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Synthesis of Fluorinated Acridines via Sequential Micellar Buchwald–Hartwig Amination/Cyclization of Aryl Bromides

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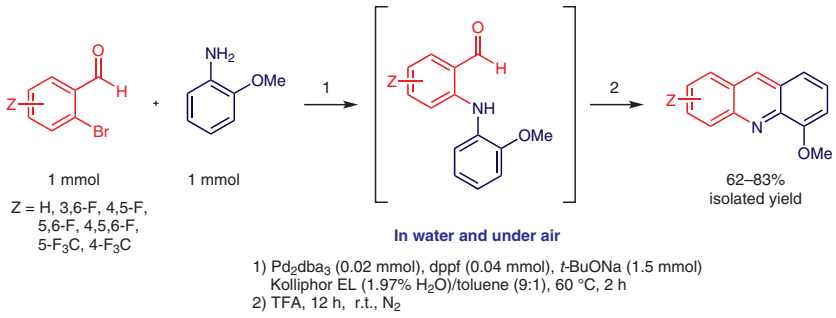

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Abstract Fluorinated unsymmetrical acridines are efficiently prepared by means of a tandem micellar Buchwald–Hartwig amination followed by an acid-promoted cyclization. The overall process is advantageous with respect to previously described protocols both in terms of efficiency and sustainability. The role of the cosolvent in the amination step is highlighted, demonstrating that rather than resorting to highly expensive catalysts, Buchwald–Hartwig aminations can be straightforwardly carried out by tuning the reaction site polarity.

Key words micellar synthesis, Buchwald–Hartwig amination, fluorinated acridines, cosolvent

Acridine derivatives are an important class of heteroaromatic compounds[1,2] having a wide range of applications ranging from medicinal chemistry,[3–6] DNA and RNA intercalation,[7] roles in dye industries,[8] fluorescence imaging, and more recently in plastic electronics and optoelectronics.[9–12] As a result, the chemistry and physics of such compounds has been thoroughly investigated aiming at the formulation of accurate structure–properties relationships to be employed as guidelines for the synthesis of new derivatives.

Acridines were first isolated in 1870 by Carl Graebe and Heinrich Caro from coal tar by extracting the corresponding salt with dilute sulfuric acid.[13] One of the earliest synthetic protocols for their preparation is the Bernthsen reaction, where a diphenylamine derivative and a carboxylic acid are directly heated (neat) at high temperature together with $ZnCl_2$.[14,15] Albeit effective, the method is clearly limited by the thermal stability of the precursors and has poor tolerance toward substituents. Whenever the corresponding 9-acridone can be prepared, i.e., by cyclization of diphenylamine-2-carboxylic acids, acridines can be prepared by subsequent reduction.[16–18] It is also possible to obtain acridines directly by the cyclization of diphenylamine-2-aldehydes or diphenylamine-2-ketones, yet the preparation of the required precursors is troublesome.[19–21] Other approaches are also documented involving dehydrogenation and C–H activation. Most of the aforementioned methods are characterized by relatively harsh conditions, limiting the number of derivatives that can be conveniently prepared. Also, such methods are particularly efficient for the preparation of symmetric derivatives.[19–21]

We became particularly interested in fluorinated unsymmetrical acridines bearing a methoxy functionality as closely related compounds, upon cleavage of the OH functionality and subsequent modification of the phenolic ring, show remarkable activity against resistant bacteria strains.[22] Amongst the methods giving access to unsymmetrical acridines, the recently reported tandem palladium amination/cyclization sequence described by Wang et al. is particularly advantageous.[23] In fact, the method allows the preparation of a wide variety of acridines starting from commercially available and inexpensive α-bromoaldehydes and anilines.

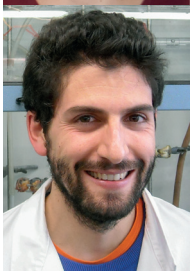
On looking for a way to make this approach more general and green chemistry compliant, we focused our attention to the growing field of micellar chemistry.[24–26] Micelles are the association colloid formed by the self-assembly of a surfactant in water reaching a certain threshold concentration known as the critical micellar concentration. The use of micelles is well established in formulation chemistry as this type of association colloid enables the dispersion in water of hydrophobic materials.[27]

In recent years, mostly thanks to the pioneering work of Prof. Lipshutz, micelles have moved from being considered a simple passive reservoir of lipophilic materials in water to a nanoreactor where a large number of chemical transformation can be efficiently carried out in water as the only solvent, at room temperature and in surprisingly short

Biographical Sketches

Luca Vaghi is from Como, Italy. He graduated in Chemical Sciences at the University of Insubria under the supervision of Prof. Giovanni Palmisano, focusing on heterocyclic synthesis. He received his Ph.D. degree in 2012 from the University of Milan under the supervision of Prof. Francesco Sannicolò, working on the synthesis of new chiral phosphane ligands. In 2013, he joined the 'Inherently Chiral Multifunctional Conducting Polymers' project at the University of Como. Since 2015, he has held a postdoctoral position at the University of Milano-Bicocca in the group of Prof. Antonio Papagni. His research activities concern the synthesis of nitrogen heterocycles for materials science and biological applications, halogen-fused carbocyclic aromatics for metal surface modifications and metal porphyrazines for organic electronics. Apart from organic chemistry he loves skiing big powder days and surfing.

