-visible spectra of compounds **2** see Supporting Information.

Direct comparison of the BDEs of the bonds involved in the process could explain

these results. The BDE of a C-H bond decreases with the higher substitution of the

carbon center, meaning that the strength of the C-H bond decreases in the same order:

$RH_2C-H > R_2HC-H > R_3C-H$.[34] In consequence, for the formation of product **3m** the

reaction might not have a thermodynamically favorable HAT from DMF, giving no

product formation (See Scheme S7). On the other hand, turnover of the catalyst must

occur in a different way than indicated for the formation of aminals and hemiaminals

3b to **3j**. Using the same reasoning, we can presume that HAT is also feasible from

DMF to q-OAc$^{+\bullet}$ (BDE [q-OAc$^+$-H] = 95-100 kcal/mol[35]) (Scheme 4b). Other

tetrahydrofuran derivatives were synthetized, as **3n** with three consecutive

stereocenters and an excellent 9:1 dr isolated in 51% yield, and product **3o** with a

newly formed quaternary carbon atom obtained in 42% yield (Scheme 5).

Further examples using *N*-alkylated leucine, phenylalanine, or glycine derivatives

with unsaturation at different distances from the formed radical were tested (Scheme

5). Cyclization in order to give the corresponding pyrrolidine **3q** was observed from the

N-(3-butenyl) derivative of phenylalanine **2q**. In the case of the leucine derivative **2p**,

pyrrolidine **3p** was isolated in 15% yield and with an excellent dr (>9:1) together with

the stable enamide **4p** as major product (35%), presumably from overoxidation of the

formed radical, and some aminodecarboxylation product (**5p**, 14% yield, see

Supporting Information). Interestingly, the submission of the *N*-(4-butenyl) derivative

of glycine **2r** to the optimized reaction conditions resulted in the formation of products

3r and **4r** as the only observed products with yields of 41% and 23%, respectively.

This result is in contrast with the observed behavior of the formed radical in the case

of product **3h**, where products derived from the cyclization were not observed.

Oxidation of the radical formed from **2h** after SET and decarboxylation under these

reaction conditions might be consequently faster than cyclization, giving **3h** as single product instead of products derived from 6-exo-trig or 7-endo-trig cyclization as observed for **3r** and **4r** respectively. In addition, the analogue ester of **2r** with an oxygen instead of a nitrogen atom at the α-position of the formed radical gave 54% of the initial acid (ester **2z**, Supporting Information) with no decarboxylation observed. These results suggest that both factors, the substituents (N or O) and the substitution of the esters (primary or secondary), affect to the outcome of the reaction.

2.4. Dimerization and hydrodecarboxylation reactions

As expected, when the tetrachlorophthalimide ester of phenylacetic acid **2a** was exposed to blue LEDs in the presence of 25 mol% of q-OAc in DMF, dimerization of the benzylic radical was observed to form **3a** in a 67% yield with a 1:1 dr, a behavior that was also observed when the diphenylacetic acid derivative **2s** was submitted to the same reaction conditions. In the latter case, not only the dimerized product **3s** was observed in 24%, but also alkene **4s** was isolated as orange needles in 18% yield (Scheme 5).

When purely alkyl radicals were formed in the reaction, hydrodecarboxylation products **3t** to **3w** were isolated in good yields ranging 62% to 75% yield (Scheme 5) under the optimized conditions (See Scheme S4). Replacing q-OAc by Ru(bpy)$_3$Cl$_2$ or Eosin Y resulted in no product formation (See Scheme S9), highlighting the importance of q-OAc in this reaction. Interestingly, the q-OAc tolerated the presence of the pendant tetrahydrophthalimide (THPhth) group in product **3w**, which was obtained in 62% yield. A formation of an EDA complex between the q-OAc and this pendant THPhth group, stronger than between the q-OAc and the active tetrachlorophthalimide moiety, could have resulted in trapping and inactivation of the catalyst. A control reaction in the absence of q-OAc gave no product formation. Remarkably, this method proved to be very selective for hydrodecarboxylation of di-substituted acids, as mono- or tri-substituted acids were unreactive (See Scheme S8). Mechanistically, the formation of these products would occur in a similar fashion as for compounds **3k** to **3o**, from decarboxylation after SET in the EDA complex to give the corresponding secondary radical, followed by HAT presumably from DMF to deliver the final product.

3. CONCLUSIONS

In summary, we have shown the potential of q-OAc as electron donor catalyst in EDA complex-mediated reactions. Furthermore, we have demonstrated a new mode of action of q-OAc as reversible SET catalyst. It was found that q-OAc can be regenerated, in contrast to most traditional chemistry where the overall reaction consumes the DA pair. Using the tetrachlorophthalimide moiety to activate a great variety of acids and q-OAc in catalytic amounts (10 to 25 mol%) we have proved the versatility of these unique reaction conditions. By precise selection of the nature of the formed radical we have been able to achieve amino- and hydro-decarboxylation reactions as well as cyclizations and dimerizations in yields up to 89%. Control reactions have shown the necessity of light and catalytic amounts of the ED catalyst q-OAc for the reaction to be effective. Interestingly, no incorporation of the q-OAc catalyst to any product was detected or derivatives of the catalyst in any of the experiments. Further investigations on the stability and versatility of q-OAc as well as other derivatives will be performed.

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ASSOCIATED CONTENT

Supporting Information. Experimental procedures, full characterization of all synthesized compounds, cyclic voltammetry experiments of the starting materials and additional experiments explained in Scheme S1 to S13 are included.

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Author Contributions

I.B. performed the experiments. The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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