Streamlined Synthesis of Aminoacridinium Photocatalysts with Improved Photostability

Markus Jakobi, and Christof Sparr*

Department of Chemistry University of Basel, 4056-Basel, Switzerland (*Email: christof.sparr@unibas.ch)

KEYWORDS: acridinium salts, cross-coupling, photocatalysis, photostability, sustainability

ABSTRACT: The efficient synthesis of photocatalysts with improved photostability from readily available resources is a requirement for more sustainable and scalable photocatalysis. Herein, we describe a strategy utilizing a high-yielding three-fold C–N cross coupling selective for three out of six arylbromide sites to avoid alkyl groups in the final catalyst structure. A subsequent triple metalation to form 1,5,5'-trifunctional organometallic reagents enables the coupling and cyclization with simple esters, whereas a third unreacted functionality is hydrolyzed upon acidic quench. This short reaction sequence results in bis(diarylamino)acridiniums with dramatically increased photostability, allowing to lower the catalyst loading to 0.100 mol% without loss in yield.

INTRODUCTION

The remarkable advances in photocatalysis strongly impacted organic synthesis by allowing an accelerated entry into new chemical space.¹⁻³ In discovery chemistry, inventive photocatalytic routes empowered many areas of application, while several challenges remained for organic processes on scale. In contrast to photoinitiator-based reactions, photocatalysts that participate in each productive catalytic cycle often require prohibitively high loadings. Particularly since precious metal polypyridyl complexes such as Ir or Ru-based catalysts⁴ are often employed in initial discovery methods, more sustainable organic photoredox catalysts are of direct significance for future industrial use. As a promising alternative, acridinium salts have shown great potential as highly versatile and modular photocatalysts.⁵⁻⁸ After the pioneering work by Fukuzumi and coworkers,⁵ acridinium salts have experienced a continuous evolution towards an optimal synthesis and suitable photophysical characteristics. As the properties largely depend on the substitution pattern on the core of the acridinium scaffold, synthetic strategies typically aim to incorporate different functionalities at the heterocycle.^{9,10} In order to achieve greater diversification, we previously developed a method utilizing 1,5-bifunctional reagents to convert various esters to aminoacridiniums (Scheme 1, top).^{7,11–13} An unexpectedly high photostability for the resulting catalysts was thereby discovered despite the presence of alkyl groups, enabling organophotocatalytic variants of various pertinent reactions. However, for reactions on large scales, a further enhancement of the photostability allowing to reduce loadings is required besides a streamlined access to the catalysts. Herein, we describe a novel class of catalysts without alkyl groups to further prevent catalyst decay. As we surmised that fully aromatic amines are ideal substituents to replace dimethylamine substituents, we selected diphenylamine and carbazoles as potential aromatic amines attached to the acridinium backbone and evaluated the utility of 1,5,5' trifunctional organometallic reagents for their synthesis (Scheme 1, bottom).

Scheme 1. Synthesis of aminoacridinium photocatalysts

Synthesis of aminoacridiniums with bifunctional organomagnesium reagents



RESULTS AND DISCUSSION

Our efforts were guided by initial work on 1,5-bifunctional organometallic reagent devoid of alkyl groups. We thereby first examined the introduction of the phenyl moiety to bis(2,4-dibromophenyl)amine 2^{14} by a Pd-catalyzed cross-coupling. However, after several ineffective attempts, we observed that Ullmann-reaction conditions¹⁵ yielded the desired triaryl amine **3** at 200 °C in 60 % isolated yield after column chromatography. Interestingly, the steric interactions at the *ortho*-positions sufficiently assisted to access intermediate **4** by a selective Pd-catalyzed double C–N cross-coupling¹⁶ to form the required precursor **4** with an isolated yield of 48 %. Scheme 2. Synthesis of the 1,5-dibromo-precursor



Having intermediate **4** in hand, we set our focus on the preparation of 2,7-diaminosubstituted acridinium catalysts. Exposure of precursor **4** to elemental magnesium in THF led to the formation of the 1,5-bifunctional organomagnesium reagent which was combined with different esters, followed by the addition of HBr. However, careful optimization of conditions to form catalysts **5a-e** in yields exceeding 25 % were unfruitful (Scheme 3). The moderate yields, the harsh conditions of the synthesis of precursor **3** and the requirement for column chromatography ultimately rendered this route undesirable for our objectives.