Alessandro Sanzone was born in 1991 in Desio, Italy. He graduated in Chemical Sciences at the University of Milano-Bicocca in 2015 under the supervision of Prof. Luca Beverina, working on the synthesis of nanocomposite materials based on conductive polymers. He is now a Ph.D. student in the same research group. His work is focused on the synthesis of new derivatives for organic electronics. Apart from chemistry, he is a CrossFit enthusiast and enjoys making beer.



Mauro Sassi was born in 1982 in Varese, Italy. In 2007, he graduated in Materials Science from the University of Milano-Bicocca under the supervision of Prof. Giorgio A. Pagani. In 2011, he received his Ph.D. in Materials Science from the same University under the supervision of Dr. Luca Beverina, with a thesis on high-performance heteroaromatic electrochromic organic materials. Since 2011, he has been employed as a postdoctoral researcher at the University of Milano-Bicocca. His research interests cover organic photovoltaics, rechargeable organic batteries, electrochromism and sustainable synthesis of organic materials. In his spare time, he enjoys playing the French horn and hiking.

Simone Pagani was born in 1993 in Brescia, Italy. He received his bachelor's degree from the University of Milan-Bicocca, under the supervision of the Prof. Antonio Papagni and Dr. Luca Vaghi, working on the synthesis of amino-cyclophanes. He is currently finishing his master's thesis with the same research group dealing with the micellar Buchwald–Hartwig synthesis of fluoro(methoxy)acridines and subsequent modifications in the search for activity against resistant bacteria, in collaboration with the University of Florida. He is also an enthusiast of artistic photography.

Antonio Papagni was born in 1954 in Bisceglie. He obtained a degree in chemistry in 1981 at the University of Milan. From 1981 to 1983 he worked as a researcher at Zambeletti Pharmaceutical Company. In 1987, he obtained his Ph.D. in Chemical Sciences. From 1987 to 1990 he worked as a researcher at Mediolanum Pharmaceutical Company. From 1990 to 1998 he was a researcher at the University of Milan and an associate professor in organic chemistry at the University of Milano-Bicocca from 1998 up until 2013. Since 2013, he has been a full professor in organic chemistry at the University of Milano-Bicocca. His present scientific interests include studies on oligothiophene- and fluoroacridine-based organic molecular systems useful in the development of organic semiconductors and electroluminescent devices (OLEDs), studies on the reactivity of perfluorinated aromatic systems toward nucleophilic substitution and their use in the preparation of polyfluorinated heteroaromatic systems with semiconducting and biological activities. His main interests outside the lab involve music (from classic to modern), reading and mountain walking.

Luca Beverina was born in 1975 in Milano, Italy. He graduated in Materials Science at the University of Milano-Bicocca in 1999. He received his Ph.D. in Materials Science from the same university in 2002 discussing a thesis on multiphoton absorption phenomena in organic conjugated materials. He later joined the group of Prof. Seth R. Marder at the Georgia Institute of Technology for a one-year postdoctoral period. He then returned to the University of Milano-Bicocca as a postdoctoral researcher for another year. In 2004, he obtained a permanent faculty position as an assistant professor of organic chemistry at the University of Milano-Bicocca. In 2014, he became an associate professor at the same university. Prof. Beverina's present research interests cover organic photovoltaics, electrochromism, rechargeable organic batteries, micellar synthesis with occasional excursions into photo- and thermoresistors. Apart from chemistry, he enjoys hiking, swimming, growing exotic varieties of chili peppers and listening to alternative music. He is particularly fond of the Norwegian band Ulver.

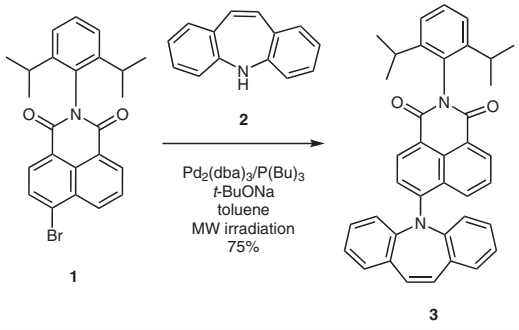
reaction times. The number of documented micellar reactions is growing constantly and includes most of the modern C–C and C–N bond-forming reactions, with or without metal catalysts being involved. To name but a few recent examples, Suzuki–Miyaura,[28–33] Stille,[34,35] Heck,[25,33,35–38] Sonogashira,[37,39] nucleophilic aromatic substitution,[40,41] gold-promoted couplings,[42–44] sp^2–sp^3 coupling of nitroalkanes,[45] metathesis and Miyaura borylations.[34,35] The catalyst loading can be greatly reduced and the recyclability of the reaction medium further helps in reducing the environmental impact of several common organic reactions.[29,30] As the Buchwald–Hartwig reaction is also reported to be particularly efficient under appropriate micellar conditions,[46–48] we decided to merge micellar amination and cyclization under Wang's conditions[23] in a new protocol for the preparation of unsymmetrically fluorinated acridine derivatives.

