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Novel Oxidative Ugi-Reaction for the Synthesis of Highly Active Visible Light Imide-Acrinium OrganoPhotocatalysts†

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Abstract: A newly designed class of acridinium-based organophotocatalysts bearing an imide group at the C9-position is presented. To achieve these unprecedented structures, a synthetic strategy based on a novel straightforward oxidative Ugi-type reaction at the benzylic position of C9-unsubstituted acridanes was developed. The introduction of the imide-unit affords a notable photocatalytic activity enhancement, allowing efficient transformations in different oxidative and reductive visible light catalytic reactions.

Visible light photoredox catalysis has been established as a powerful tool for the synthesis of molecules by selective activation of bonds under mild conditions. Therefore, access to unique reactivities are possible, including those thermally forbidden or difficult to carry out by other methodologies.^[1] The catalysts involved in most of the photocatalytic processes are based on Ru(II) and Ir(III) complexes.^[2] More recently, the possibility of using organic photoredox catalysts for synthetic transformations has been extensively investigated.^[3] This type of photocatalysts are suitable for industrial applications because of their remarkable photophysics and electrochemical properties (e.g. as powerful oxidant).^[3] In addition, the low price and low toxicity of these photoredox active organic dyes compared to the commonly used transition metal-based photocatalysts make them very attractive.

Among well-established organophotocatalysts, acridinium derivatives represent a specific family that contains extended conjugated π -systems and absorb light in the visible region (Figure 1, left).^[4] In the excited state, acridinium ions are usually powerful oxidants, whereas they are weak reductants. In addition, they show good quantum yields in some reactions and extremely long lifetime of fluorescence.^[4d,5] However, the first generation of this group of photocatalysts, unsubstituted or C9-aryl substituted *N*-methyl acridinium ions (type I), has only found limited use due to its susceptibility to the nucleophile addition at the 9-position in the ground state, or by the addition of radical species to its corresponding acridinyl radical (Figure 1, I and II, respectively).^[6,7] In order to avoid this drawback, in 2004 Fukuzumi introduced a mesityl group at the C9-position. Therefore, the stability of the photocatalyst under the reaction conditions was increased by blocking the access of the nucleophiles and radical species to the photocatalyst (Figure 1, III).⁸ Although the stability of the Fukuzumi's catalyst III was substantially enhanced with respect to the first generation, the kinetic of the reactions was significantly

diminished. The negative impact of this substitution in the kinetics of photocatalytic reactions can be attributed to the steric hindrance imposed by the mesityl group. Although there are several publications related to the use of acridinium salts as photocatalysts, only compounds that present alkyl and aryl substituents at the C9-position have been reported.^[9,10] Therefore, in order to achieve a higher performance and broaden synthetic applicability, new acridinium-type catalysts bearing different functional groups are needed.

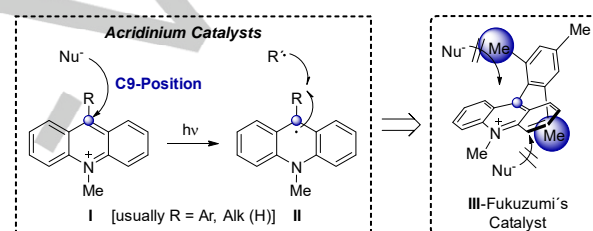


Figure 1. Previous acridinium-photocatalysts and reactivity at the C9-position.

Based on our extended experienced on oxidative C-H functionalization^[11] for the synthesis of biological and important pharmaceutical compounds,^[12] we decided to introduce a polar group at C9 by exploiting the direct C-H bond functionalization technology on acridane scaffolds, followed by an oxidative aromatization to the corresponding acridinium salts (Scheme 1).^[12a] For this purpose, we focused on the Ugi multicomponent reaction (Ugi-MCR), as one of the most potent and convenient methodology for the synthesis of a large variety of bisamides and imides.^[13] The Ugi reaction implies a cascade of elementary chemical transformations between amines, aldehydes (or ketones), isocyanides and carboxylic acids to assemble, via the formation of a key iminium intermediate, a single amide-type product. Despite the outstanding applications developed in the past decades, all the reported few examples on oxidative Ugi multicomponent reactions (Ox-Ugi-MRC), which proceed by a (sp³)C-H bond oxidation at the substrate, relay on the formation of a key iminium salt.^[14] Moreover, as far as we know, the synthesis of acridinium imide derivatives has not been reported to date. In addition, the synthesis of these acridinium derivatives (top, Scheme 1) required the use of Grignard or organolithium derivatives, high temperatures or strong acids,^[15] making essentially these methodologies functional group non-tolerant. Concern by the lack of precedents, and in order to achieve our targeted imide-photocatalyst, we envisioned the development on a novel Ugi-multicomponent reaction based on an in situ generated key carbocation electrophilic intermediate (or vinylogous iminium ion), which will allow to easily tune the substitution on the final structure (Scheme 1, bottom).

