

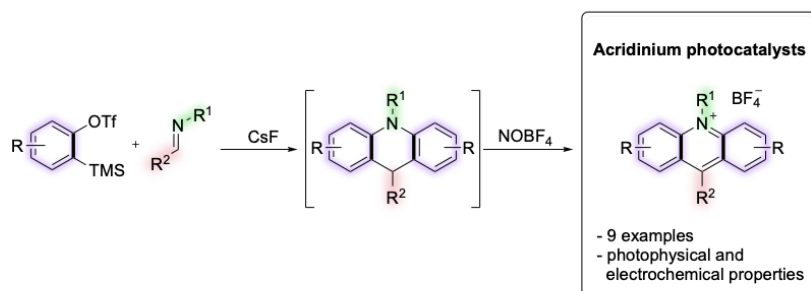
The Versatility of the Aryne-Imine-Aryne Coupling for the Synthesis of Acridinium Photocatalysts

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Dedicated to Prof. Shunichi Fukuzumi on the occasion
of this 70th Birthday

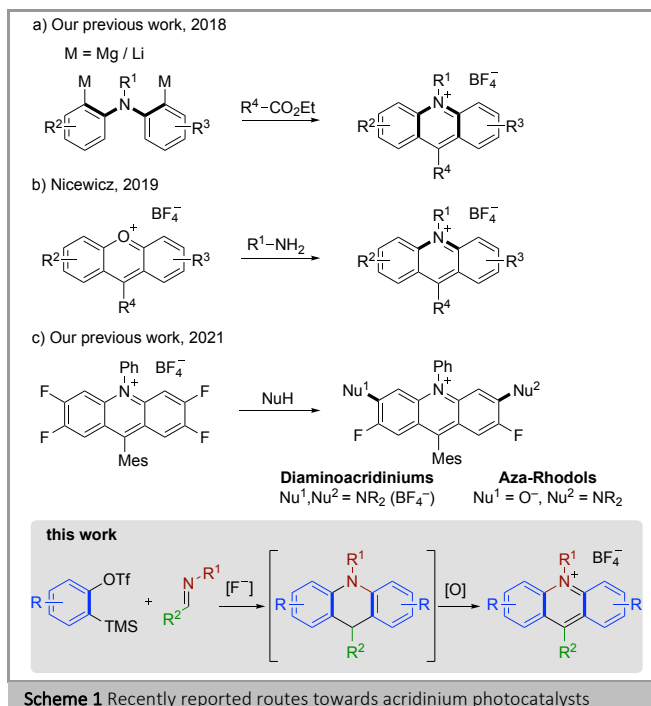


Abstract The increasing use of acridinium photocatalysts as sustainable alternative to precious metal-based counterparts encourages the design and efficient synthesis of distinct catalyst structures. Herein, we report our exploration of the scope of the aryne-imine-aryne coupling reaction combined with a subsequent acridane oxidation for a short two-step approach towards various acridinium salts. The photophysical properties of the novel photocatalysts were investigated and the practical value was demonstrated by a cation-radical accelerated nucleophilic aromatic substitution reaction.

Key words acridinium salts, aryne, organocatalysis, photoredox catalysis, synthesis

The rapid conceptual advances in photoredox catalysis incentivizes the further development of novel transformations that are unattainable via conventional mechanisms.¹⁻³ Owing to their favorable photophysical properties, ruthenium and iridium polypyridyl complexes are thereby broadly used for exploratory photoredox catalysis.⁴⁻⁸ However, the high price along with the need for precious metals encourages the development of more sustainable alternatives to metal-based photocatalysts. Pioneered by Fukuzumi,⁹ acridinium photocatalysts proved as efficient excited-state oxidants for numerous transformations.¹⁰⁻¹³ The preparation of the acridinium scaffold typically involves a (5+1)-strategy for the formation of the heterocyclic core. In our previous work, we employed a reaction between 1,5-bifunctional organometallic reagents and esters to prepare aminoacridinium salts (Scheme 1a).¹⁴⁻¹⁶ The Nicewicz group reported an alternative route by the direct conversion of xanthylum salts to acridinium derivatives (Scheme 1b).¹⁷ Although the numerous new strategies towards acridinium salts impactfully fueled sustainable photoredox organocatalysis, the most common routes still suffer from a limited scope and the requirement for multiple-step synthesis.¹⁸

Recently, our group investigated an approach towards acridinium photocatalysts that exploited an ad hoc, late-stage



derivatization of the tetrafluorinated acridinium derivative via nucleophilic aromatic substitution reactions (Scheme 1c).¹⁹ The required tetrafluorinated acridinium salt was prepared in two steps by the aryne-imine-aryne coupling reaction²⁰ affording the corresponding acridane, which was subsequently oxidized with nitrosonium tetrafluoroborate. To expanding the scope of organic photocatalysts with a broad range of photophysical properties,¹⁶ we questioned whether our synthetic route towards the late-stage diversification substrate could also be applied for the preparation of other novel acridinium photocatalysts. We hence set out to explore the versatility of this two-step procedure using different imines and aryne precursors.