The key factor in a successful micellar reaction is the selection of the surfactant. The literature reports an increasing number of both commercially available and 'designer' surfactants.[25,36] We became particularly interested in commercially available Kolliphor EL (a polyethoxylated castor oil derivative) as this surfactant combines reasonable performances in Suzuki–Miyaura reactions with an unprecedented resistance to an oxygenated environment.[45] Indeed, reactions performed in a Kolliphor (2% by weight) solution in water occur identically under nitrogen and standard laboratory atmospheres.

We thus decided to explore the suitability of Kolliphor EL as the medium for the Buchwald–Hartwig (B-H) amination under air, firstly to characterize the reaction in general, and secondly to implement the protocol in the amination/cyclization scheme established by Wang et al.[23]

In order to optimize the micellar B-H protocol, we selected the test reaction shown in Scheme 1. Derivative **3** was previously prepared by our group via the reaction of bromide **1** and azepine **2** according to a microwave-enhanced protocol, with toluene as the solvent and working under a nitrogen atmosphere. This molecule behaves as a fluorescent molecular rotor and finds application in the monitoring of the self-assembly process of relevant block copolymers in water.[49] We have become increasingly aware of the need to improve sustainability in the preparation of organic semiconductors. As such, we decided to use this particular reaction as an opportunity to widen the scope of our previous studies on the Suzuki–Miyaura micellar synthesis of conjugated molecules.

Micellar B-H amination has a relevant track record in the dedicated literature. Whilst there is little doubt that second generation TPGS-750-M (DL-α-tocopherol methoxypolyethylene glycol succinate) is the surfactant of choice, several studies have highlighted the critical role of both the precatalyst/phosphine system and the base employed in the reaction kinetics and yield. Restricting to readily available materials, Takesago's cBRIDP phosphine and (allyl)$PdCl_2$ are generally considered a good starting point while optimizing a method.[46,48] The group of Christophe Salomé and Martine Schmitt later made an extensive screening of the possible catalytic systems, concluding that [(cinnamyl)$PdCl]_2$/*t*-BuXPhos is advantageous both in terms of generality and of performance of the reaction over different nitrogen-containing nucleophiles.[47,48]



Scheme 1 Test reaction selected to optimize the Buchwald–Hartwig amination protocol

It is also important to note that the role of the employed base is crucial. In fact, the group of Lipshutz pointed out that in order to achieve co-localization of all reaction partners within the micelle core, the lipophilicity of the base is crucial. As such, the addition of commercially available TIPS-OH to the standard *t*-BuOK (obviously corresponding to a KOH/*t*-BuOH mixture while working in water) greatly reduces reaction times due to the formation in situ of lipophilic TIPS-OK.[50]

From the standpoint of the surfactant employed, we did not expect Kolliphor EL to be drastically different from TPGS-750-M. Both derivatives in fact share a polyoxyethylene hydrophilic part, an ester linkage and an aliphatic long chain as the lyophilic part. As for the base and catalyst, we decided to test *t*-BuOK and the (allyl)$PdCl_2$/cBRIDP system first, having in mind a cost/performance trade-off. Quite surprisingly, we observed no reaction both while working at room temperature and at 50 °C, even for very prolonged reaction times (Table 1, entries 1 and 2). According to our previous experience with standard B-H amination of **1**, *t*-Bu_3P proved to be particularly efficient. We thus explored the (allyl)$PdCl_2$/*t*-$Bu_3P^*HBF_4$ catalytic system, but unfortunately again to no avail (entries 3 and 4). We also tested different precatalysts by using $Pd(OAc)_2$/*t*-$Bu_3P^*HBF_4$ and $Pd_2(dba)_3$/*t*-$Bu_3P^*HBF_4$, but analysis of the reaction mixtures gave, in both cases, mostly starting materials (entries 5 and 6). In order to highlight the possible role of the surfactant, we finally tested TPGS-750-M, again working with $Pd(OAc)_2$/*t*-$Bu_3P^*HBF_4$ for consistency. In this case the reactions gave a trace amount of the product (4% yield) when working at room temperature for 24 hours, and slightly better results (23% yield) when working at 50 °C.

Table 1 Buchwald–Hartwig Amination of **1** under Micellar Conditions

Entry	Surfactant	Catalyst	Base	Time/Temp	Yield[a]
1	Kolliphor EL (2%)	(allyl)$PdCl_2$/cBRIDP	*t*-BuOK/TIPS-OH	24 h/r.t	–
2	Kolliphor EL (2%)	(allyl)$PdCl_2$/cBRIDP	*t*-BuOK/TIPS-OH	24 h/50 °C	–
3	Kolliphor EL (2%)	(allyl)$PdCl_2$/*t*-$Bu_3P^*HBF_4$	KOH/TIPS-OH	24 h/r.t.	–
4	Kolliphor EL (2%)	(allyl)$PdCl_2$/*t*-$Bu_3P^*HBF_4$	KOH/TIPS-OH	24 h/50 °C	–
5	Kolliphor EL (2%)	$Pd(OAc)_2$/*t*-$Bu_3P^*HBF_4$	KOH/TIPS-OH	24 h/50 °C	–
6	Kolliphor EL (2%)	$Pd_2(dba)_3$/*t*-$Bu_3P^*HBF_4$	*t*-BuONa	24 h/50 °C	2%
7	Kolliphor EL (2%)	$(allylPdCl)_2$/cBRIDP	*t*-BuOK	24 h/r.t.	–
8	Kolliphor EL (2%)	$(allylPdCl)_2$/cBRIDP	*t*-BuOK	24 h/50 °C	3%
9	TPGS-750M (2%)	$Pd(OAc)_2$/*t*-$Bu_3P^*HBF_4$	*t*-BuOK/TIPS-OH	24 h/r.t.	4%
10	TPGS-750M (2%)	$Pd(OAc)_2$/*t*-$Bu_3P^*HBF_4$	*t*-BuOK/TIPS-OH	24 h/50 °C	23%

[a] Yield of isolated product.

