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Merging Micellar Catalysis and C–H Activation: Silver-Free Direct Arylation of Fluoroarenes in Water

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ABSTRACT

The direct arylation of fluoroarenes is a powerful but sustainability-limited transformation, as most established protocols rely on organic solvents and stoichiometric silver additives. Here, we report the first silver-free palladium-catalyzed C–H arylation of fluoroarenes in water containing self-assembled surfactant structures (micelles) as reaction medium. Using the designer surfactant PS-750-M, this sustainable method enables the coupling of diverse pyridines and fluoroarenes under mild conditions, displaying broad functional-group tolerance while fully eliminating organic co-solvents. Mechanistic studies, including kinetics, FT-IR spectroscopy, dynamic light scattering (DLS), and freeze-fracture combined transmission electron microscopy (FF-TEM), reveal the nature of interactions between the catalyst, substrates and distinct micellar domains, providing insight into microenvironmental effects on reactivity and selectivity. The robustness of the catalytic system further allows tandem one-pot sequences, such as C–H arylation/S_NAr reactions, without intermediate workup or adding an additional catalyst. This work demonstrates how merging micellar catalysis with C–H activation unlocks a practical, environmentally responsible platform for cross-coupling chemistry, expanding the utility of aqueous media for sustainable synthesis.

1 | Introduction

The development of sustainable catalytic methodologies is a central objective of modern organic synthesis, both to minimize environmental impact and to meet the growing demand for efficient and scalable processes in industry [1, 2]. Among the 12 principles of green chemistry, the reduction of waste and the adoption of safer solvents and mild reaction conditions are particularly critical [3]. In majority of processes delivering fine chemicals and pharmaceuticals, the solvent represents the main waste, even more importantly than stoichiometric reagents or byproducts [4]. Consequently, replacing traditional volatile and often toxic organic solvents with environmentally benign alternatives is one of the effective ways to reduce the

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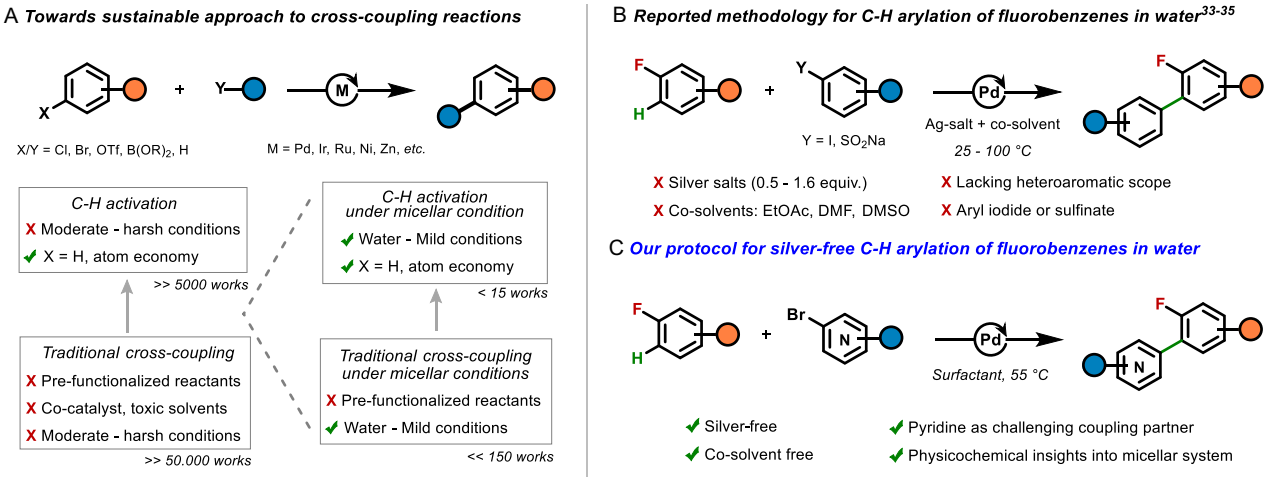
environmental footprint of synthetic chemistry [5–7]. Water, in this regard, is an ideal reaction medium: it is safe, inexpensive, and sustainable [8, 9]. Although its appealing attributes, the widespread use of water in transition-metal catalysis remains challenging due to the poor solubility of organic compounds and the potential instability of reactive intermediates or catalysts in aqueous media [10, 11]. Despite some development in this field, most classical cross-coupling reactions—such as Suzuki-Miyaura [12], Buchwald-Hartwig [13], Negishi [14], or Sonogashira-Hagihara [15] couplings—have been developed mainly in organic solvents, which remain the dominant media for these transformations.

Over the last decades, micellar catalysis has emerged as a powerful strategy to enhance organic reactions in water [16, 17]. Micelles and nano- or microdroplets form spontaneously when small amounts of surfactant are dissolved in water, creating self-assembled "nanoreactors" with a hydrophobic core and a hydrophilic surface. By overcoming the solubility issues in water, these confined environments not only allow nonpolar substrates to react in aqueous media but also concentrate reactants, accelerate reaction rates, and even influence selectivity, making them an attractive tool for sustainable transition-metal catalysis [18–20]. In parallel, C–H activation became a general but still developing strategy for constructing carbon–carbon bonds in a direct and atom-economical manner, avoiding the need for pre-functionalized substrates. The common need for harsh reaction conditions and organic solvents strongly hamper the sustainability of these reactions and their potential for large-scale green industrial production [21, 22].

While classical cross-couplings are relatively well-known under micellar conditions [23, 24], more sustainable metal-catalyzed C–H activation reactions remain rather rare [25, 26]. The combination of micellar catalysis with C–H activation offers a unique opportunity to advance modern sustainable chemistry, providing a platform that merges environmentally benign reaction media with the efficiency of direct C–H functionalization [27]. Nevertheless, despite the intuitive advantages of merging C–H activation and micellar catalysis, the first pioneering work was reported by Lipshutz [28] only in the early 2010s, and this field is still strongly underdeveloped with only a few contributions illustrating the feasibility of the metal-catalyzed C–H activation under micellar conditions (Scheme 1A) [26, 29–32].

