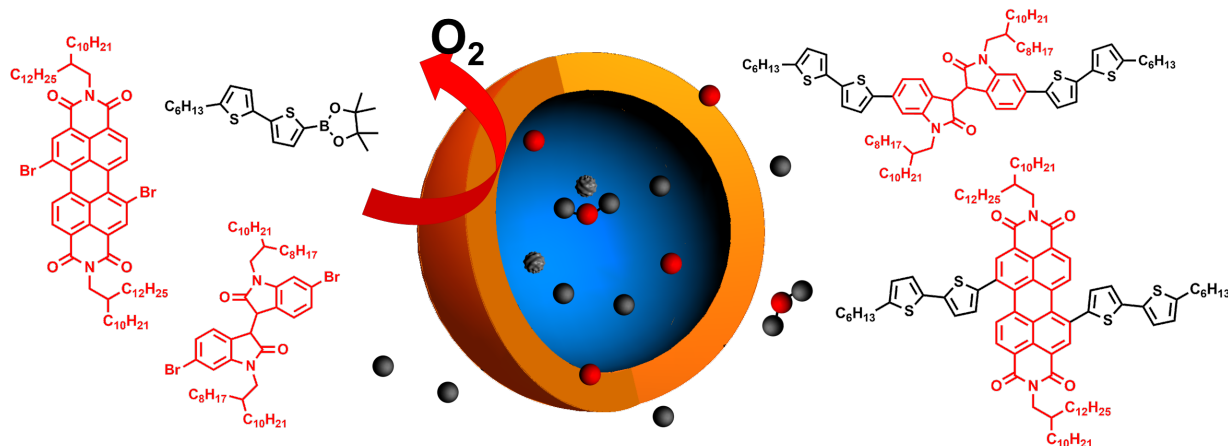


Suzuki-Miyaura micellar Cross-Coupling in water, at room temperature and under aerobic atmosphere

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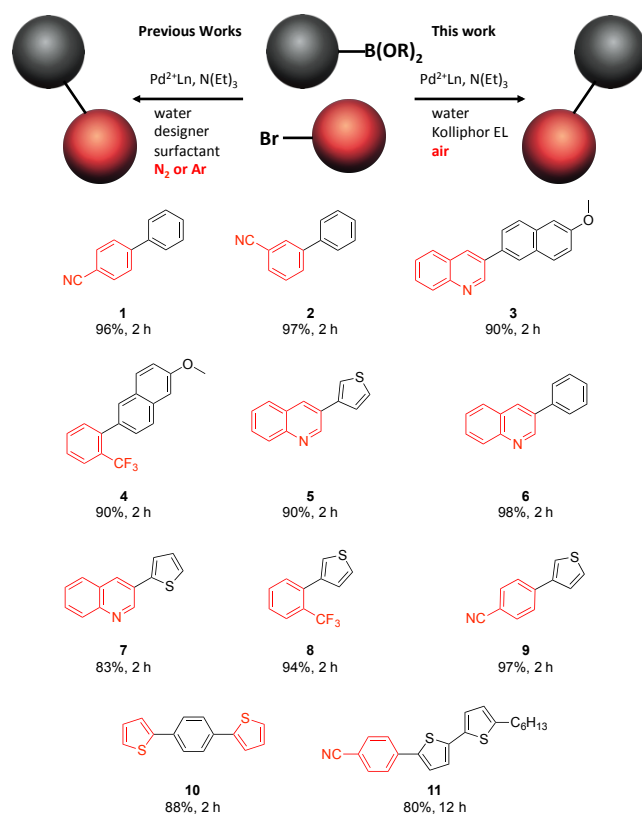
ABSTRACT: Recently, oxygen equilibrated water solutions of Kolliphor EL, a well-known surfactant, have been seen to form nanomicelles with oxygen free cores. This has prompted the successful testing of the core environment as a green medium for palladium catalyzed Suzuki-Miyaura cross couplings. The versatility of these conditions are endorsed by several examples, including the synthesis of relevant molecular semiconductors. The reaction medium can also be recycled, opening the way for an extremely easy and green chemistry compliant methodology.