Though encouraging, such results where far from satisfactory and hinted at a particularly sluggish reaction with respect to other examples already described in the literature. Also, the different behavior of the two surfactants hinted at a problem with the localization of the reactive species, more than an unsuitable catalytic system. Indeed, in entry 6 (Table 1), we used the very same catalyst that afforded satisfactory results with the standard non-aqueous approach.

Rather than exploring the wide variety of catalytic systems/surfactants that could afford better results in terms of localization within the micellar core of all the reactive species, we turned to the so called 'cosolvent' approach, originally proposed by the Lipshutz group. The use of a small amount (10% by volume with respect to the water employed) of an organic solvent within a micellar solution leads to swelling of the micelles (in the case of water-miscible solvents) or formation of a (micro)emulsion (with water-immiscible solvents). In both cases, the volume fraction of the lipophilic cores with respect to water is increased—thus leaving more space for the reactions to happen—and the polarity of the core itself is tuned. In other words, the hydrophilic–lipophilic balance (HLB) of the micellar nanoreactor is changed. Indeed, when working with a 10% by volume of toluene within a 2% by weight Kolliphor EL solution, we were able to go from no reaction at all to 80% isolated yield in just 4 hours at 60 °C while using the very simple and affordable $Pd(OAc)_2$/*t*-$Bu_3P^*HBF_4$ catalytic system (Table 2, entries 1–3). The yield increased to 89% when the well-established Buchwald–Hartwig $Pd_2(dba)_3$/dppf catalytic system was used (entry 4).

Even more interestingly, the reaction could be performed directly in air, confirming the peculiar resistance to oxygen of Kolliphor EL micelles even in the presence of a cosolvent. We also tested acetone and THF as cosolvents, but with inferior results (Table 2, entries 2 and 3). The poor stability to a strong alkaline environment is the likely reason for the poor performance with acetone. THF performed only slightly less efficiently than toluene.

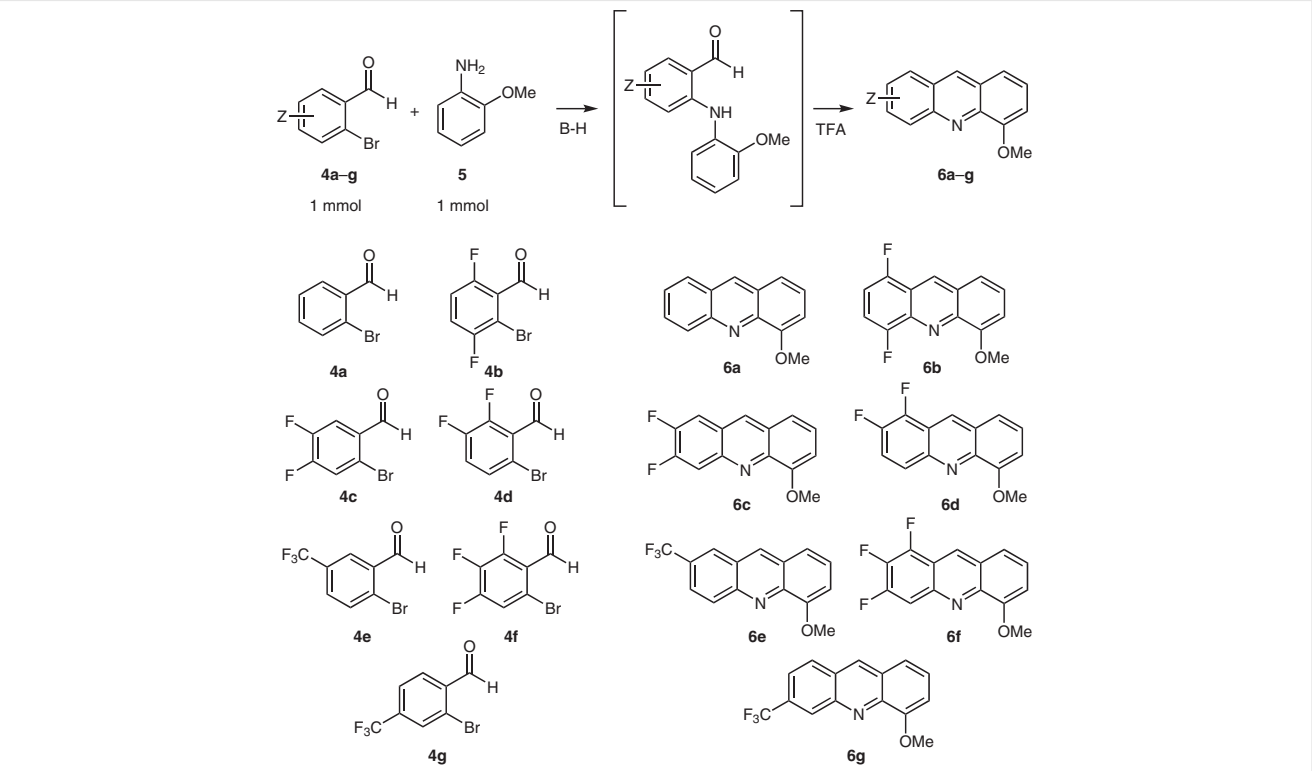
Having optimized the B-H method with the synthesis of **3**, we thus turned our attention to the synthesis of fluorinated acridines via amination/cyclization. The general reaction is reported in Scheme 2.