Herein, the straightforward synthesis of a novel family of imide-acridinium photocatalysts based on the first modular, mild oxidative Ugi-type reaction on dibenzylic substrates is presented. Furthermore, their photochemical properties, applications as highly potent organophotocatalyst, and their distinct reactivity

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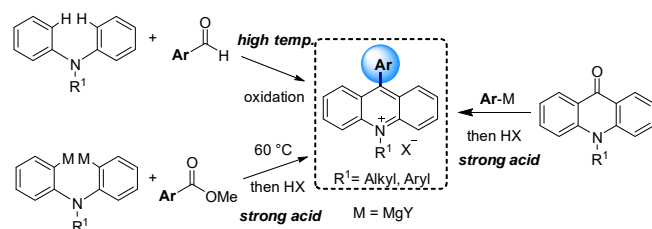
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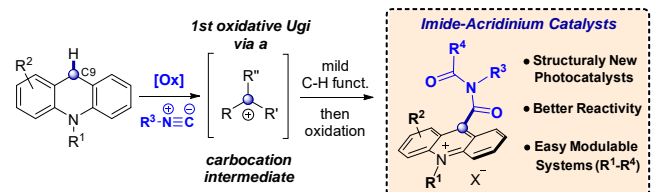
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respect to a commercially available and well-established acridinium salt, are discussed.

Established approaches to acridinium fluorophores:



This work: new oxidative C-H funct. approach \Rightarrow different C9-substitution now allowed



Scheme 1. Described synthesis of acridinium salts and our synthetic approach.

We started the optimization of the oxidative Ugi-type reaction with *N*-methyl acridane (**1a**) as model substrate and commercially available cyclohexyl isocyanide (**2a**) in acetonitrile at room temperature (Table 1). Initially, several common peroxides were tested as oxidants (Table 1, entries 1–4). Unexpectedly, the use of hydroperoxides such as *t*BuOOH (TBHP) in the presence of benzoic acid as additive, which was already described in previous oxidative Ugi reactions with amine-substrates,^[14,16] did not lead to the desired product **3a** (entry 1). Similarly, the aprotic dialkylperoxide *t*BuOO*t*Bu or PhCO-OO-*t*Bu were also unsuccessful (entries 2 and 4). Next, our recently developed Cu(OTf)₂/bipyridyl/benzoyl peroxide (BPO) oxidative system for C(sp³)-H bond functionalization reactions was employed (entry 3).^[11a] In this case, the reagent BPO had a double role as both the oxidant and the carboxylic acid or carboxylate source. Therefore, the addition of an external carboxylic acid was not required to obtain the imide Ugi-products **3**. Accordingly, the desired product **3a** was obtained in a promising 29% yield. However, two of the main issues of this reaction are the low stability of the products **3** under oxidative conditions and the competition between the desired Ugi-type reaction and the over-oxidation of the substrate to the acridone or the aromatic acridine. Therefore, to avoid the formation of undesired by-products, both shorter reaction times and an excess of isocyanide were explored. We found that the use of two equivalents of **2a** and 4 hours reaction time led to the best results, providing **3a** in a synthetically useful 61% yield, which was improved to 66% when the reaction was scaled up 20 times (entry 6). It is important to mention that the reaction was sensitive to moisture (entry 7), being needed anhydrous conditions to achieve satisfactory results.^[17] Finally, the increase or decrease of the catalyst loading (15 or 5 vs. 10 mol%, entries 8 and 9), the increase of the oxidant (entry 10), or the use of standard oxidative aerobic photocatalytic conditions with [Ru(bpy)₃](PF₆)₂ (entry 11), led to significant less efficient reactions.

