Micellar Catalysis as a Tool for C-H Bond Functionalization Toward C-C Bond Formation

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ABSTRACT: Micelles generated upon dissolving surfactants in water can be employed as nano-vessels for catalytic transformations, in the so-called micellar catalysis methodology. This review is focused onto the use of micellar catalysis in the context of the catalytic functionalization of carbon-hydrogen bonds. The micelles accumulate catalyst and reactants in their inner volume in such a high local concentration that kinetics are favored. The consequence is that in most cases, processes that in conventional organic solvents require high temperatures and long reaction times are achieved in milder conditions when micellar catalysis is employed.

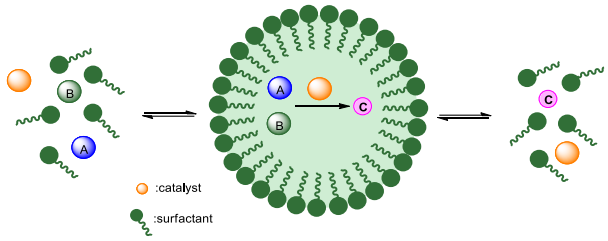
INTRODUCTION

The transition-metal-catalyzed C-H activation and functionalization through homogenous catalysis is one of the most versatile and useful synthetic strategies in modern chemistry.[1] In many cases, the inertness of such moieties, due to their high values of bond dissociation energies, causes that these reactions are carried out under conditions far of being considered mild or atom-economic. This is the origin of the increasing interest in promoting such processes under more sustainable and environmentally friendly conditions, with optimized values of E factor.[2] One major approach is the consideration of alternative, non-conventional solvents as the reaction medium.[3] This is the case of reactions carried out under solvent-free conditions, or employing ionic liquids, supercritical fluids, fluorous solvents or water. From the perspective of green chemistry, water as solvent is the most attractive alternative for perform organic reactions,[4] because it is a non-flammable, non-toxic and available solvent at nearly no cost. It is also worth mentioning that environmental factor or E factor, introduced by Sheldon,[2] does not account for water when employed as solvent.

Examples of C(sp^2 or sp^3)-H bond activation using water as reaction medium have been reported.[5] However, the low solubility of many organic molecules and/or the low stability of many transition metal complexes used as catalysts, limit the use of the water as solvent. Very often, most of these reactions displays a heterogeneous nature, and are better defined as reactions "on water" better than "in water".[6]