In their original paper, Wang and co-workers reported the synthesis of several unsymmetrical acridine derivatives, according to a standard B-H amination followed by an $AlCl_3$-catalyzed cyclization, with yields ranging from good to excellent.[23] In our hands, the reactions were not quite as efficient. We repeated the protocol exactly as reported in order to prepare **6a**, but with only a 43% yield of isolated product being obtained. In order to improve the reaction outcome, we tested trifluoroacetic acid[20] and thermal induction in boiling xylene[10] in place of $AlCl_3$ for the cyclization step. The reaction carried out with TFA resulted in a 53% yield of **6a**, while the reaction in boiling xylene alone gave only a 32% yield of the desired product; we thus consistently used TFA in all our subsequent experiments, micellar or not.

Table 2 Buchwald–Hartwig Amination of **1** under Micellar Conditions Aided by a Cosolvent[a]

Entry	Cosolvent	Catalyst	Time	Yield[b]
1	toluene	$Pd(OAc)_2$/*t*-$Bu_3P^*HBF_4$	4 h	50%
2	acetone	$Pd(OAc)_2$/*t*-$Bu_3P^*HBF_4$	4 h	30%
3	THF	$Pd(OAc)_2$/*t*-$Bu_3P^*HBF_4$	4 h	80%
4	toluene	$Pd_2(dba)_3$/dppf	24 h	89%

[a] Base: *t*-BuOK. Reaction temperature: 60 °C.
[b] Yield of isolated product.



Scheme 2 General synthetic access and the structures of unsymmetrically substituted acridines **6a–g**

Thus, the corresponding fluorinated aldehydes **4b–d** were reacted with 2-methoxyaniline (**5**) in toluene at 80 °C for 24 hours in the presence of K_2CO_3 as the base and with the common $Pd_2(dba)_3$/dppf catalytic system, under nitrogen. The crude reaction mixture was directly submitted to TFA-catalyzed cyclization to give acridines **6b–d** in isolated yields of 26%, 55% and 59%, respectively (Table 3).

In order to make a more direct comparison between the micellar and the standard methods, we purposely decided not to change the catalytic system and performed all the reactions using $Pd_2(dba)_3$/dppf as the catalyst, and employed our optimized toluene-improved micellar conditions using Kolliphor EL. All the reactions were carried out under air and were quenched following 2 hours at 60 °C (after checking that conversion was complete). Work-up of the amination reaction required removal of all volatiles and filtration through a pad of silica. The crude filtrate was then subjected to the cyclization reaction according to the conditions of the control experiment. As summarized in Table 3, in all of the cases, the micellar protocol gave yields that were comparable, if not better, than those obtained in an organic solvent. Obviously, as we did not isolate the intermediate in both the control and micellar experiments, we cannot confirm that the overall improvement is due to a more efficient B-H step. Yet, from the standpoint of access to the final target acridines, our process is advantageous both in terms of efficiency and sustainability.

Table 3 Outcomes of the Tandem Micellar B-H/TFA-Catalyzed Cyclization

Entry	Aldehyde	Product	Organic solvent B-H step[a,b]	Aqueous micellar B-H step[a,c]
1	**4a**	**6a**	53%	71%
2	**4b**	**6b**	26%	72%
3	**4c**	**6c**	55%	62%
4	**4d**	**6d**	59%	83%
5	**4e**	**6e**	–	78%
6	**4f**	**6f**	–	72%
7	**4g**	**6g**	–	74%

[a] Yield of isolated product.
[b] Aldehydes **4** were reacted with 2-methoxyaniline (**5**) in toluene at 80 °C for 24 hours with K_2CO_3 as base and $Pd_2(dba)_3$/dppf as the catalyst. The crude reaction mixture was directly submitted to TFA-catalyzed cyclization.
[c] Aldehydes **4** were reacted with 2-methoxyaniline (**5**) in a mixture of Kolliphor EL (2% water solution) and toluene (9:1 volume ratio) at 60 °C for 2 hours with *t*-BuONa as the base and $Pd_2(dba)_3$/dppf as the catalyst. The crude reaction mixture was evaporated, and the residue was submitted directly to TFA-catalyzed cyclization.

In order to explore the generality of this method, we explored three other commercially available α-bromoaldehydes **4e–g**, again leading to the corresponding acridines **6e–g** with yields in all of the cases exceeding 70% for the two steps.