Fluoroarenes and their derivatives find utility in medicinal chemistry [33], agrochemistry [34] and materials science [35]. Over the past decade, several strategies have been developed for the direct arylation of fluoroarenes, mainly employing palladium catalysis, in traditional organic solvent systems [36]. In contrast, analogous transformations in water remain scarce. Fagnou and coworkers (2010) reported a biphasic system that enabled C–H arylation at room temperature, though the use of silver salts proved essential for reactivity [37]. Chen and colleagues (2012) achieved direct arylation of polyfluoroarenes in pure water using a simple PPh_3 ligand yet again requiring silver carbonate as a halide scavenger [38]. Complementary approaches have been described, such as the desulfitative arylation with sodium arene sulfinates disclosed by Miao (2013), but these methods still rely on silver additives and organic co-solvents [39]. Although these advances highlight the feasibility of performing C–H activation in aqueous environments, their reliance on stoichiometric silver salts and co-solvents significantly limits their sustainability and practicality, while the lack of heterocyclic examples further underscores the intrinsic challenges of using water as a reaction medium (Scheme 1B).

In this work we report a silver-free protocol for the palladium-catalyzed C–H arylation of fluoroarenes in water, enabled under micellar catalysis. This approach eliminates the need for organic co-solvents and stoichiometric silver additives [40], while operating under mild conditions. Complementary physicochemical analyses elucidate the interaction between the catalytic system and the micellar environment, providing insights into the microstructural organization. The combination of C–H activation with designer surfactants provides a green and practical alternative to previous aqueous arylation methods. Our work thus represents the first example of direct arylation of fluoroarenes under purely micellar conditions, highlighting the potential of micellar catalysis to expand the methodological scope of C–H functionalization in sustainable synthesis (Scheme 1C).



SCHEME 1 | Combining micellar catalysis and cross-coupling reactions. (A) General scheme of cross-coupling and comparison of C–C bond formation in organic versus aqueous media. (B) Reported methodology for C–H arylation of fluorobenzenes in water. (C) Developed silver-free C–H arylation of fluorobenzenes in water under micellar condition.

2 | Result and Discussion

Recently, we developed a methodology for the direct C–H arylation of fluorobenzene in a green solvent [41]. Building on this work, and with the aim of establishing a complementary approach in water, we set out to explore micellar catalysis as a platform for developing a silver-free protocol in water under mild conditions. Among well-established surfactants, PS-750-M was chosen based on its potential in recent cross-coupling reactions and its characteristic physicochemical profile [42, 43].

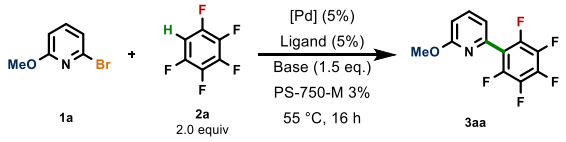
After extensive exploration using 2-bromopyridine as the coupling partner, which consistently led to unsuccessful outcomes, we turned to 2-bromo-6-methoxypyridine, as substitution on the pyridine ring is expected to enhance reactivity (see Supplorting Information, Tables S1, S2) [41]. In our first attempt, evaluation of different bases (Table S3 for all data) demonstrated that PivOK outperformed the others (selected examples in Figure 1A, entries 1-3). Notably, the use of a silver base, which also acts as a halogen scavenger, proved detrimental, giving a complex crude mixture and affording the desired product only in traces (Figure 1A, entry 2). Moreover, silver is known to engage in C–H activation of fluoroarenes, which can open parallel pathways that may operate alongside the Pd-mediated transformation [44, 45]. Subsequent testing of ligands, including PPh_3 (reported to be effective under aqueous conditions [36]; Table S4 for all data), revealed SPhos as the superior ligand (Figure 1A, entry 4). Screening of various Pd(II) and Pd(0) catalysts likewise showed no significant impact of the Pd-source on the reactivity (Table S5 for all data), although a modest increase in yield was observed with the ferrocene-based catalyst $PdCl_2$(dppf) (Figure 1A, entry 5). The best performance was ultimately achieved using $PdCl_2$(dtbpf) (Figure 1A, entry 6).

Encouraged by the initial results, we systematically varied the reaction parameters (amount of catalyst, temperature, reaction time, co-solvent, additive) to examine their influence on the reaction outcome (Figure 1B). While performing the reaction in the presence of ArI or ArCl (Figure 1B, entry 1), only complex reaction mixture was obtained in case of ArI. Whereas ArCl delivered the desired product albeit with decreased efficiency. The good reactivity of bromo and chloro substrates is particularly valuable, as these derivatives are more abundant and cost-effective than iodides or sulfinates [46, 47]. Lower catalyst loading (2%) resulted in reduced yield (Figure 1B, entry 2), while increasing the loading to 8% afforded the desired product in 81% yield (Figure 1B, entry 3), which improved to 87% upon extending the reaction time to 24 h with full conversion (Figure 1B, entry 4). Similar result was achieved at 10% catalyst loading (Figure 1B, entry 5). These conditions were therefore selected as the optimized protocol to ensure consistent conversion and operational robustness for subsequent scope evaluation. Variation of the reaction temperature showed that both milder and harsher conditions were tolerated (Figure 1B, entries 6–7), with a moderate reduction in reactivity observed near room temperature (Table S6 for all data). Concentration had only a minor influence (Table S6) and attempts to enhance reactivity using co-solvents or co-catalysts were unsuccessful, affording the less efficient product formation (Figure 1B, entries 8–9, and Table S6). Finally, other commercially available surfactants (Table S7 for all data), such as TPGS-750-M (Figure 1B, entry 10), were tested but consistently underperformed compared to PS-750-M. Running the reaction in the absence of surfactant afforded only unsatisfactory amount of the product (Figure 1B, entry 11).