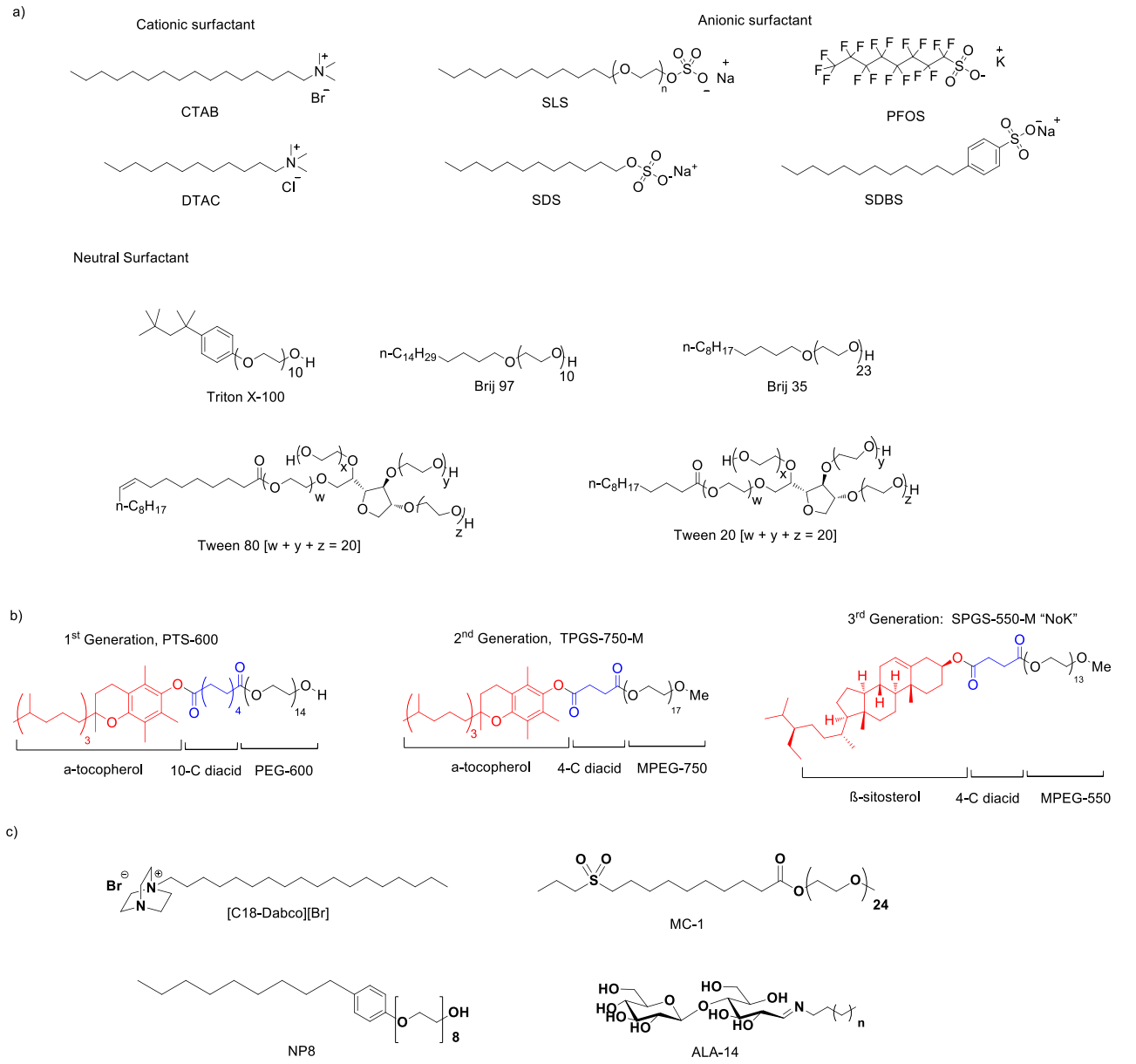
In the last two decades, micellar catalysis has emerged as an attractive tool for performing reactions using water as the bulk solvent but providing hydrophobic environments for the reactants and the catalyst.[7] Scheme 1 shows a general view of this strategy. The addition of a surfactant, a molecule containing a polar end and a non-polar chain to water originates the spontaneous aggregation into micelles, which can accommodate reactants and catalyst in the inner region, triggering the catalytic reaction given their high local concentration, usually much higher than under homogeneous conditions. The micelles undergo continuous aggregation/disaggregation processes, favoring reactant/product exchange.

Scheme 1. Overview of micellar catalysis.



In this contribution we aim at providing the current state of the art of the use of micellar catalysis for transition metal-catalyzed carbon-hydrogen bond functionalization reactions. After a brief introduction about surfactants, a comprehensive description of the different reactions classified according with the type of C-H bond involved is presented. Most if not all examples display better yields and/or milder conditions than the corresponding experiments in organic solvents, as a general feature. We refer to the main corresponding authors in all cases, albeit it is obvious the recognition to all co-workers in each work.

Scheme 2. Representative surfactants a) Traditional cationic, anionic and neutral surfactants b) First introduced designer or green surfactants c) Representative new designer surfactant



MICELLAR CATALYSIS, MICELLES AND SURFACTANTS

Micelles are supramolecular aggregates which are formed by surfactants in water or other water-like media. Surfactants are amphiphilic molecules containing a hydrophobic tail and a hydrophilic head, which allow surfactants to interact with both polar and non-polar compounds. When surfactants are dissolved in water above a certain minimum concentration, named critical micellar concentration (CMC), the micelles are formed, showing a hydrophobic core. When employed in catalysis,[7] the low or non-polar reactants and catalyst will be concentrated in that inner region of the micelle. The outer hydrophilic surface (cationic, anionic or neutral) is responsible of the solubility in the polar media. The high local concentration of reactants and catalyst inside the micelle favors their interactions and can increase the reaction rates up to orders of magnitude, compared with corresponding experiments in organic solvents. Furthermore, the rapid equilibrium between the surfactant monomers and the aggregates facilitates the trapping of reactants and release of products in the catalytic reactions (Scheme 1). All these properties of micellar catalysis allow numerous organics reactions being carried out under mild conditions in water.

The concept of micellar catalysis is known for nearly a century, but it has not been considered as a possible green alternative to traditional homogeneous catalysis until the

last few decades.[7] A number of studies has allowed the development of this strategy, with particular mention to the group of Lipshutz,[8] which has delivered many examples to promote different organic transformations. Toward that end, a great variety of commercial surfactants and designer surfactants (Scheme 2) have been employed. The tuning of each system with the appropriate surfactant has allowed that reactions, which required hard reaction conditions in traditional media, can be carried out under mild conditions with the same catalyst as in organic solvents.