In conclusion, we have demonstrated that B-H amination of aryl bromides can be efficiently carried out with catalytic systems much simpler and cheaper than those previously described as being ideal for this kind of reaction. The beneficial effects are due to the details of the particular formulation strategy employed to tune the characteristics of the micellar nanoreactors with respect to the requirements of the reaction being performed. The method was successfully applied to the high-yield preparation of a molecular fluorescent probe at low temperature and in air. The developed B-H protocol was then employed as the first step of the amination/cyclization synthesis toward a series of fluorinated unsymmetrical acridine derivatives. In all case, this novel protocol gave better results than those obtained by employing an organic-solvent-based literature procedure. The prepared acridines, mostly original, are currently under investigation as potential antibiotics against resistant bacterial strains.

Bromoaldehydes were purchased from Fluorochem Ltd. and were used without further purification. Kolliphor EL was purchased from Sigma-Aldrich. Chromatographic purifications were performed using Merck 9385 silica gel, pore size 60 Å (230–400 mesh). Melting points were measured with a Stanford Research Systems Optimelt apparatus. IR spectra were recorded with a Perkin Elmer Spectrum 100 FT-IR spectrometer equipped with a universal ATR sampling accessory. ^{1}H, ^{13}C and ^{19}F NMR were recorded with a Bruker AVANCE III HD 400 MHz spectrometer. Mass analyses were performed using a VG 7070 EQ-HF instrument. Elemental analyses were obtained with an Elementar vario MICRO cube instrument.

Acridines 6; General Procedure

α-bromoaldehyde **4a–g** (1 mmol), 2-methoxyaniline (**5**) (1 mmol), $Pd_2(dba)_3$ (0.02 mmol), dppf (0.04 mmol) and *t*-BuONa (1.5 mmol) were added to a mixture of Kolliphor EL (1.8 mL, 1.97% H_2O) and toluene (0.2 mL) and stirred (500 rpm) at 60 °C for 2 h. After cooling to r.t., EtOH was added (about 10 mL, until the reaction mixture became homogeneous) and the solvents were removed under reduced pressure. The residue was eluted with toluene over a short pad of silica gel and the solvent was evaporated. TFA (2 mL) was added to the solid residue under a nitrogen atmosphere and the mixture was left to stir overnight at r.t. The solution was slowly added to a saturated aqueous solution of $NaHCO_3$ (50 mL) and the resulting suspension was extracted with CH_2Cl_2 (3 × 30 mL). The organic layers were dried (Na_2SO_4) and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (SiO_2) to afford the desired acridine in pure form.

4-Methoxyacridine (6a)

The general procedure was applied using 2-bromobenzaldehyde (**4a**) (185 mg, 1 mmol) to afford acridine **6a** (131 mg, 71%) as a yellow solid; mp 121–122 °C; R_f = 0.11 (CH_2Cl_2/EtOH, 99:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.72 (s, 1 H, 9-H), 8.40 (d, *J* = 9.0 Hz, 1 H, 5-H), 7.97 (d, *J* = 8.4 Hz, 1 H, 8-H), 7.80–7.71 (m, 1 H, 7-H), 7.60–7.51 (m, 2 H, 6-H, 1-H), 7.46–7.40 (m, 1 H, 2-H), 7.04 (d, *J* = 7.5 Hz, 1 H, 3-H), 4.16 (s, 3 H, CH_3).

The spectroscopic data corresponded to those reported in the literature.[23]

1,4-Difluoro-5-methoxyacridine (6b)

The general procedure was applied using 2-bromo-3,6-difluorobenzaldehyde (**4b**) (221 mg, 1 mmol) to afford acridine **6b** (159 mg, 72%) as a yellow solid; mp 183–185 °C; R_f = 0.15 (CH_2Cl_2).

IR (ATR): 3086, 3065, 2959, 2930, 1651, 1619, 1536, 1477, 1442, 1403, 1355, 1321, 1247, 1222, 1162, 1117, 1070, 1042, 1023, 966, 912, 836, 774, 737, 703, 628 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.99 (d, *J* = 1.1 Hz, 1 H, 9-H), 7.62 (ddd, *J* = 8.5, 1.2, 0.5 Hz, 1 H, 8-H), 7.53 (dd, *J* = 8.5, 7.5 Hz, 1 H, 3-H), 7.36 (ddd, *J* = 10.1, 8.3, 4.7 Hz, 1 H, 2-H), 7.14–7.07 (m, 2 H, 6-H, 7-H), 4.16 (s, 3 H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 155.4 (s, C-5), 154.5 (dd, *J* = 255.6, 4.2 Hz, C-4), 153.5 (dd, *J* = 253.3, 4.0 Hz, C-1), 142.2 (s, C-10a), 138.5 (d, *J* = 17.9 Hz, C-4a), 130.0 (m, C-8a), 127.5 (d, *J* = 2.1 Hz, C-9), 127.2 (s, C-8), 120.0 (s, C-7), 119.2 (d, *J* = 19.0 Hz, C-9a), 111.4 (dd, *J* = 22.1, 8.9 Hz, C-3), 107.8 (s, C-6), 107.3 (dd, *J* = 21.9, 7.3 Hz, C-2), 56.2 (s, CH_3).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –139.78 (d, *J* = 17.2 Hz), –148.66 (d, *J* = 17.0 Hz).

MS (EI): *m*/*z* = 245 [M]$^+$.

Anal. Calcd for $C_{14}H_9F_2NO$: C, 68.57; H, 3.70; N, 5.71. Found: C, 68.63; H, 3.78; N, 5.54.