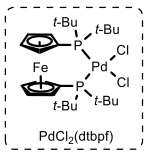
2.1 | Investigation of the Reaction Scope

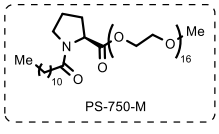
With the optimal conditions in hand, we next turned our attention to explore the reaction scope with various pyridines and fluoroarenes. The initial focus was on examining how different substituents influence the reactivity of the pyridine core along with the

A Preliminary explorarion



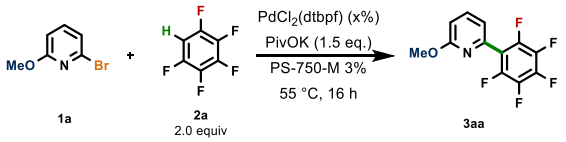
Entry[a]	Base	Ligand	Catalyst	Yield (%)*
1	PivOK	Sphos	$Pd(OAc)_2$	15
2	Ag_2CO_3	Sphos	$Pd(OAc)_2$	Traces
3	TEA	Sphos	$Pd(OAc)_2$	5
4	PivOK	PPh_3/dppe	$Pd(OAc)_2$	Traces
5	PivOK	-	$PdCl_2$(dppf)	30
6	**PivOK**	-	**$PdCl_2$(dtbpf)**	**72**





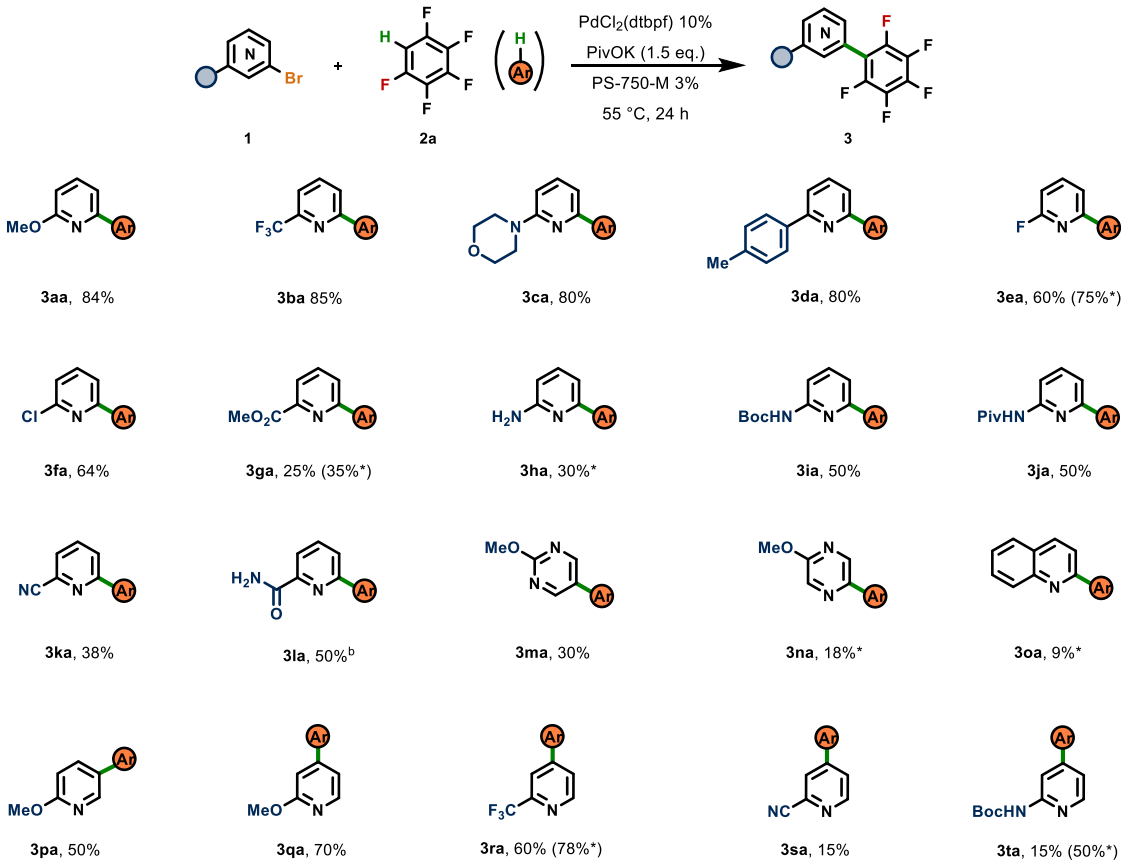
Fine tuning and exploration

B In-depth investigation



Entry[a]	Catalyst [%]	Variation	Yield (%)*
1	5	Ar-Cl / Ar-I	50 / Complex crude
2	2	-	43
3	8	-	81
4	8	24 hours	87
5	**10**	**-**	**90 (83)**
6	8	45 °C	64
7	8	65 °C	75
8	5	CH_3CN (20% v/v)	56
9	5	$ZnCl_2$ (20%)	24
10	8	TPGS-750-M	73
11	5	Only Water	38

FIGURE 1 | Optimization of the reaction conditions: (A) Preliminary screening for the palladium-catalyzed arylation of pentafluorobenzene with 6-bromo-2-methoxypyridine. (B) In-depth investigation for the palladium-catalyzed arylation of pentafluorobenzene with 6-bromo-2-methoxypyridine. [a] 0.15 mmol of Ar-Br, 2.0 equiv. of pentafluorobenzene, 0.5 mL of surfactant (3% w/w in water), 55°C, 16 h, argon atmosphere. *Spectroscopic yield calculated with ^{1}H-NMR using CH_2Br_2 as internal standard. Isolated yield in .parentheses.