With the best conditions in hand, Cu(OTf)₂/bipyridyl as catalytic system and benzoyl peroxide as oxidant in acetonitrile at r.t. (Table 1, entry 6), the reaction with different substituted acridanes **1** was investigated (Table 2). Acridanes with various *N*-protecting groups such as methyl, benzyl and phenyl efficiently reacted, giving the desired products **3a-c** in good yields (61–70%).

The reaction also tolerated different electron donating (R² = Me, Ph, MeO; **3d-g**, 41–68%,) and electron withdrawing (R² = Br, F; **3h-j**, 32–63%) groups at the acridane core. It is also interesting to note that the steric hindered substrate **1k** (1,4-dimethyl substituted) was also well tolerated, leading to **3k** in a good 57% yield. Regarding the isocyanide reagent, the system worked well with other alkyl groups such as *n*Bu (**3l-m**), *t*Bu (**3n-o**) and benzyl (**3p-q**), as well as aryl (**3r-s**) substituents, providing the corresponding imides in moderate to good yields.

Table 1. Optimization of the conditions for the oxidative Ugi reaction with **1a**.^[a]

Ent	Catalyst (mol%) ^[b]	Oxidant (eq.)	2a (eq.)	t (h)	Yield- 3a (%) ^[c]
1	Cu(OTf) ₂ (10)/bpy (30)	<i>t</i> BuOOH (1.2)	1.2	18	— ^[d]
2	Cu(OTf) ₂ (10)/bpy (30)	<i>t</i> BuOO <i>t</i> Bu (1.2)	1.2	18	— ^[d]
3	Cu(OTf) ₂ (10)/bpy (30)	(PhCO ₂) ₂ (1.2)	1.2	18	29
4	Cu(OTf) ₂ (10)/bpy (30)	(PhCO ₂) ₂ O <i>t</i> Bu (1.2)	1.2	18	—
5	Cu(OTf) ₂ (10)/bpy (30)	(PhCO ₂) ₂ (1.2)	2.0	18	36
6	Cu(OTf) ₂ (10)/bpy (30)	(PhCO ₂) ₂ (1.2)	2.0	4	61(66) ^[e]
7	Cu(OTf) ₂ (10)/bpy (30)	(PhCO ₂) ₂ (1.2)	2.0	4	35 ^[f]
8	Cu(OTf) ₂ (15)/bpy (45)	(PhCO ₂) ₂ (1.2)	2.0	4	42
9	Cu(OTf) ₂ (5)/bpy (15)	(PhCO ₂) ₂ (1.2)	2.0	4	52
10	Cu(OTf) ₂ (10)/bpy (30)	(PhCO ₂) ₂ (1.5)	2.0	4	22
11	[Ru(bpy) ₃](PF ₆) ₂ (1)	air, blue LEDs	2.0	18	30 ^[d,g]

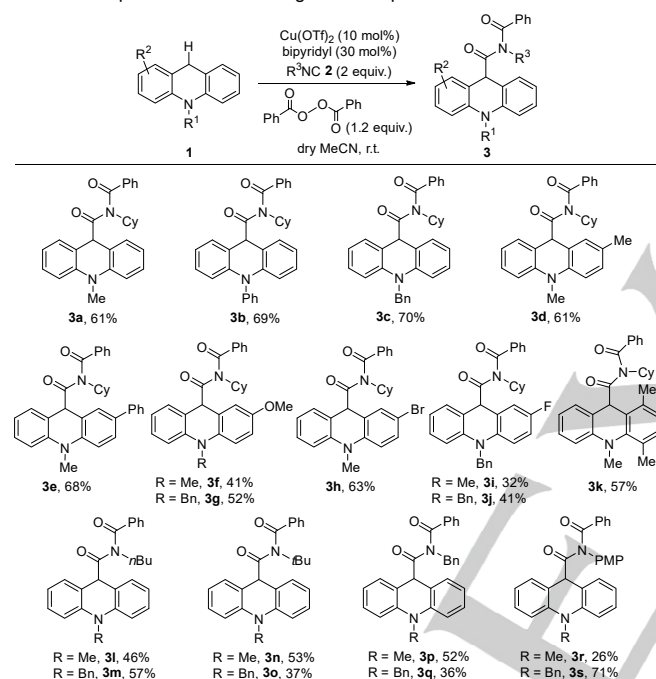
[a] **1a** (0.1–0.2 mmol), oxidant, catalyst, CyNC in MeCN (0.1 M) at the room temperature in a sealed tube. [b] Cu(OTf)₂ was pre-dried under vacuum at 60 °C. [c] Isolated yields. [d] Reaction in the presence of 1.2 equiv. of PhCO₂H. [e] 2 mmol scale reaction in brackets. [f] Cu(OTf)₂ was not pre-dried. [g] Full conversion observed after 18 h (30% conv., 3.5 h). A mixture of **3a**, acridone and acridine was obtained.