2,3-Difluoro-5-methoxyacridine (6c)

The general procedure was applied using 2-bromo-4,5-difluorobenzaldehyde (**4c**) (221 mg, 1 mmol) to afford acridine **6c** (152 mg, 62%) as a yellow solid; mp 157–159 °C; R_f = 0.20 (CH_2Cl_2).

IR (ATR): 3032, 2960, 2920, 2851, 1647, 1620, 1569, 1532, 1487, 1468, 1433, 1406, 1344, 1309, 1292, 1239, 1280, 1208, 1178, 1154, 1135, 1103, 1065, 978, 918, 870, 832, 761, 731, 719 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.59 (s, 1 H, 9-H), 8.16–8.05 (m, 1 H, 4-H), 7.60 (dd, *J* = 10.2, 8.7 Hz, 1 H, 1-H), 7.48 (m, 2 H, 7-H, 8-H), 7.05 (dd, *J* = 7.3, 1.3 Hz, 1 H, 6-H), 4.15 (s, 3 H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 154.9 (s, C-5), 153.4 (dd, *J* = 257.5, 17.9 Hz, C-2), 150.4 (dd, *J* = 255.0, 17.7 Hz, C-3), 145.2 (d, *J* = 11.4 Hz, C-4a), 141.9 (s, C-10a), 135.2 (dd, *J* = 7.1, 2.2 Hz, C-9a), 127.3 (d, *J* = 1.6 Hz, C-8a), 126.2 (s, C-8), 123.7 (d, *J* = 8.1 Hz, C-9), 119.6 (s, C-7), 115.2 (d, *J* = 15.7 Hz, C-1), 111.8 (dd, *J* = 17.6, 1.8 Hz, C-4), 107.1 (s, C-6), 56,2 (s, CH_3).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –128.74 (d, *J* = 18.7 Hz), –134.01 (d, *J* = 19.1 Hz).

MS (EI): *m*/*z* = 245 [M]$^+$.

Anal. Calcd for $C_{14}H_9F_2NO$: C, 68.57; H, 3.70; N, 5.71. Found: C, 68.52; H, 3.82; N, 5.68.

1,2-Difluoro-5-methoxyacridine (6d)

The general procedure was applied using 6-bromo-2,3-difluorobenzaldehyde (**4d**) (221 mg, 1 mmol) to afford acridine **6d** (183 mg, 83%) as a yellow solid; mp 192–194 °C; R_f = 0.16 (CH_2Cl_2).

IR (ATR): 3068, 3008, 2959, 2934, 2834, 1657, 1619, 1590, 1527, 1481, 1460, 1406, 1320, 1302, 1280, 1240, 1224, 1169, 1152, 1119, 1063, 935, 906, 863, 820, 799, 764, 737, 636, 604 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.93 (s, 1 H, 9-H), 8.19 (dddd, *J* = 9.7, 4.4, 1.9, 0.9 Hz, 1 H, 4-H), 7.62 (td, *J* = 9.9, 8.4 Hz, 1 H, 3-H), 7.56 (dd, *J* = 8.6, 1.0 Hz, 1 H, 8-H), 7.47 (dd, *J* = 8.5, 7.5 Hz, 1 H, 7-H), 7.05 (dd, *J* = 7.5, 1.0 Hz, 1 H, 6-H), 4.16 (s, 3 H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 155.1 (s, C-5), 145.2 (dd, *J* = 249.7, 11.3 Hz, C-1), 144.5 (s, C-10a), 142.8 (dd, *J* = 256.7, 12.9 Hz, C-2), 141.8 (d, *J* = 2.1 Hz, C-8a), 129.0 (dd, *J* = 8.6, 3.3 Hz, C-9a), 127.2 (m, C-4), 126.9 (s, C-4a), 121.4 (s, C-8), 121.2 (s, C-7), 119.9 (s, C-9), 119.1 (dd, *J* = 13.4, 2.4 Hz, C-3), 107.1 (s, C-6), 56.2 (s, CH_3).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –139.78 (d, *J* = 17.2 Hz), –148.66 (d, *J* = 17.0 Hz).

MS (EI): *m*/*z* = 245 $[M]^+$.

Anal. Calcd for $C_{14}H_9F_2NO$: C, 68.57; H, 3.70; N, 5.71. Found: C, 68.75; H, 3.79; N, 5.66.

5-Methoxy-2-(trifluoromethyl)acridine (6e)

The general procedure was applied using 2-bromo-5-(trifluoromethyl)benzaldehyde (**4e**) (253 mg, 1 mmol) to afford acridine **6e** (197 mg, 78%) as a yellow solid; mp 160–162 °C; R_f = 0.19 (CH_2Cl_2).