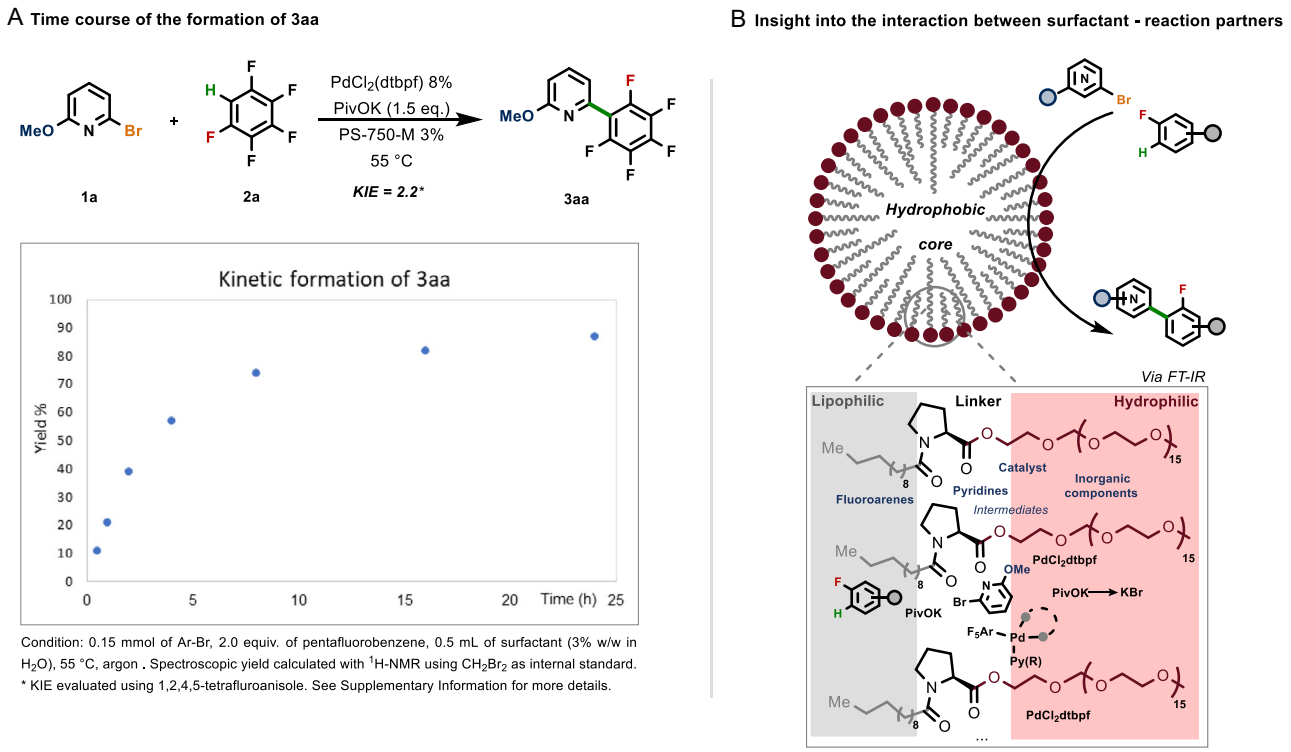
SCHEME 2 | Scope exploration for the Pd-catalyzed cross-coupling reaction between 2-bromopyridines and related *aza*-heterocycles with pentafluorobenzene. Reaction conditions: (a) 0.5 mmol of Ar-X, 2.0 equiv. pentafluoroarene, 1.6 mL of PS-750-M (3% w/w in water), argon atmosphere, 24 h. (b) Product obtained using 6-bromopyridine-2-carbonitrile as a starting material and 3.0 equiv of PivOK. *Yield of the product quantified by ^{1}H-NMR with internal standard. All other cases isolated yields are disclosed. For more details, see Supporting Information.

functional group tolerance (Scheme 2 and Supplementary Information for further details of specific substrates).

In addition to the model substrate (**3aa**); trifluoromethyl (**3ba**), morpholine-1-yl (**3ca**), 4-methylphenyl (**3da**), and halogen substituents (**3ea**, **3fa**) were well tolerated under the reaction conditions and afforded the desired products in good yields (60%–85%). Owing to the higher intrinsic reactivity of aryl bromides over chlorides (Figure 1B, entry 1), selective cross-coupling at the bromide site of 2-bromo-6-chloropyridine (**1f**) was achieved, offering opportunities for subsequent diversification [48]. Next, methyl ester (**1g**) and free amine (**1 h**) were evaluated, affording the products **3ga** and **3ha** in modest yields. Notably, the free amine was well tolerated and no C–N coupling was observed. *N*-Boc protected amine (**1i**) and pivalic amide (**1j**) showed better reactivity affording the desired products (**3ia** and **3ja,** respectively) in reasonable yields (50%). The intrinsic reactivity of the cyano group under the reaction conditions led to a mixture of products, i.e., the desired product **3ka** was obtained in 38% yield next to the detection of the corresponding amide (**3la**) originated from hydrolysis. Repeating the reaction with an excess of PivOK (3 equiv.) ensured complete hydrolysis and furnished **3la** in 50% yield. The protocol was next evaluated on related *aza*-heterocycles. The pyrimidine substrate displayed good reactivity but afforded **3ma** in only modest yield. As well, lower yields were obtained for pyrazine (**3na**, 18%) and quinoline (**3oa**, 9%), despite conversions of 75%–100%. These results indicate that these heterocycles are sufficiently reactive under the optimized conditions, but product selectivity is reduced. Given that these motifs typically display comparable or even higher reactivity than pyridines [49, 50], the diminished yields likely result from competing side reactions (such as homocoupling of the heteroaryl partners detected by LC-MS), which can outcompete the relatively slow C–H arylation process (see Figure 2A, formation of **3aa** vs. time). To test the effect of the substitution pattern on pyridine, we compared 2-methoxy-5-bromopyridine (**1p**) and 2-methoxy-4-bromopyridine (**1q**) at different catalyst loading (2% and 10%, Table S8). Substrate **1p** showed lower efficiency, providing **3pa** in only modest yield (50%), whereas **1q** exhibited reactivity comparable to that of **1a**, affording **3qa** in good yield (70%). Under the standard conditions, additional substrates also proved competent, delivering **3ra**, **3sa**, and **3ta** in modest to good yields (15%–60%).