Micellar couplings enable the use of established C-C and C-N bond forming strategies at room temperature in water.¹⁻³ Several examples of standard⁴⁻⁷ and designer^{8,9} surfactants have been reported in the literature to provide green environments for popular reactions such as the Suzuki-Miyaura, Stille, Buchwald-Hartwig, Heck and Sonogashira couplings. In recent years, the advantages of such approaches have been demonstrated, such as the reduction in energy consumption and organic waste.¹⁰ It has also been demonstrated that Pd-doped Fe nanoparticles used in connection with the micellar environment results in an excellent route for Suzuki-Miyaura coupling with very low palladium concentrations.¹¹ Examples of nickel catalyzed micellar reactions have also been reported.¹² New and very active phosphine ligands afford state of the art results at very low palladium loading and with chlorides as well as bromides.¹³ Micelles also provide an ideal reaction environment for reactions other than palladium-mediated couplings.¹⁴ In particular, the Lipshutz group recently demonstrated that the high solubility of oxygen in organic media, including micelles, can be very profitably exploited to

carry out the aerobic oxidation of water insoluble arylalkynes to β -ketosulphones under very mild conditions. Precisely because of such high oxygen content, palladium catalyzed micellar cross coupling reactions require deoxygenation of the reaction environment. Recently we demonstrated that the commercially available surfactant Kolliphor EL, assembles into nanomicelles with oxygen free cores having an average hydrodynamic diameter of 6-7 nm.¹⁵ This unexpected property, still under investigation, was confirmed by means of the platinum porphyrin luminescence method.^{16,17} We here show that such micelles provides suitable medium for the Suzuki-Miyaura cross coupling in water at room temperature under an oxygenated environment. We show that such a surfactant, used directly in air, is competitive in terms of yield with other designer surfactants described in the literature. We also show that Kolliphor EL can be profitably exploited for the synthesis of popular molecular semiconductors pertaining to the classes of diarylanthracenes,¹⁸ diketopyrrolopyrroles,¹⁹⁻²¹ diarylbenzothiadiazoles,²² isoindigos²³ and perylene diimides.²⁴⁻²⁷

In order to comparatively test Kolliphor EL with established coupling promoting surfactants, we tested the method under a set of experimental conditions generally accepted as appropriate in the dedicated literature: room temperature, a 2wt% solution of the surfactant in distilled water, 0.5 M concentration of the halide (bromide in all our reactions), [1,1'-bis(di-tert-butylphosphino)ferrocene]dichloropalladium(II) (Pd(dtbpf)Cl₂) 2 mol% with respect to the bromide as the catalyst and triethylamine (N(Et)₃) as the base.⁸ The reaction scope is shown with examples of cross coupling reactions in Scheme 1. Derivatives **2-5** have isolated yields comparable with literature data obtained with two popular and efficient designer surfactants, Nok and TPGS-750-M.⁸ Results are generally comparable, with the relevant difference of Kolliphor reactions being carried out under standard oxygenated environment.

Scheme 1. Micellar couplings in water and under oxygenated environment.

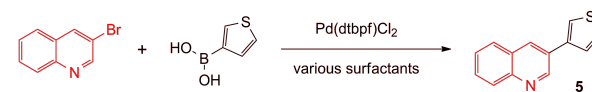


Aryl bromides (in red) and arylboronic acids (in black) coupled in 2wt% Kolliphor EL solution in deionized water. Conditions: 0.75 mmol of boronic acid, 0.5 mmol of arylbromide, 1.5 mmol of N(Et)₃ and 0.02 mmol of Pd(dtbpf) in 1 mL of surfactant solution at room temperature and in the air. For compound 10: 0.5 mmol of 1,4-phenylbisboronic acid and 1.5 mmol of 2-bromothiophene. Isolated yields and reaction times are given.