The designer or *green* surfactants were developed by Lipshutz and appeared in successive generations (Scheme 2).[9] The first- and second-generation surfactants, PTS and TPGS-750-M, are formulated as racemic vitamin E derivatives, while the third-generation surfactant, Nok o SPGS-550M, is based on natural phytosterol, *β*-sitosferol. Many designer surfactants have appeared in the literature, a very complete review article on this topic have been reported by Scarso.[9c]

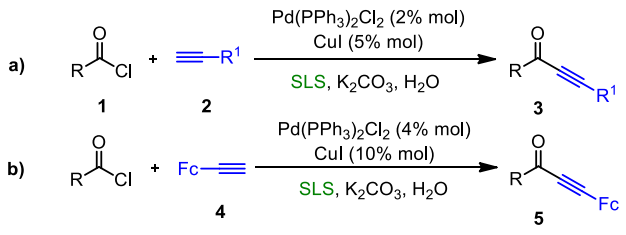
1. C(sp)-H BOND FUNCTIONALIZATION

Sonogashira-coupling reactions

The Sonogashira coupling consists in the carbon-carbon cross-coupling of terminal alkynes with aryl- or vinyl-halides, using palladium(II) as catalyst and copper(I) as co-catalyst. This type of reactions has allowed obtaining a wide variety of organic products with biological, pharmaceutical, and industrial interest. In recent years, Sonogashira couplings have been achieved in the presence of several commercial cationic and anionic surfactants and first, second and third generation designer surfactants (Scheme 2). Actually, Sonogashira couplings have become the most useful and studied method for the C(sp)-C (sp^2) bond formation in micellar media.

Synthesis of ynones. First examples of Sonogashira couplings under micellar conditions were tested using sodium lauryl sulfate (SLS) as surfactant. In 2004, Li and Chen[10] described a highly effective direct coupling of acid chlorides with terminal alkynes catalyzed by $PdCl_2(PPh_3)_2$/CuI in the

Scheme 3. Synthesis of ynones

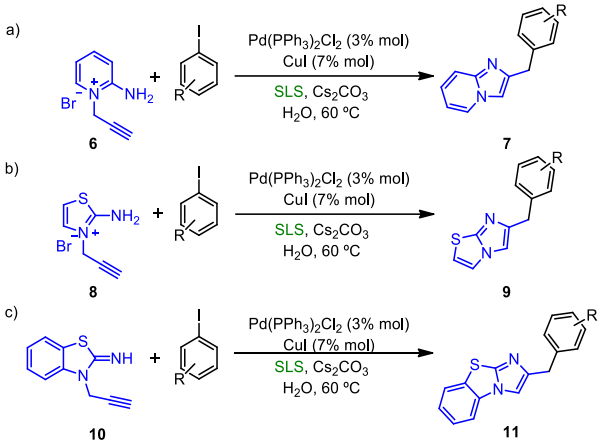


presence of SLS and K_2CO_3 as base. The desired ynones were obtained with yields within the interval 66-99% (Scheme 3a). Later, Lv and co- workers developed a similar method.[11] A wide variety of ferrocenylethynyl ketones were synthetized by the coupling reaction of ferrocenylethyne with different acyl chlorides using SLS as surfactant and K_2CO_3 as base (Scheme 3b). In both cases, the presence of surfactant was essential for the coupling reactions, also assessing its key role in protecting and stabilizing the acyl chloride reactants against hydrolysis.

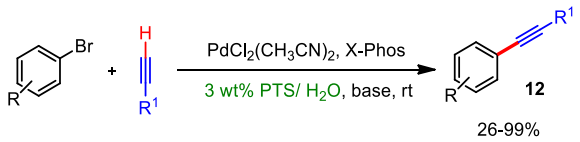
Arylation of heterocycles. Heterocyclic compounds have also been synthesized by the Sonogashira coupling under mild and micellar conditions, following a combination of the cross-coupling process with internal electrophilic cyclization. Bakherad[12] has succeeded in obtaining several types of heterocyclic compounds, such as imidazopyridines (**7**), imidazothiazoles (**9**) and imidazobenzothiazoles (**11**), by the coupling of aryl iodides with the corresponding aminopyridines, aminothiazoles and aminobenzothiazoles bromides using SLS as surfactant and Cs_2CO_3 as base at 60 °C (Scheme 4).

In 2021, Taddei reported[13] the synthesis of 2-substituted indoles by a tandem Sonogashira-cyclization reaction using Pd(OAc)2/XPhos as catalyst, in absence of copper, employing a 3 wt% TPGS-750-M water solution, affording desired products with moderate yields.