Scheme 3. Initial photocatalyst synthesis



^a Isolated yields; ^b 100 μ mol scale, 1.0 mL THF, 100 μ mol ester in 500 μ L THF; ^c an increase to 1.40 eq. of ester showed no significant increase in yield

To circumvent the high reaction temperature in the Ullmanntype coupling and the inefficient synthesis of the acridinium catalyst, a new and simplified synthetic route was anticipated with the readily available triphenylamine selected as preferred starting material (Scheme 4). Since halogenations of triphenylamine occur with high selectivity in *para* positions,¹⁷ our initial strategy was aiming at a fivefold bromination followed by *para*-selective cross-couplings with a final transformation of the 1,5bifunctional organomagnesium reagent into the desired acridinium photocatalysts. However, suitable conditions for a fivefold bromination were not identified, whereas a sixfold bromination of triphenylamine provided excellent yields with a small excess of Br_2 .¹⁸ Although this procedure introduces an additional bromine moiety, subsequently leading to a trifunctionalized reagent, the aqueous acidic workup with HBr after the reaction with esters was considered to not only induce elimination to form the aromatic acridinium, but also to protonate the third unreacted metalated site, rendering defunctionalization unproblematic.

Scheme 4. Synthetic plans



Notably, a modification of the protocol of Bauld and co-workers¹⁸ allowed to obtain desired hexabrominated triphenylamine 7 as colorless crystalline solid in 96 % yield after precipitation from methanol (Scheme 5). With similar conditions as used before for 4, the *para*-selective threefold C–N-cross-coupling gave precursor 8a in an isolated yield of 94 % without the need for a purification by column chromatography. With this efficient procedure in hand, the introduction of two carbazole moieties was likewise considered for the synthesis of an additional subclass of photocatalysts. The protocol by Yamakawa and coworkers¹⁹ thereby allowed a highly selective and efficient triple C–N cross-coupling to obtain carbazole substituted precursor 8b with an isolated yield of 94 %.

Scheme 5. Synthetic routes to tribromo precursors



Having established robust and efficient synthetic pathways to access precursors 8a and 8b, we set our focus towards the formation of the anticipated acridinium photocatalysts. As polymer formation was previously not observed in the reaction of esters with 1,5-bifunctional organomagnesium reagents, we anticipated that the 1,5,5'-trifunctional reagents could lead to a monometalated intermediate after the double addition to couple and cyclize to the ester. The third functionalized site would thus be hydrolyzed by HBr in concert with the formation of the acridinium salts. Notably, the precursor 8a was efficiently converted into the 1,5,5'-trifuntional organomagnesium reagent with elemental magnesium in THF. The slow addition of a solution of carboxylic acid ester in THF allowed to obtain the desired photocatalysts (Scheme 6) in good yields (76% resp. 72%, 69% on 7.86 mmol scale). Conversely, precursor 8b required an equimolar mixture of iPrMgCl and sec-BuLi as exchange reagent²⁰ for an effective formation of the 1,5,5'-trifunctional reagent. Subsequently exposure of this 1,5,5'-trifunctional mixed metal reagent to the esters suitably afforded acridiniums 9c and **9d**, however in somewhat compromised yields (56% and 49%).