Table S1 of the Supporting Information gives additional examples, including also reactions carried out with less reactive catalysts like [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (Pd(dppf)Cl₂) and palladium acetate. Whenever a thiophene residue was present, the use of Pd(dtbpf)Cl₂ gave best results. We carried out a comparative study on the coupling of 3-thiopheneboronic acid and 3-bromoquinoline by using two popular micelle forming surfactants: Triton X-100 and the designer surfactant TPGS-750-M. Table 1 shows that under otherwise identical conditions, the reaction with Kolliphor leads to 90% yield whilst the reactions with Triton X-100 and TPGS-750-M afford the product in a more modest 68% and 69% yield respectively. As an extra benefit, in the case of Kolliphor the coupling product can be readily isolated by filtration. This prompted us to recycle the aqueous phase for a second consecutive reaction, without adding a fresh catalyst. The reaction behaved satisfactorily, leading to an isolated yield of 70% after 2 h.

The role of oxygen in explaining the different behavior of Kolliphor, Triton and TPGS-750-M enhanced reactions was further confirmed by repeating the reactions with Triton X-100 and TPGS-750-M under nitrogen atmosphere and with nitrogen saturated water. Indeed, we were able to increase the yield from 68 to 80% in the case of Triton X-100 and from 69 to 95% in the case of TPGS-750-M. The absolute higher yield obtained with the latter surfactant is not surprising; TPGS-750-M is a designer surfactant, specifically engineered to perform cross coupling reactions. Conversely, Kolliphor EL is just an emulsifier, unoptimized for micellar couplings. The real gain on using Kolliphor is thus the oxygen insensitivity rather than the absolute performance (in any case remarkable).

Table 1. Test reaction between 3-bromoquinoline and 3-thiopheneboronic acid in different surfactants.



entry	medium	run	atmosphere	time (h)	yield (%)
1	Kolliphor EL	I	air	1	90
2	Kolliphor EL	II	air	2	70
5	Triton X-100	I	air	2	68
6	Triton X-100	I	N ₂	2	80
7	TPGS-750-M	I	air	2	69
8	TPGS-750-M	I	N ₂	2	95

Conditions: 0.75 mmol of boronic acid, 0.5 mmol of arylbromide, 1.5 mmol of $N(Et)_3$ and 0.02 mmol of $Pd(dtbpf)Cl_2$ in 1 mL of surfactant solution at room temperature.

To further substantiate this point, we carried out an additional experiment using the oxygen sensitive catalyst tetrakis(triphenylphosphine)palladium(0) ($Pd(PPh_3)_4$). We prepared two identical dispersions – one with Kolliphor EL and one with TPGS-750-M - of 10 mg of $Pd(PPh_3)_4$ in 2 mL of 2% by weight surfactant solution in water. Such dispersion, both featuring the characteristic yellow coloration of fresh $Pd(PPh_3)_4$, were left under stirring at room temperature for 24 h and under standard laboratory environment. After aging, the TPGS-750-M dispersion darkened significantly (Figure 1). Both dispersions were thus charged with 6-methoxynaphthalene-2-boronic acid, 9-bromoanthracene and $N(Et)_3$. Figure S1 of the Supporting information shows the GC-MS trace of both reactions after 3 h stirring. The Kolliphor EL dispersion gives the expected product, conversely the TPGS-750-M reaction leads to negligible conversion, coherently with extensive catalyst degradation.