Aiming to shed some light into the mechanism of the oxidative Ugi-reaction, several experiments were carried out (Scheme 2). Firstly, the *N*-methyl acridinium salt **1a'** was prepared by simple oxidation of the acridane **1a** with trityl perchlorate.^[12a] The carbocation salt **1a'** was then enrolled in the Ugi-type reaction with cyclohexyl isocyanide (**2a**) with two different reagents: *p*-toluic acid (equation i-a) or sodium *p*-toluate (equation i-b, Scheme 2). While no reaction was observed with *p*-toluic acid, the imide derivative **3t** was obtained in moderate yield (39%) when *p*-TolCO₂[−] was used as the corresponding carboxylate. The lower yield obtained compared to the reaction with the in situ generated cationic species could be explained due to the high instability of the stoichiometrically employed C9-unsubstituted acridinium salt **1a'**, showing the more synthetic utility of our employed oxidative C-H functionalization approach. Therefore, under the catalytic conditions the reactive carbocation intermediate is formed and present in the media in low amounts, allowing an efficient and selective conversion into the desired product **3**. Next, a competition experiment was performed between the in situ formed benzoate from the benzoyl peroxide and an external added carboxylic acid with a similar pK_a, such as *p*-toluic acid (Scheme 2, eq. ii). The reaction involved 1.2 equivalent of benzoyl peroxide, forming at most 2.4 equivalents of benzoic acid/benzoate, and 1.2 equivalents of the *p*-toluic acid. The two possible Ugi-type

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products **3a** and **3t** were then obtained in a perfect statistical 2:1 ratio (**3a**:**3t**, 66:33) in a 45% overall yield. Based on the experimental observations, a plausible reaction mechanism was postulated (eq. iii, Scheme 2). Consequently, the reaction occurs via a copper-catalyzed radical-initiated oxidation of the benzylic C9-position to produce the carbocation **A**.^[18] Then, the addition of the isocyanide (to form **B**) and sequential attack of the in situ formed benzoate, provides the neutral intermediate **C**, which rapidly undergoes an Ugi-type rearrangement process to give the desired product **3**.

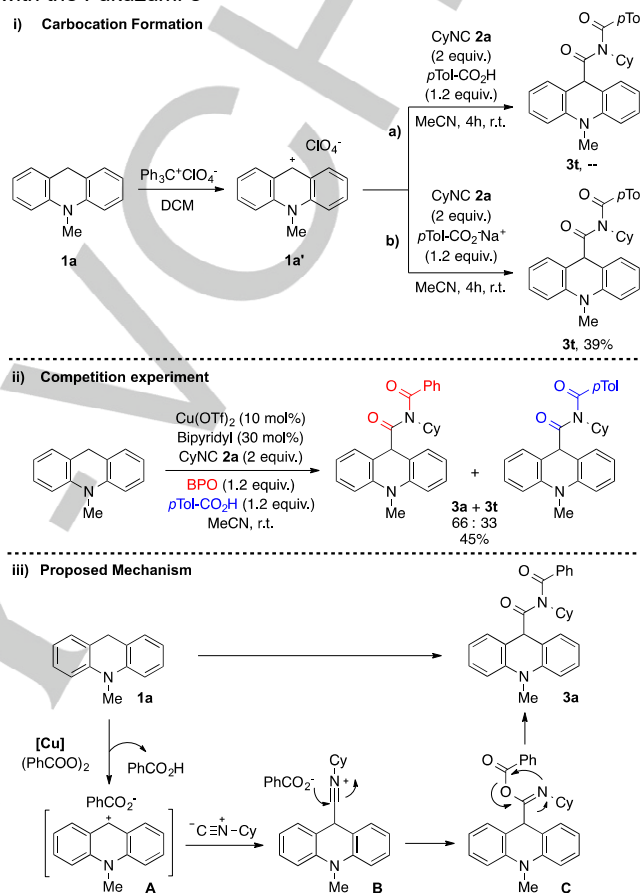
Table 2. Scope for the oxidative Ugi-multicomponent reaction.^[a,b]



[a] The reactions were performed in a 0.1–0.4 mmol scale in CH_3CN (see S.I.).
[b] Isolated yields after flash chromatography. PMP = *p*-methoxyphenyl.