Scheme 6. Streamlined photocatalyst synthesis



^a Isolated yield; ^b Conditions A: 200 μ mol scale, 1.40 eq. tribromo species, 8.40 eq. Mg, 1.2 mL THF, 6 h 65 °C *then* 200 μ mol ester in 1.5 mL THF; ° 7.86 mmol scale; ^d Conditions B: 70 μ mol scale, 1.00 eq. tribromo species, 105 μ mol sec-BuLi + 105 μ mol *i*PrMgCl, 500 μ L THF, 1 h 0 °C *then* 70.0 μ mol ester in 1.0 mL THF

It is noteworthy that only minor differences in the photophysical properties were observed between catalysts bearing two diphenylamine groups (catalysts **5a–5e**) and the ones bearing three diphenylamine groups (catalysts **9a+9b**) with exited state redox potentials of $E_{1/2}(P^*/P^-)$ of $+1.74 \pm 0.3$ V (Table 1). Furthermore, catalysts **9c** and **9d** showed very weak emissions, hampering suitable measurements to evaluate the photophysical properties. By comparison of the redox potentials of catalysts **5a–5e** and **9a–9b** with the redox potential of the Fukuzumi system [MesMeAcr⁺BF₄⁻ $E_{1/2}(P/P^-) = -0.57$ V; $E_{1/2}(P^*/P^-) = 2.06$ V], a decrease in $E_{1/2}(P^*/P^-)$ of ca. 0.30 V was measured.

Table 1. Electrical and spectrophotometric data

PC	λ_{max} (abs)	$E_{0,0}$ [eV]	E _{1/2} (P/P ⁻) [V] ^a	E _{1/2} (P*/P ⁻) [V]
5a	546 nm	2.32	-0.59	+1.73
5b	545 nm	2.33	-0.60	+1.77
5c	544 nm	2.32	-0.61	+1.71
5d	547 nm	2.31	-0.60	+1.73
5e	545 nm	2.33	-0.60	+1.73
9a	545 nm	2.33	-0.61	+1.73
9b	547 nm	2.33	-0.62	+1.71

^a Measured in 100 μ mol L⁻¹ *n*-Bu₄NPF₆ in degassed, dry MeCN against SCE.

Having accessed and analyzed the newly prepared photocatalysts, we set out to determine their photostability and performance within a photocatalytic reaction. In a first experiment, the inherent photostability was evaluated using a 0.05 mol L⁻¹ solution of catalyst 9a in MeCN irradiated with 465 nm blue light while monitoring the decrease in concentration by RP-HPLC (area %). A decrease in concentration of only 13% was observed over the course of 60 minutes (see Supporting Information for details), prompting us to further investigate the stability of catalyst 9a in a Ni-catalyzed esterification reaction. Remarkably, in this reaction, we detected a rapid initial decrease of the photocatalyst to approximately 70% of the original concentration within 15 minutes, at which it subsequently plateaued over 2.5 hours (see Supporting Information for details). This significant increase in stability compared to previous acridinium photocatalysts therefore further encouraged us to investigate the minimal catalyst loading required for an efficient photocatalytic reaction.^[7] To benchmark catalyst performance, we first utilized 0.50 mol% 9a, giving a 40% yield for product 12 (Table 2).

Table 2. Photocatalytic Ni cross-coupling reaction

aut	able 2. I hotocatalytic for closs-coupling reaction								
Ĺ	N Boc OMe	OMe -	10.0 mol% NiCl ₅ *glyme 15.0 mol% 22*bpy 1.50 eq. K ₂ CO ₃						
	10 1.50 eq.	11 1.00 eq.			12				
En- try	Time [h]ª	Photo- catalyst	Load- ing ^d [mol%]	Wave- length [nm]	Yield [%] ^b				
1	3	9a	0.50	465	40				
2	6	9a	1.00	465	77				
3	6	9a	0.50	465	70				
4	3	9a	1.00	525	-				
5	18	9a	1.00	465	91				
6	18	9a	0.50	465	95				
7	18	9a	0.10	465	94				
8	18	-	-	465	-				
^a 50.	^a 50.0 µmol scale, 3.0 mL DMF, ^b Yield determined by								