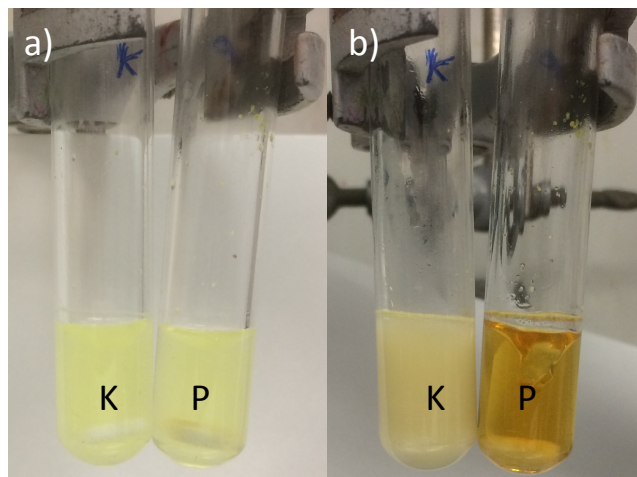


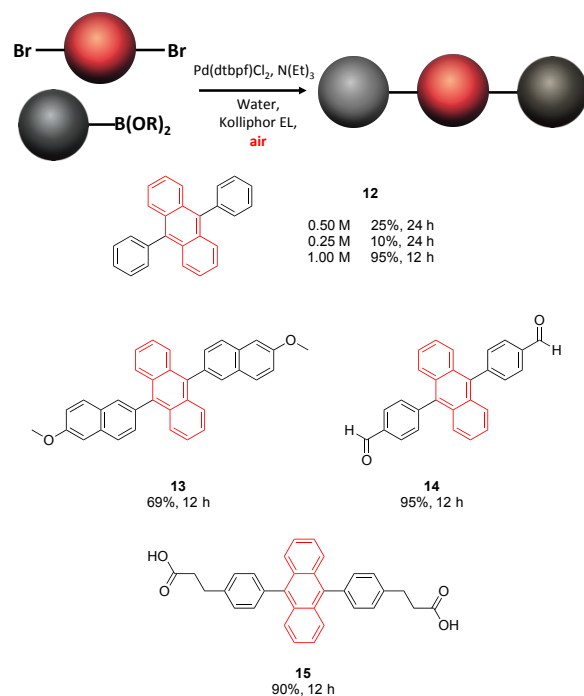
Figure 1. a) As prepared dispersions of 5 mg of $Pd(PPh_3)_4$ in Kolliphor EL (denoted with K) and PTS (denoted with P); b) Dispersions after 24 h aging at room temperature and under oxygenated environment.

Kolliphor EL is mostly known for being an excellent dispersant of relatively insoluble drugs such as Taxol and its derivatives.²⁸ We decided to challenge its dispersion capabilities in a series of cross coupling reactions involving organic semiconductors pertaining to the classes of 9,10-diarylanthracenes, diketopyrrolopyrroles, diarylbenzothiadiazoles, perylene-diimides and isoindigos. Such compounds possess solid track records in a variety of organic devices.^{29,30} The availability of an exceedingly simple procedure for their late stage functionalization would be of high value for the organic materials community. Working with such starting compounds required further optimization of the reaction conditions.

Scheme 2 shows a series of reactions involving 9,10-dibromoanthracene (DBA) and three arylboronic acids, bearing different functional groups. The reaction with phenylboronic acid was tested to optimize reaction conditions. We consistently obtained the highest yield by increasing reaction mixture concentrations. In particular, dilution of the reaction mixture favored formation of the homocoupling biphenyl side product. This process is commonly connected with oxygen being present in the reaction mixture.³¹ Conversely, when working at 1M bromide concentration, we obtained a 95% yield after crystallization and no isolated biphenyl.

Working under the same conditions, we isolated all other cross coupling products with yields between 69 and 95%. Table S2 of the Supporting Information shows details for every reaction, including the structure and yield of the homocoupling products (where present). In the same section we also discuss a rationalization of such concentration dependency, based on a previous observation that Kolliphor micelles possess oxygen free cores but oxygenated shells.¹⁵