We began our investigation with the preparation of the Kobayashi aryne precursors **2a-2d** and imines **3a-3d** based on the standard literature procedures (Table 1).²¹ Notably, according to the proposed mechanism for aryne-imine-aryne coupling, the imine requires sterically demanding substituents near the C-terminus to prevent an undesired 6π -electrocyclization.²⁰ Therefore, imines with di-*ortho*-substituted phenyl groups (R^2) were synthesized with the consequence, that the acridinium salts prepared utilizing this two-step strategy possess a sterically shielded C9 position to further prevent photobleaching via nucleophilic attack or light-promoted radical-radical couplings.²²

Having all starting materials in hand, we centered our attention on the exploration of the reaction scope (Table 1). As the preparation of acridinium salt **1aa** was earlier reported by our group,¹⁹ we tested these established conditions for synthesis of other tetrafluorinated acridinium salts. Gratifyingly, the reactions between difluorinated aryne precursor **2a** and imines **3b** and **3c** afforded the desired acridanes that were successfully oxidized with nitrosonium tetrafluoroborate yielding products **1ab** and **1ac**, albeit with lower yields than for compound **1aa**. Nonetheless, the oxidation step proceeded rapidly and did not give any undesired side-products. We then sought to evaluate the compatibility of the protocol with more electron-rich arynes possessing alkyl substituents, while the choice of compounds **2b** and **2c** as substrates is further motivated by the expected stability of the resulting acridinium salts as the alkyl substituents were anticipated to block the positions susceptible to nucleophilic attack at the acridinium core.²² As it was found, the reaction between both **2b** and **2c** with imine **3a** under standard conditions was significantly slower compared to our previous observations with **2a** as a substrate. Therefore, modified reaction conditions involving heating to 50°C for 18 hours were applied. As a result, full imine conversion was observed after the first step of the synthetic sequence, and good isolated yields over two steps 44% (**1ba**) and 41% (**1ca**) were obtained after the acridane oxidation. Encouraged by these results, we drew our attention to the diversification of alkyl-substituted acridinium salts at C9- and *N*-substitution which can be achieved by the reaction of **2b** and **2c** with different imines. Therefore, fluorine- and iodine-containing imines were subjected to the reaction with **2b** yielding acridinium salts **1bb** and **1bc** with moderate overall yields. Furthermore, products **1bd** and **1cd** were successfully prepared to demonstrate that the reaction scope is not limited to imines that contain methyl groups in the *ortho*-positions of the C-terminus. Next, we focused on the unsubstituted aryne generated from **2d** aiming at the preparation of the BF₄-Fukuzumi acridinium photocatalyst **1da**. To our delight, the application of the methodology using compounds **2d** and **3a** as substrates afforded this venerable photocatalyst **1da** with good yield over two steps (59%).

We next examined photophysical and electrochemical properties of prepared acridinium salts (Table 1). To our delight, fluorescence lifetimes sufficient for photocatalytic applications were obtained for all acridinium salts from time-correlated single-photon counting studies. Notably, the presence of the electron-withdrawing fluorine atoms in the acridinium core (**1aa**, **1ab**, **1ac**) is reflected in the reduced lifetime due to the

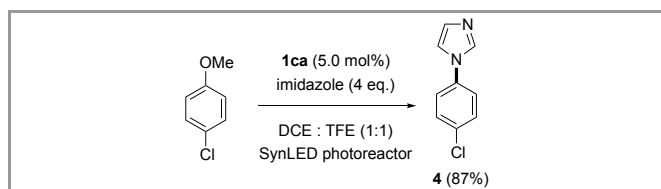
Table 1 Scope and Photophysical Properties of Prepared Acridinium Salts^a

PC	$E_{0,0}$ [eV]	$E_{1/2}(\text{PC}/\text{PC}^*)$ [V] ^a	$E_{1/2}(\text{PC}^*/\text{PC})$ [V]	$\tau(^1\text{PC})$ [ns]
1ab	2.33	-0.33	2.00	5.2
1bb	2.69	-0.71	1.98	17.8
1ac	2.35	-0.32	2.03	5.6 (80%); 2.5 (20%)
1ba	2.70	-0.74	1.96	16.3
1bc	2.69	-0.71	1.98	12.8
1bd	2.67	-0.61	2.06	11.4
1ca	2.65	-0.69	1.96	0.7 (4%); 11.4 (96%)
1cd	2.62	-0.59	2.03	0.5 (5%); 12.4 (95%)
1da	2.67	-0.52	2.15	0.1 (2%); 7.3 (98%)

Isolated yields over two steps are shown. ^aValues measured in 0.1 molL⁻¹ n-Bu₄NP₆ in degassed, dry CH₃CN against SCE; ^b50°C. PC = photocatalyst

pronounced donor-acceptor effect within the structure, leading to a stronger charge-transfer character of the excited singlet state (Table 1). This tendency is also observed by the comparison of the measured data for the compounds **1da** and **1ba** which shows that introduction of electron-donating alkyl substituents to the acridinium core causes an increased excited state lifetime. While excited-state reduction potentials ($E_{1/2}(\text{PC}^*/\text{PC}^-)$) of studied acridinium salts are in the same range (1.96-2.15 V), a higher ground-state reduction potential ($E_{1/2}(\text{PC}/\text{PC}^-)$) is observed for tetrafluorinated acridinium derivatives.