For the synthesis of the photoactive acridinium salts, the final aromatization process was carried out for some selected imide-acridanes **3** with tritylperchlorate as mild hydride abstractor in dry acetonitrile,^[19] yielding the corresponding acridinium perchlorate salts **4** in a range from 36 to 79% yield (top, Scheme 3). The photochemical properties of the newly obtained acridiniums were next investigated. The acridinium salts **4** display two maximum absorption bands (355–380 nm and 420–460 nm), which depend on the substituents at the imide and acridinium nitrogen-atom (top right-Scheme 3, see S.I. for further details). As a result, modifications of the substituents (R^1 , R^2 and R^3) allowed an easy tuning of the excited state properties of these acridinium salts. Interestingly, when a methoxy substituent was present ($\text{R}^2 = \text{MeO}$), acridiniums **4f** and **4g** showed a strong bathochromic shift of both characteristic bands up to $\lambda_{\text{max}} = 380$ and 460 nm. Moreover, the ground-state redox potentials of the catalysts were determined by cyclic voltammetry (CV) in acetonitrile as solvent (see S.I.). The ground state reduction of catalysts **4** occurs at low potentials (around -0.3 V vs. SCE) with a relative excited state reduction potential around 2.4 V (showing slightly variations depending on the substituents), which are above the values of the Fukuzumi's photocatalyst **III** ($E_{1/2} = +2.18$ V vs. SCE).^[3] After obtaining these appealing results, the catalytic activity of **4** was then investigated in the dehydrogenative lactonization of 2-

phenylbenzoic acid (**5**) as model reaction (see the optimization Table S2 in S.I.).^[20] This transformation is known to proceed through a reductive quenching cycle and was already reported with the Fukuzumi's

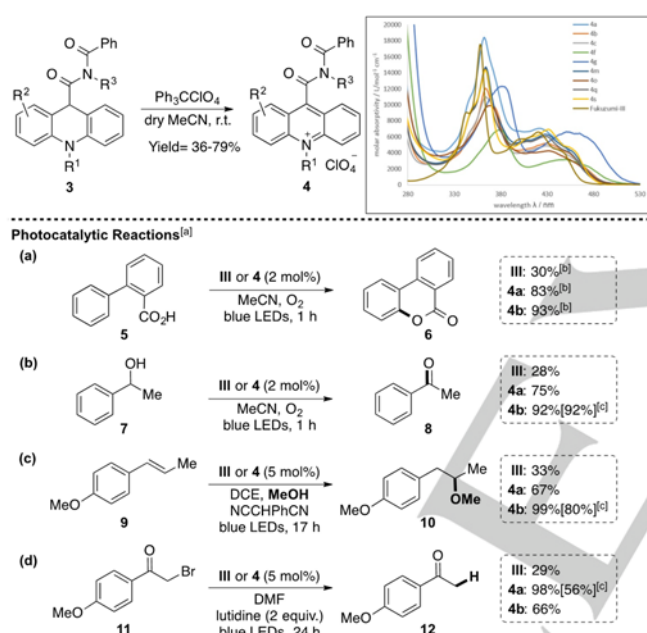


Scheme 2. Oxidative Ugi-reaction: Mechanistic experiments and proposal.