Scheme 2. Micellar couplings on 9,10-dibromoanthracene



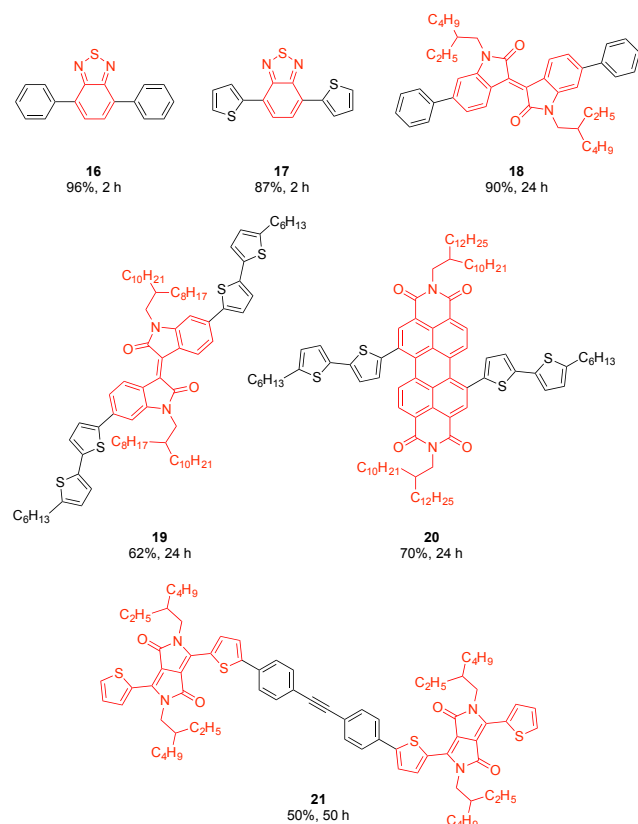
Couplings of 9,10-dibromoanthracene (in red) and different arylboronic acids (in black) performed in a 2wt% Kolliphor EL solution in deionized water. Conditions: 0.5 mmol of bromide, 1.5 mmol of arylboronic acid, 3.0 mmol of $N(Et)_3$ and 0.03 mmol of $Pd(dtbpf)$ in 0.5 mL of surfactant solution (apart from compound 12) at room temperature and in the air. Isolated yields, after crystallization, are given.

Reaction conditions leading to diarylanthracenes were also successfully employed for the synthesis of the organic semiconductors shown in Scheme 3. Derivatives **16** and **17** are

known fluorescent molecules and behave in a similar way to diarylantracene compounds. These are poorly soluble crystalline derivatives; they can be directly filtered from the reaction medium and purified by crystallization. Derivatives **18** and **19** are examples of heavily functionalized compounds that could interfere with the micellar structure of Kolliphor EL in solution. Characteristics of such isoindigo derivatives made the reaction mixture difficult to efficiently stir, as most of the material formed an oily and sticky residue on the walls of the reaction flask. To deal with the problem, we mechanically shook the reaction mixture and increased the reaction time to 24 h. Derivatives **20** and **21** are examples of coupling reaction involving a boronic ester instead of an acid. The reactions proved to be significantly slower, again mostly due to the high viscosity of the reaction mixture.

All products could, in any case, be isolated after chromatographic purification in moderate to good yields. Further optimization of our method will likely require the devising of improved mixing procedures. The use of co-solvents might also be helpful.³²

Scheme 3. Micellar synthesis of selected molecular semiconductors



Couplings of brominated precursors (in red) and arylboronic acids or esters (in black) performed in a 2wt% Kolliphor EL solution in deionized water. Conditions: 0.5 mmol of bromide, 1.5 mmol of arylboronic acid, 3.0 mmol of $N(\text{Et})_3$ and 0.03 mmol of

$\text{Pd}(\text{dtbpf})\text{Cl}_2$ in 0.5 mL of surfactant solution. For compound **22**: 0.5 mmol of diphenylacetylene-4,4'-diboronic acid bis(pinacol) ester and 1.5 mmol of bromide. Isolated yields and reaction times are given.

In conclusion, we have demonstrated that Kolliphor EL, a cheap, readily available and well-established drug emulsifier and surfactant, can be used with a simple room temperature method to access a wide variety of Suzuki-Miyaura coupling products affording high yield in air. The scope of the reaction is demonstrated with the coupling of a wide variety of aryl and heteroaryl bromides with various boronic acids and esters, including examples of well-established organic molecular semiconductor cores. All reactions can be carried out directly in a standard oxygenated environment in deionized water. The reaction medium can be recycled. In the case of crystalline compounds, the coupling products can be isolated directly by filtration. Comparing Kolliphor EL to other designer surfactants we have demonstrated that Kolliphor EL alone provides an environment suitable for efficient oxygen insensitive reactions. In short, we demonstrated an exceedingly simple, economically convenient and sustainable bench-top protocol for efficient Suzuki-Miyaura coupling. We are currently exploring polymerization reactions according to the same method with very encouraging results.

ASSOCIATED CONTENT

Supporting Information

General experimental procedures, additional examples and full characterization data for all compounds.

The Supporting Information is available free of charge on the ACS Publications website.

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Author Contributions

The manuscript was written through contributions of all authors. / All authors have given approval to the final version of the manuscript.

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