^a 50.0 μ mol scale, 3.0 mL DMF, ^b Yield determined by ¹H-NMR

By increasing the reaction time to 6 h using 1.00 and 0.50 mol% **9a**, we measured an increase in yield to 77 % and 70%, respectively (entries 2 and 3). Changing the wavelength from 465 nm to 525 nm proved to be ineffective and no conversion was observed (Entry 4). Intriguingly, by extending the reaction time to 18 h, nearly full conversion could be achieved, even when lowering the amount of photocatalyst to 0.10 mol% (entries 5–7). A further decrease of the catalyst loading led to inconclusive outcomes likely caused by a combination of effects that requires further detailed study of both, the reaction and the reactor system.

CONCLUSION

In summary, a streamlined synthetic approach to more photostable acridinium salts was developed. A hexabromination followed by a selective three-fold C–N cross coupling and a final acridinium formation using 1,5,5'-trifunctional organometallic reagents allowed a drastic increase in overall yields. Nine different catalysts where synthesized by this simplified synthetic procedure and a strong increase in photostability was identified in a prototypical photocatalytic reaction.

EXPERIMENTAL SECTION

General Information. All experiments were performed under an argon atmosphere and in oven dried glassware. Solvents and reagents were obtained from commercial sources and used without further purification. For details see Supporting Information.

2-Bromo-N¹,N¹-bis(2-bromo-4-(diphenylamino)phenyl)-

 N^4 . N^4 -diphenvlbenzene-1,4-diamine (8a): Prepared according to a modified literature protocol.^[16] To a 500 mL two-neck round bottom flask were added tris(2,4-dibromophenyl)amine (7, 14,4 g, 20.0 mmol, 1.00 eq.), diphenylamine (10.2 g, 60.0 mol, 3.00 eq.), Pd(OAc)₂ (44.9 mg, 200 µmol, 0.100 mol%), Xantphos (116 mg, 200 µmol, 1.00 mol%), and NaOt-Bu (17.3 g, 180 mmol, 9.00 eq.). The flask was evacuated and back filled with argon three times. Toluene (200 mL) was added and the reaction was stirred at 110 °C for 3 h. After cooling to 40 °C, water (200 mL) was added and the mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were dried over Na₂SO₄ and then concentrated under reduced pressure. The residue was suspended in MeOH (100 mL) and the solvent was removed in vacuo to give the desired product as a pale brown powder (18.9 g, 96%, m.p. 251.3 - 252.7 °C): R_f 0.50 (cyclohexane:EtOAc 100:3); v_{max} (neat): 3034w, 1566m, 1458s, 1272s, 1076w, 1031m, 946w, 895w, 816w, 750s, 691s, 637s; ¹H-NMR (500 MHz, CDCl₃, 298 K) δ = 7.21 (3H, d, ⁴J 2.6, C3H), 7.17 (12H, td, ³J 7.4, ⁴J 4.3, C2'H), 7.00 (12H, m, C2'H), 6.94 (6H, tt, ³J 7.4, ⁴J 1.1, C4'H), 6.85 (3H, dd, ³J 8.7, ⁴J 2.6, C3H), 6.70 (3H, d, ³J 8.7, C6H); ¹³C-NMR (125 MHz, CDCl₃, 298 K) δ = 147.4 (C1'), 145.0 (C4), 140.5 (C1), 129.5 (C3'), 129.0 (C3), 127.3 (C6), 124.5 (C2'), 123.3 (C4'), 123.0 (C5), 121.7 (C2); ESI-Ms: m/z calcd. for C54H39Br3N4⁺ 980.0725 found 980.0698 [M⁺].