IR (ATR): 3066, 2965, 2922, 2853, 1638, 1620, 1565, 1526, 1461, 1444, 1423, 1410, 1330, 1271, 1259, 1219, 1155, 1123, 1052, 917, 840, 808, 768, 754, 720, 680, 656, 629 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.73 (s, 1 H, 9-H), 8.49 (dd, *J* = 9.2, 0.8 Hz, 1 H, 4-H), 8.26–8.23 (m, 1 H, 1-H), 7.87 (dd, *J* = 9.2, 2.0 Hz, 1 H, 3-H), 7.52 (dd, *J* = 8.6, 0.9 Hz, 1 H, 8-H), 7.45 (dd, *J* = 8.5, 7.4 Hz, 1 H, 7-H), 7.07 (dd, *J* = 7.4, 1.1 Hz, 1 H, 6-H), 4.15 (s, 3 H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 155.1 (s, C-5), 148.1 (s, C-4a), 143.2 (s, C-10a), 137.4 (s, C-4), 131.5 (s, C-9), 127.9 (s, C-8a), 127.7 (q, *J* = 32.8 Hz, C-2), 126.6 (s, C-8), 126.2 (q, *J* = 4.7 Hz, C-1), 125.1 (s, C-9a), 125.0 (q, *J* = 2.0 Hz, C-3), 124.0 (q, *J* = 272.7 Hz, CF_3), 119.98 (s, C-7), 107.69 (s, C-6), 56.23 (s, CH_3).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –62.77 (s).

MS (EI): *m*/*z* = 277 $[M]^+$.

Anal. Calcd for $C_{15}H_{10}F_3NO$: C, 64.98; H, 3.64; N, 5.05. Found: C, 64.90; H, 3.75; N, 5.08.

1,2,3-Trifluoro-5-methoxyacridine (6f)

The general procedure was applied using 6-bromo-2,3,4-trifluorobenzaldehyde (**4f**) (239 mg, 1 mmol) to afford acridine **6f** (172 mg, 72%) as a yellow solid; mp 179–180 °C; R_f = 0.15 (CH_2Cl_2).

IR (ATR): 3064, 3029, 2961, 2920, 2839, 1669, 1620, 1592, 1537, 1478, 1436, 1410, 1329, 1291, 1246, 1187, 1171, 1161, 1114, 1042, 987, 929, 909, 859, 763, 731, 723, 682, 654 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.89 (s, 1 H, 9-H), 7.99–7.89 (m, 1 H, 4-H), 7.57 (d, *J* = 7.8 Hz, 1 H, 8-H), 7.50 (t, *J* = 7.4 Hz, 1 H, 7-H), 7.10 (d, *J* = 6.6 Hz, 1 H, 6-H), 4.17 (s, 3 H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 154.8 (s, C-5), 153.3 (ddd, *J* = 256.2, 14.6, 4.0 Hz, C-1), 144.2 (ddd, *J* = 258.2, 11.0, 5.5 Hz, C-3), 142.8–142.6 (m, C-4a), 142.5 (s, C-10a), 137.4 (ddd, *J* = 255.7, 20.3, 14.2 Hz, C-2), 129.5 (m, C-8a, C-9), 126.8 (s, C-8), 119.9 (s, C-7), 116.2 (d, *J* = 13.5 Hz, C-9a), 110.5 (dd, *J* = 17.4, 4.7 Hz, C-4), 107.7 (s, C-6), 56.3 (s, CH_3).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –127.89 (d, *J* = 15.7 Hz), –145.02 (d, *J* = 12.6 Hz), –159.12 (t, *J* = 17.1 Hz).

MS (EI): *m*/*z* = 263 $[M]^+$.

Anal. Calcd for $C_{14}H_8F_3NO$: C, 63.88; H, 3.06; N, 5.32. Found: C, 64.02; H, 3.11; N, 5.27.

5-Methoxy-3-(trifluoromethyl)acridine (6g)

The general procedure was applied using 2-bromo-4-(trifluoromethyl)benzaldehyde (**4g**) (253 mg, 1 mmol) to afford acridine **6g** (187 mg, 74%) as a yellow solid; mp 155–157 °C; R_f = 0.17 (CH_2Cl_2).

IR (ATR): 3065, 3026, 2962, 2932, 2839, 1620, 1523, 1460, 1439, 1405, 1330, 1304, 1253, 1218, 1173, 1140, 1110, 1098, 1051, 948, 911, 865, 810, 762, 740, 723, 684, 667 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.83–8.81 (m, 1 H, 4-H), 8.81 (s, 1 H, 9-H), 8.11 (d, *J* = 8.9 Hz, 1 H, 1-H), 7.70 (dd, *J* = 8.8, 1.7 Hz, 1 H, 8-H), 7.64–7.60 (m, 1 H, 2-H), 7.54 (dd, *J* = 8.5, 7.4 Hz, 1 H, 7-H), 7.12 (dd, *J* = 7.5, 1.0 Hz, 1 H, 6-H), 4.20 (s, 3 H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 155.1 (s, C-5), 146.3 (s, C-4a), 142.7 (s, C-10a), 136.2 (s, C-1), 131.6 (q, *J* = 32.6 Hz, C-3), 129.3 (s, C-9), 128.5 (s, C-8a), 128.2 (q, *J* = 4.5 Hz, C-4), 127.4 (s, C-9a), 127.1 (s, C-8), 126.9 (q, *J* = 288.1 Hz, CF_3), 121.4 (q, *J* = 2.8 Hz, C-2), 119.9 (s, C-7), 107.5 (s, C-6), 56.3 (s, CH_3).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –63.17 (s).

MS (EI): *m*/*z* = 277 $[M]^+$.

Anal. Calcd for $C_{15}H_{10}F_3NO$: C, 64.98; H, 3.64; N, 5.05. Found: C, 64.85; H, 3.72; N, 5.12.

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Supporting Information

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