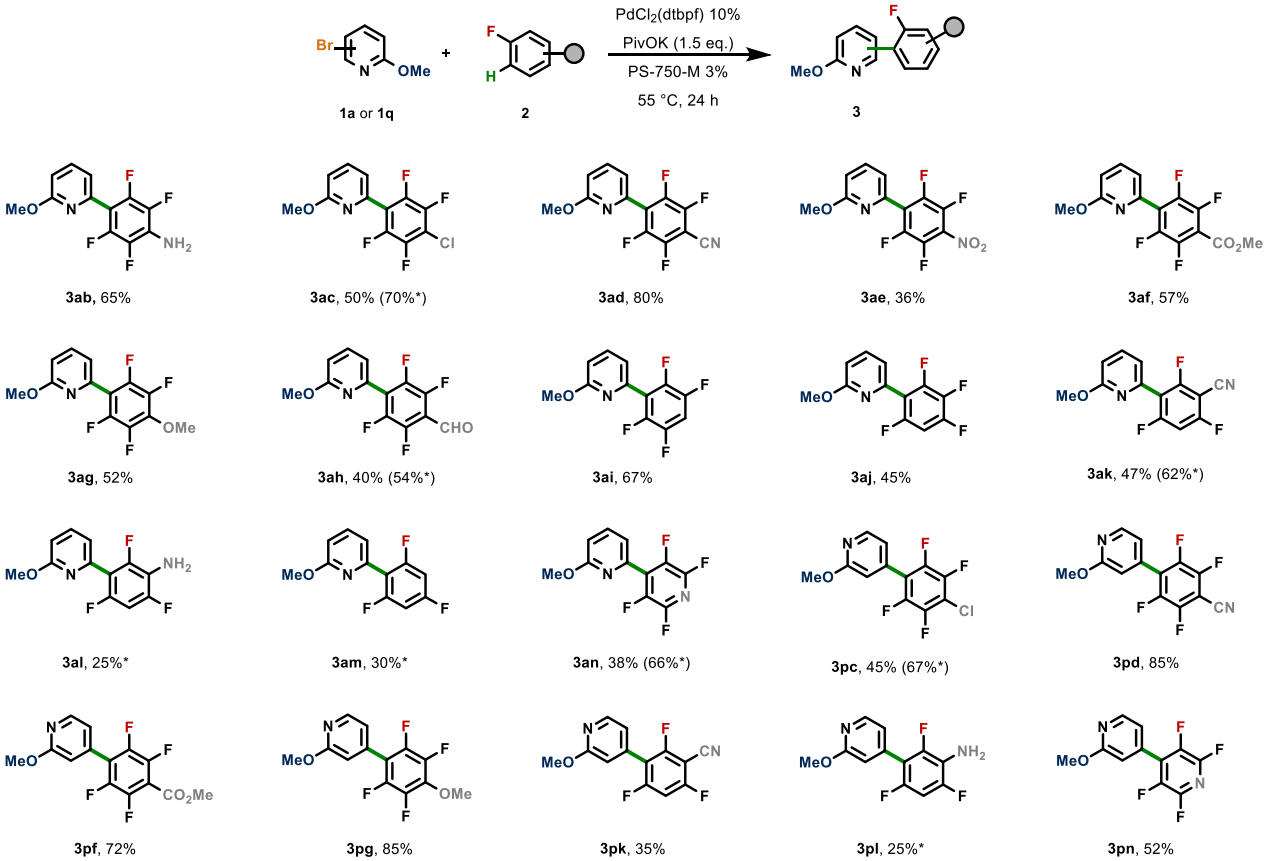
After establishing the reactivity profile of the pyridine core, we next examined the fluoroarene coupling partners to evaluate functional-group tolerance and assess how substituents influence reactivity. Given that the reactivity of the C–H bond in fluorinated arenes correlates with both the number and position of fluorine atoms [51, 52], we challenged the reaction with progressively less activated fluoroarenes to delineate the operational limits of the catalytic system (Scheme 3).

At first, a free amine substrate (**2b**) delivered the product **3ab** in good yield, showing excellent tolerance with no evidence of C–N



Condition: 0.15 mmol of Ar-Br, 2.0 equiv. of pentafluorobenzene, 0.5 mL of surfactant (3% w/w in H_2O), 55 °C, argon . Spectroscopic yield calculated with ^{1}H-NMR using CH_2Br_2 as internal standard.
* KIE evaluated using 1,2,4,5-tetrafluoroanisole. See Supplementary Information for more details.

FIGURE 2 | Mechanistic insight into the C–H arylation of fluorobenzene in the micellar environment. Panel 2A: Time-dependent evaluation of the formation of product **3aa**. See Supporting Information for more details. Panel 2B: FT-IR insight into the interaction and positioning of the reaction partners and presumed moieties into specific domains of the surfactant (vide infra).



SCHEME 3 | Scope exploration for the Pd-catalyzed cross-coupling reaction between bromo-methoxypyridines with different fluoroarenes. Reaction conditions: (a) 0.5 mmol of Ar-X, 2.0 equiv. pentafluoroarene, 1.6 mL of PS-750-M (3% w/w in water), argon atmosphere, 24 h. *Yield of the product quantified by ^{1}H-NMR with internal standard. All other cases isolated yields are disclosed. For more details, see Supplementary Information.