To explore the catalytic performance of the synthesized acridinium photocatalysts, we briefly confirmed their catalytic applicability with the cation-radical accelerated nucleophilic aromatic substitution reaction developed by Nicewicz and co-workers (Scheme 2).²³ Acridinium salt **1ca** thereby showed a suitable performance, giving the desired product **4** in high isolated yield. These results are approaching the reported yields for the photocatalyst optimized for this reaction indicating that acridinium salts prepared by the combination of an aryne-imine-aryne coupling with an operationally simple oxidation can be successfully applied to photocatalytic transformations.



Scheme 2 Application of acridinium photocatalysts for nucleophilic aromatic substitution reaction

In conclusion, we have described the versatility of the aryne-imine-aryne coupling as efficient route towards acridinium salts when combined with an efficient acridane oxidation. This new approach is a short alternative to the reported multistep routes towards acridinium photocatalyst and utilizes readily available starting materials.²⁴ The generality of the strategy was demonstrated by the preparation of a broad range of acridinium salts and their photophysical and electrochemical properties were evaluated. The utility of the catalysts was confirmed by the photocatalytic cation-radical accelerated nucleophilic aromatic substitution reaction.

General procedure A for the synthesis of Kobayashi aryne precursors:

Aryne precursors were prepared according to a modified literature procedure:²¹ To a solution of the corresponding *o*-bromophenol (1 eq.) in anhydrous THF (0.3 molL⁻¹) was added HMDS (2 eq.) under an Ar atmosphere. The reaction mixture was stirred at reflux for 2 hours. After cooling to room temperature, the crude product was attained by removing the solvent in vacuo and was used for the next step without isolation. The crude material of the first step was dissolved in anhydrous THF (0.3 molL⁻¹) under an Ar atmosphere and cooled to -78°C. *n*-BuLi (1.1 eq.) was added dropwise to the mixture and the reaction was stirred for 1 hour at -78°C. After that, Tf₂O (1.2 eq.) was added dropwise to the mixture at -78°C and the reaction was stirred for another hour. The reaction mixture was quenched with cold

saturated aqueous NaHCO₃ at -78°C and warmed to room temperature. The aqueous layer was extracted with MTBE three times, the combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (from cyclohexane to cyclohexane:EtOAc (100:1)) to afford the aryne precursors.

General procedure B for the synthesis of imines:

The amine (1.5 eq. or 1 eq.) and the corresponding aldehyde (1 eq.) were dissolved in dry toluene (0.1 molL⁻¹ (aldehyde concentration)). *p*-TsOH·H₂O (0.05 eq.) and 4 Å molecular sieves were added to the obtained solution. The reaction mixture was stirred at reflux for 18 hours. The solvent was removed under reduced pressure (5 mbar) to yield the desired imine. When aniline was used as a substrate, the excess of aniline was removed afterwards under high vacuum (<0.1 mbar, 60°C).

General procedure C for the acridinium salt synthesis:

The reaction flask charged with CsF (8 eq.) was evacuated at 100°C for 2 hours and cooled to room temperature before imine (1 eq.), dry acetonitrile (0.1 molL⁻¹ (imine concentration)) and benzyne precursor (2.2 eq. or 2.5 eq.) were added. The reaction progress was monitored by NMR. After the reaction was completed, the acetonitrile was removed in vacuo. The residue was dissolved in dichloromethane and washed with water. The organic layer was dried over Na₂SO₄, the solvent was evaporated and the crude product was subjected to silica-gel column chromatography (starting from Et₂O:cyclohexane (1:100) to Et₂O:cyclohexane (1:10)). The obtained acridane was then dissolved in CH₂Cl₂ (0.1 molL⁻¹) and nitrosonium tetrafluoroborate (2 eq.) was added. The reaction was monitored by NMR and after its completion, the reaction mixture was diluted with CH₂Cl₂ and washed with water twice. The organic layer was dried over Na₂SO₄ and the solvent was removed under reduced pressure. The residue was triturated with Et₂O (upon sonification), the obtained precipitate collected and washed several times with Et₂O.

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Supporting Information

YES (this text will be updated with links prior to publication)

Primary Data

NO (this text will be deleted prior to publication)

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