2,7-Bis(diphenylamino)-10-(4-(diphenylamino)phenyl)-9-(**4-fluorophenyl)acridin-10-ium bromide (9a):** To a 500 mL two-neck round bottom flask were added 2-bromo- N^1 , N^1 -bis(2-bromo-4-(diphenylamino)phenyl)- N^4 , N^4 -diphenylbenzene-1,4-diamine (**8a**, 10.8 g, 11.0 mmol, 1.40 eq.) and magnesium (1.61 g, 66.0 mmol, 8.40 eq.). The flask was evacuated and back filled with argon three times. THF (48.4 mL) and 1,2dibromoethan (3 drops) were added and the mixture was stirred at 65 °C for 6 h. Methyl 4-fluorobenzoate (1.21 g, 1.02 mL, 7.86 mmol, 1.40 eq.) in THF (60 mL) was added and the mixture was stirred at 65 °C for 14 h. After cooling to RT, aq. HBr (2.00 mL, 48%) was added. The mixture was extracted with EtOAc (3 x 50 mL), washed with water (100 mL), dried over Na₂SO₄, concentrated *in vacuo* and purified by column chromatography to give the desired product as a dark solid (5.08 g, 69%, decomp. at 150 °C): R_f 0.63 (cyclohexane:EtOAc 10:1); ¹H-NMR (500 MHz, CDCl₃, 298 K) δ = 7.71 (2H), 7.47 (2H), 7.43 (2H), 7.37 (4H), 7.30 (12H), 7.22 (4H), 7.16 (2H), 7.24 (12H), 6.99 (4H); ¹³C-NMR (125 MHz, CDCl₃, 298 K) δ = 151.5, 150.7, 147.2, 146.3, 145.4, 137.4, 132.4, 131.9, 131.8, 130,0, 130,0, 128.7, 128.5, 126.1, 125.9, 125.7, 125.2, 121.7, 120.7, 115.9, 115.7, 112.6; ¹⁹F-NMR (377 MHz, CDCl₃, 298 K) δ = -110.6.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, photophysical characterizations and NMR-spectra can be found in the supporting information.

The Supporting Information is available free of charge at

Experimental details, photostability assessment, spectrophotometric and electrochemical data, NMR data and characterization data (PDF)

AUTHOR INFORMATION

Corresponding Author

Christof Sparr – Department of Chemistry, University of Basel, 4056 Basel, Switzerland; orcid.org/0000-0002-4213-0941; Email: christof.sparr@unibas.ch

Author

Markus Jakobi – Department of Chemistry, University of Basel, 4056 Basel, Switzerland

The authors declare no competing financial interest.

ACKNOWLEDGMENT

The authors acknowledge the University of Basel for financial support. The authors are grateful to Björn Pfund and Oliver Wenger (both University of Basel) for their advice and access to equipment for measuring photophysical and electrochemical data and Solvias AG for valuable discussions.

REFERENCES

(1) Romero, N. A.; Nicewicz, D. A. Organic Photoredox Catalysis. *Chem. Rev.* **2016**, *116*, 10075–10166.

(2) Twilton, J.; Le, C.; Zhang, P.; Shaw, M. H.; Evans, R. W.; Mac-Millan, D. W. C. The merger of transition metal and photocatalysis. *Nat. Rev. Chem.* **2017**, *1*, 0052

(3) Glaser, F.; Wenger, S. O. Recent progress in the development of transition-metal based photoredox catalysts. *Coord. Chem. Rev.* **2020**, *405*, 213129–213140.

(4) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. Visible Light Photoredox Catalysis with Transition Metal Complexes: Applications in Organic Synthesis. *Chem. Rev.* **2013**, *113*, 5322–5363. (5) Fukuzumi, S.; Kotani, H.; Ohkubo, K.; Ogo, S.; Tkachenko, N. V.; Lemmetyinen, H. Electron-Transfer State of 9-Mesityl-10-Methylacridinium Ion with a Much Longer Lifetime and Higher Energy Than That of the Natural Photosynthetic Reaction Center. *J. Am. Chem. Soc.* **2004**, *126*, 1600–1601.