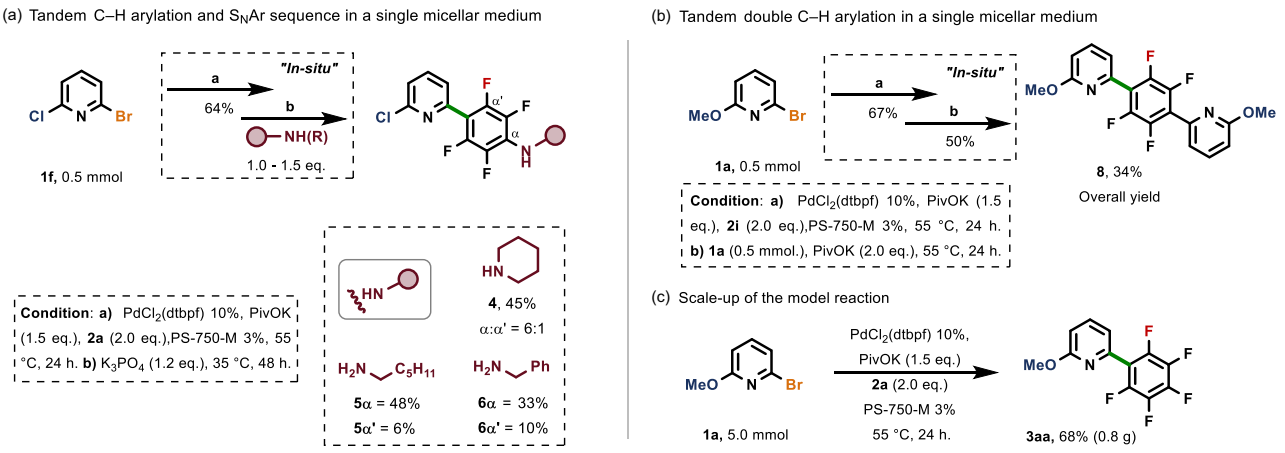
coupling side products. Chemoselectivity was also demonstrated for substrate **1c**, where the chlorine substituent remained intact during the cross-coupling, affording **3ac** in good yield and offering opportunities for further diversification [48]. Substrate **1d** furnished **3ad** in very good yield without any hydrolysis of the nitrile group, unlike what was observed for **3ka**. Although nitro groups often hinder palladium catalysis, **3ae** was synthetized in acceptable yield, indicating a fair tolerance toward this valuable functionality [53]. The methyl ester on the fluorophenyl moiety displayed superior reactivity and stability compared with the carboxymethylpyridine analog, giving **3af** in higher yield (57% vs. 25%). Substrates bearing methoxy or formyl substituents were also well tolerated, affording **3ag** and **3ah** in moderate yields. Tetrafluorinated arenes reacted smoothly under the optimized conditions: 1,2,4,5-tetrafluorobenzene provided **3ai** in 67% yield, while 1,2,3,5-tetrafluorobenzene afforded **3aj** in 45% yield. For both **3ai** and **3aj** bis-pyridylated products were also detected in LC-MS. The cyano derivative gave **3ak** in good yield, whereas the free amino derivative, although less reactive, furnished **3al** in modest yield with excellent C–H arylation selectivity. Notably, trifluorobenzene-containing motifs are prevalent in numerous bioactive molecules, making these transformations attractive for future late-stage functionalization of drug-like scaffolds [54–58]. The catalytic system was subsequently challenged with increasingly deactivated fluoroarenes; 1,3,5-trifluorobenzene, for instance, displayed only modest reactivity, providing the product **3am** in 30% yield. Finally, a fluorinated pyridine (**2n**) was examined as the C–H cross-coupling partner, given its comparable reactivity to fluoroarenes. It exhibited very good performance under the developed conditions, affording the nonsymmetric pyridine in good yield, which represents a valuable substrate type [59, 60]. Applying the same strategy to a broader set of fluoroarene substrates, starting from **1q**, gave consistent results: overall, products **3pc**, **3pd**, **3pf**, and **3pg** were obtained in very good yields, while **3pl** and **3pn** were isolated in moderate yields.

Encouraged by these results, we next explored the feasibility of performing a tandem transformation within the same micellar medium (Scheme 4). Such one-pot sequences enhance process sustainability by reducing solvent use, purification steps, and waste generation. The robustness of the catalytic system and the stability of the micellar environment make this approach well-suited for multistep synthesis in water, highlighting the potential of micellar catalysis for integrated and resource-efficient reaction design [61]. Building on the developed method [17, 62], we applied the optimized C–H arylation conditions to a tandem C–H arylation and S_NAr sequence (Scheme 4A). This two-step, one-pot protocol enables sequential C–C and C–N bond formations without intermediate workup, illustrating how micellar catalysis can integrate distinct transformations within a single, sustainable reaction environment. Piperidine as a secondary amine and primary amines (hexylamine and benzylamine) were employed as nucleophiles, affording the corresponding products in good overall yields with only minor isomer formation. In addition, the developed methodology enabled a tandem double C–H arylation, in which a single fluoroarene was sequentially coupled with two distinct but identical pyridines (Scheme 4B). Notably, the second transformation proceeded without the need for any additional catalyst, indicating that the catalytic system remained active after the first step.

To evaluate the practical feasibility and scalability of the methodology, the reaction was carried out on a 5.0 mmol scale of **1a** (10x scale-up). The process proceeded smoothly under identical conditions, confirming the robustness of the system and delivering the desired product **3aa** in 68% isolated yield (Scheme 4C). Beyond the transformations shown, further derivatization of the arylated products, such as C–F cross-coupling or related reactions, could be envisioned to increase molecular complexity and broaden synthetic utility [63–66].