commercial catalyst **III**. In fact, when other less oxidative catalysts like $[\text{Ru}(\text{bpy})_3](\text{BF}_4)_2$ ($E^*_{1/2} = +0.77$ V vs SCE)^[2] or Eosin-Y ($E^*_{1/2} = +0.83$ or 1.23 vs SCE)^[3] were employed, no conversion was found. On the contrary, the stronger oxidant catalyst **III** ($E^*_{1/2} = +2.18$ V vs SCE)^[3] gave the lactone **6** with a moderate 30% yield (equation a, Scheme 3). Outstandingly, our designed acridinium catalysts **4** led to the lactone **6** in notable higher yields (46–93%, see Table in S.I.) under the same conditions and reaction time. In particular, **4a** and **4b** turned out to be the optimal photo-organocatalysts, providing **6** in 83% and 93% yield, respectively (eq. a, Scheme 3). In order to generalize the good catalytic performance of catalysts **4**, the activity of both the parent *N*-methyl derivative **4a** and the best catalyst **4b** was compared with the Fukuzumi's catalyst **III** in different photoredox reactions (equations b–d). Initially, oxidative transformations such as the oxidation of alcohols to aldehydes and ketones were explored. Acridinium catalysts such as **III** can oxidize primary and secondary benzylic alcohols under oxygen atmosphere^[21] by oxidation of the arene to its radical cation and subsequent deprotonation.^[3] To our delight, after one hour the alcohol **7** was oxidized to **8** in 28% conversion with catalyst **III**, whereas **4a** and **4b** gave a significant improved 75% and 92% conversion, respectively (Scheme 4, eq. a). Furthermore, the *anti*-Markovnikov hydro-functionalization of alkenes, which has extensively been studied employing mesityl acridinium type

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catalysts,^[3] was investigated. In the chosen case of the intermolecular hydroetherification of alkenes such as **9** with methanol (10 equiv.), a redox-active hydrogen atom transfer agent such as 2-phenyl malononitrile (0.5 equiv.) was used to improve the yields.^[22] As in the previous reaction, the photocatalysts **4a** and **4b** gave higher conversions than the Fukuzumi's catalyst **III** under the same conditions (17 h, 67 and 99% vs. 33%; Scheme 4, eq. b). In addition, although acridinium salts are known to be weak reductants, the reduction of the bromo-ketone derivative **11** ($E_{1/2} = -0.49$ V vs SCE) with **4** was also challenged.^[2] Surprisingly, excellent results were also obtained in this type of reaction, in which the *N*-methyl derivative **4a** showed better results than **4b** (98% vs. 66% conversion). Moreover, both photocatalysts **4** proved again to be more active than **III** (29% conversion) (Scheme 3, eq. c).



Scheme 3. Comparative photocatalytic reactions with **III**, **4a** and **4b**. ^(a) NMR-conversions. ^(b) Isolated yields. ^(c) NMR yields in brackets

In conclusion, the designed novel imide-acridinium organophotocatalysts **4** were prepared in a simple 2-steps approach by a new oxidative C-H functionalization/Ugi-type reaction of acridanes, followed by an aromatization process. The developed oxidative Ugi reaction has allowed the introduction of a polar functional group at the C9-position, which proceeds from benzoyl peroxide that is used as both oxidant and carboxylate source. Furthermore, the methodology is rather flexible and tolerates a wide range of substituents. In terms of reactivity, the imide-acridiniums **4** led to a notable higher activity than the commercially available, commonly used Fukuzumi's catalyst in both oxidative and reductive reactions.

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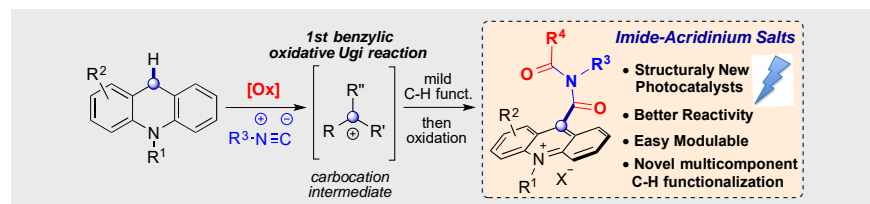
Keywords: C-H functionalization • Oxidative Ugi reaction • Acridinium salts • Photocatalysis • Multicomponent

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Novel Oxidative Ugi-Reaction for the Synthesis of Highly Active Visible Light Imide-Acrdinium OrganoPhotocatalysts

Sweet'n Salt: The first, mild, modular, oxidative Ugi-reaction on benzylic substrates, such acridanes, allows the development of an unprecedented family of imide-acridinium visible light photocatalysts with boosted reactivities in both oxidative and reductive processes.