(6) Joshi-Pangu, A.; Lévesque, F.; Roth, H. G.; Oliver, S. F. Campeau, L.; Nicewicz, D.; DiRocco, D. A. Acridinium-based Photocatalysts: A Sustainable Option in Photoredox Catalysis. *J. Org. Chem.* **2016**, *81*, 7244–7249.

(7) Fischer, C.; Sparr, C.; Direct Transformation of Esters into Heterocyclic Fluorophores. *Angew. Chem. Int. Ed.* **2018**, *57*, 2436–2440.

(8) White, A. R.; Wang, L.; Nicewicz, D. A. Synthesis and Characterization of Acridinium Dyes for Photoredox Catalysis. *Synlett.* **2019**, *30*, 827–832.

(9) Tlili, A.; Lakhdar, S.; Acridinium Salts and Cyanoarenes as Powerful Photocatalysts: Opportunities in Organic Synthesis. *Angew. Chem. Int. Ed.* **2021**, *60*, 19526–19549.

(10) Hutskalova, V.; Sparr, C. Synthesis and Applications of Acridinium Salts. *Science of Synthesis Knowledge Updates* 15.9.4. **2022**

(11) Zilate, B.; Fischer, C.; Schneider, L.; Sparr, C. Scalable Synthesis of Acridinium Catalysts for Photoredox Deuterations. *Synthesis* **2019**, *51*, 4359–4365.

(12) Fischer, C.; Kerzig, C.; Zilate, B.; Wenger, O. S.; Sparr, C. Modulation of Acridinium Organophotoredox Catalysts Guided by Photophysical studies. *ACS Catal.* **2020**, *10*, 210–215.

(13) Hutskalova, V.; Sparr, C. Ad Hoc Adjustment of Photoredox Properties by the Late-Stage Diversification of Acridinium Photocatalysts. *Org. Lett.* **2021**, *23*, 5143–5147.

(14) Choi A.; Miller S. Silicon Substitution in Oxazine Dyes Yields Near-Infrared Azasiline Fluorophores That Absorb and Emit beyond 700 nm. *Org. Lett.* **2018**, *20*, 4482–4485.

(15) Ando, M.; Sakai, M.; Ando, N.; Hirai, M.; Yamaguchi, S. Planarized *B*,*N*-phenylated dibenzoazaborine with a carbazole substructure: electronic impact of the structural constraint. *Org. Biomol. Chem.* **2019**, *17*, 5500–5504.

(16) Kanazawa, Y.; Yokota, T.; Ogasa, H.; Watanabe, H.; Hanakawa, T.; Soga, S.; Kawatsura, M.; Chemoselective amination of bromoiodobenzenes with diarylamines by palladium/Xantphos or ligand free copper catalysts. *Tetrahedron* **2015**, *71*, 1395–1402. (17) Sahu, D.; Tsai, C.; Wei, H.; Ho, K.; Chang, F.; Chu, C. Synthesis and application of novel low bandgap star-burst molecules containing a triphenylamine core and dialkylated diketopyrroloy-prrole arms for organic photovoltaics. *J. Mater. Chem.* **2012**, *22*, 7945–7953.

(18) Yueh, W.; Bauld, N. L.; Mechanistic Criteria for Cation Radical Reactions: Aminium Salt-Catalyzed Cyclopropanation. J. Am. Chem. Soc. **1995**, 117, 5671–5676.

(19) Ohtsuka, Y.; Yamamoto, T.; Miyazaki, T.; Yamakawa, T.; Palladium-catalyzed Selctive Amination of Aryl(haloaryl)amines with 9*H*-Carbazole Derivatives. *Adv. Synth. Catal.* **2018**, *360*, 1007–1018.

(20) Link, A.; Fischer, C.; Sparr, C. Direct transformation of Esters into Arenes with 1,5-Bifunctional Organomagnesium Reagents. *Angew. Chem. Int. Ed.* **2015**, *54*, 12163–12166.

ABBREVIATIONS

Cbz Carbazole

For Table of Contents Only