2.2 | Mechanistic Insight

The kinetic profile of the model reaction leading to **3aa** was examined under the optimized conditions (Figure 2A). The transformation reaches full conversion after 24 h. A noticeable plateau is observed after about 8 h, indicating that the reaction rate gradually decreases over time. Based on our previous study, we hypothesized a similar catalytic pathway in which the C–H activation step proceeds through a concerted metalation–deprotonation (CMD) mechanism [41]. Furthermore, FT-IR analysis (Figure 2B) offered insight into how the reaction partners interact with and situate within distinct surfactant domains,



SCHEME 4 | Tandem reactions and scale-up for the Pd catalyzed cross-coupling reaction between 2-bromopyridines and fluoroarenes. Panel A: Tandem C–H arylation and S_NAr. Panel B: Tandem double C–H arylation. For both tandem reactions, no reaction optimization was undertaken. Panel C: Scale-up of the model reaction. For more details, see Supporting Information.

revealing key information about the likely site of the transformation (see below). Last, pH-dependence test (pH 2.5–9.5) was performed, confirming that a basic environment is essential for maintaining reactivity (see Supporting Information).

2.3 | FT-IR Spectroscopy

To gain a closer insight into the interaction between micelle – reaction partners, IR spectra were recorded on mixtures of reagents–detergent pairs [67]. At first, the Pd-based catalyst was added as a methanol solution to the PS-750-M micelle suspension, and the resulting aqueous suspension was then dried by gentle solvent evaporation under ambient conditions on the top of the ATR crystal. The subtracted spectrum (by subtraction of pure PS-750-M spectrum), indeed, reveals the presence of catalyst in aqueous phase (Figure 3iA). The observed variations in band intensities compared with the native Pd-based catalyst spectrum suggest changes in the catalyst's geometry, indicating an interaction with the detergent micelles. Moreover, the appearance of a negative C–O–C stretching band at 1080 cm^{-1} in the subtracted spectrum indicates that the conformation of the PEG moieties in the PS-750 M micelles is also altered.

Although pentafluorobenzene could not be analyzed due to its high volatility; we assumed that, owing to its lipophilic nature, the

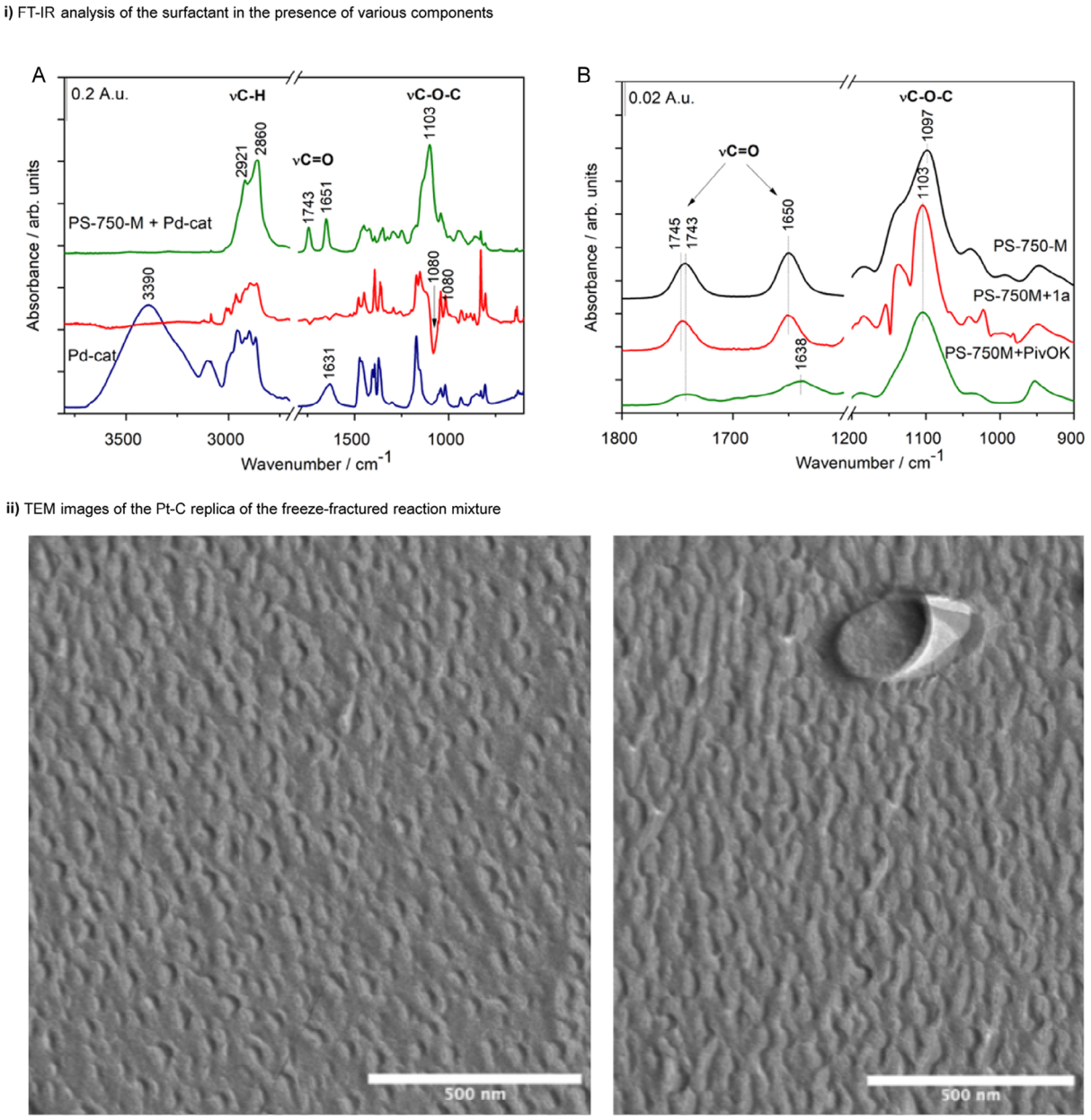


FIGURE 3 | FT-IR and freeze-fracture combined transmission electron microscopy (FF-TEM) analysis of the reaction mixture. Panel 3(i)A: Spectra of PS-750-M + Pd-cat mixture (green line) and after spectral subtraction of pure PS-750-M (red line). For comparison, the spectrum of pure Pd-cat is also shown (blue line). Panel 3iB: Spectral marker absorption bands corresponding to C = O and C-O-C groups of PS-750 M micelle: pure detergent (dark-blue line) and mixture with **1a** (red line) and PivOK (green line), respectively. The mixture spectra are shown after subtraction of the corresponding pure reagent spectra. (ii) TEM images of the Pt-C replica of the freeze-fractured reaction mixture. Typical micellar morphology can be observed on the fractured surfaces, and occasionally larger aggregates or emulsion droplets are also visible.

fluoroarene motif is located at the lipophilic domain of the surfactant. In the cases of PS-750-M + 2-bromo-6-methoxypyridine (**1a**) and PS-750-M + potassium pivalate (PivOK) pairs (Figure 3iB), the spectra obtained from the aqueous phase were dominated by features of the reagents. After spectral subtraction, however, changes in the C = O and C–O–C vibrations of the proline and PEG-moieties of the PS-750-M detergent suggest that the environment of these groups are altered in the presence of reagent molecules [68]. It is interesting to note that **1a** is localized in the vicinity of ester carbonyl (near PEG moieties) while PivOK affects the amide carbonyl vibrations, too.

2.4 | Dynamic Light Scattering (DLS) and Freeze-Fracture Combined Transmission Electron Microscopy (FF-TEM)

The mode diameter of PS-750-M micelle suspension measured by dynamic light scattering (DLS) was found to be 6.6 nm in agreement with data reported by Kaur et al. (see Supporting Information) [69]. The addition of 2-bromo-6-methoxypyridine resulted in the increase of the diameter to 166 nm indicating the appearance of larger micellar aggregates or emulsion droplets. Due to its heterogeneous nature, the whole reaction mixture was not measurable by DLS. FF-TEM, however, revealed the in-solution morphology of the reaction mixture, which resembles that of micellar systems. Nevertheless, the occasional presence of larger aggregates in the size range of 100–500 nm explains why this system could not be reliably characterized by DLS.

Taken together, DLS and FF-TEM analyses confirmed the nanostructured nature of the system, revealing predominantly micellar assemblies accompanied by occasional larger aggregates [70]. FT-IR spectroscopy revealed that both the Pd-based catalyst and the reagent molecules interact with the PS-750-M micelles, leading to detectable changes in the vibrations of the C = O and C–O–C groups. These spectral shifts indicate modifications in the local environment and conformation of the PEG and amide moieties, evidencing specific interactions between the micelles, catalyst, and reagents. The FT-IR data also suggest that the two reaction partners experience distinct microenvironments within the micellar system. The results indicate that pyridine derivatives are more likely positioned in the hydrophilic region, where they can interact with the polar PEG and amide moieties of the surfactant. This localization could make them more susceptible to side reactions occurring in aqueous environments [71, 72]. For instance, hydrolysis of the cyano group was observed for the pyridine substrates **1k** and **1s**, whereas the same functionality on the fluorobenzene analogs (**2d**, **2k**) remained intact. Calculating the logP values of the pyridines (by molinspiration.com and chemicalize.com) we found that those having log$P > 2$ gave higher yields than 50%, while if logP was <2 the yields were also usually lower. So, the more lipophilic pyridines could be localizing closer to the lipophilic fluoroarenes that are expected to reside around the hydrophobic core of the micelles. Differences in reactivity between methyl esters and other functionalities suggest the influence as well of microenvironmental effects. Nevertheless, such physicochemical factors alone cannot fully account for the observed trends, as additional parameters, such as steric and electronic properties of the substrates, are also likely to contribute.

3 | Conclusion

In summary, we have developed the first silver-free protocol for the palladium-catalyzed direct arylation of fluoroarenes in water under micellar conditions. This method combines the sustainability of aqueous media with the efficiency of C–H activation, obviating the need for organic co-solvents or stoichiometric additives while operating under mild conditions. The transformation shows good substrate scope and functional-group tolerance, enabling the coupling of diverse pyridine and fluoroarene derivatives. FT-IR, DLS, and TEM analyses reveal that the catalyst and reagents interact specifically with the micellar interface, suggesting that the microenvironment governs substrate positioning and may influence selectivity and side reactivity. Overall, this study demonstrates how micellar catalysis can be effectively merged with C–H activation to deliver practical, environmentally responsible synthetic methodologies. Beyond expanding the scope of aqueous cross-coupling chemistry, these findings suggest that the structural features of the surfactant and its interaction with the catalyst can guide the design of more sustainable catalytic systems.

Author Contributions

F. B. conceived the work, designed the experiments with input from **K. N. G.**, optimized the reaction conditions, preliminary explored the scope, managed the project, and wrote the article. **K. N. G.** synthesized the compounds, participated in the DLS and TEM analysis, performed the FT-IR analysis, and cowrote the article. **Z. V.** supervised the DLS, TEM, and FT-IR analysis, and cowrote the article. **J. M.** supervised the DLS and TEM analysis, performed the FT-IR analysis, and cowrote the article. **P. H.** performed the surfactant screening. **T. H.** and **G. M. K.** contributed to project management and acquired funding. **F. G.** and **J. W. D.** contributed to the research concept and manuscript preparation. **P. Á.- B**. supervised the research, designed the experiments, and cowrote the article.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. Supporting Information contains experimental details, compound characterization data, and information on the analytical techniques used (TEM, FT-IR, DLS).