Scheme 4. Synthesis of a) 2-substituted imidazo[1,2-*a*]pyridines; b) 6-substituted imidazo[2,1-*b*]thiazoles; c) 2-substituted imidazo[2,1-*b*][1,3]benzothiazoles



Scheme 5. Arene alkynylation in water with PTS as surfactant, with no copper added

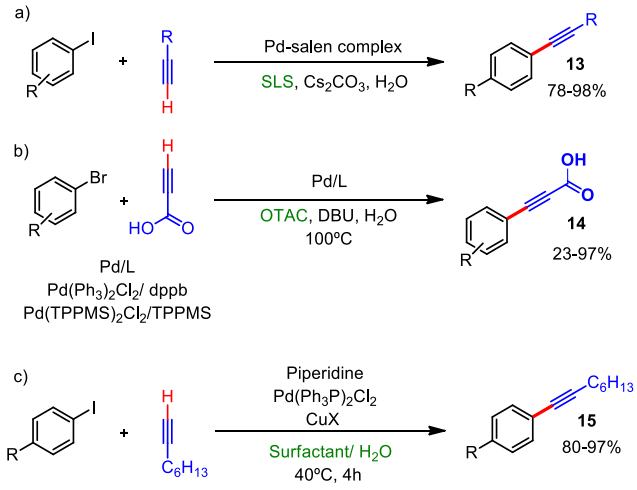


Alkynylation of arenes. Coupling reactions of terminal alkynes and aryl bromides or iodides have been carried out in the presence of a wide variety of surfactants, obtaining excellent results. In 2008, Lipshutz reported the first example of a cross-coupling reaction between lipophilic terminal alkynes and aryl bromides using the designer surfactant, PTS (Scheme 5).[14] The addition of this surfactant allowed the efficient formation of desired products in the absence of copper, in water and at room temperature. For instance, the

coupling reaction between phenyl acetate and bromobenzene in the presence of PTS led to 83% isolated products while without surfactant the conversion was just 34%. Subsequently, Lipshutz improved the efficiency of this type of cross-coupling reactions using the surfactants TPGS-750-M-M14 and Nok.[9] These results showed the potential of the third generation of surfactants (Nok), replacing the previous ones which are based on the more expensive vitamin E.

The coupling reactions between terminal alkynes and aryl halides have also been described in the presence of different types of common and inexpensive surfactants. For these type reactions, Bakherad[15] and Lee[16] independently developed catalytic systems which gave excellent yields in absence of copper and using SLS (Scheme 6a) and octadecyl trimethyl ammonium chloride (OTAC) as surfactants (Scheme 6b), respectively. On the other hand, Woo[17] described the Sonogashira coupling between aryl bromides or iodides and 1–octyne catalyzed by $Pd(PPh_3)_2Cl_2$ in the presence of commercial surfactants SDS, CTAB, Triton X-100 and Na-Cholate (Scheme 6c). In these cases, the use of Cu(I) salts as co-catalyst was necessary to achieve high yields.

Scheme 6. Sonogashira coupling between terminal alkynes and aryl halides



Aryl iodides and 1-octyne led to yields of 80-97 %, when SDS or CTAB were used as surfactant and CuI or CuBr as co-catalyst (40%-60% in the absence of these salts). This group also showed that the nature and the concentration of surfactants has significant influence in the reaction outcome: neutral Triton X-100 was not as efficient as the ionic SDS or CTAB.

New catalytic systems operating in the absence of copper and under micellar conditions have been recently disclosed. The key of success of such systems stands on a substantial lipophilicity of the catalyst, since it has been demonstrated that it enhances the interaction with the inner hydrophobic core of micelles with subsequent improvement of the catalytic efficiency. [18]

Lipshutz described the new ligand HandaPhos,[19] a monodentate cyclic phosphine, which led to Sonogashira couplings with catalyst loadings as low as 0.1 mol% (copper-free), and with TPGS-750-M as the surfactant. Later, the commercially available cBRIDP ligand yet allowed the use of the palladium catalyst at the ppm level. Likewise, other catalytic systems based on phosphine ligands, such commercially available catalyst CataCXium® A Pd G3 also led to 98% with catalyst loading <1% in TPGS-750-M and using glucose as additive and THF as co-solvent.[20] These studies confirmed the important role that the nature of the ligands performed in the reactions carried out under micellar conditions. On the other hand, the use of other phosphine ligands such as tBuXPhos, BI-DIME or DPEPhos led to very low yields (Scheme 7).

Scheme 7 phosphin

Scheme 10. Sonogashira couplings in water using thermoresponsive copolymers (TC) as micelle precursors

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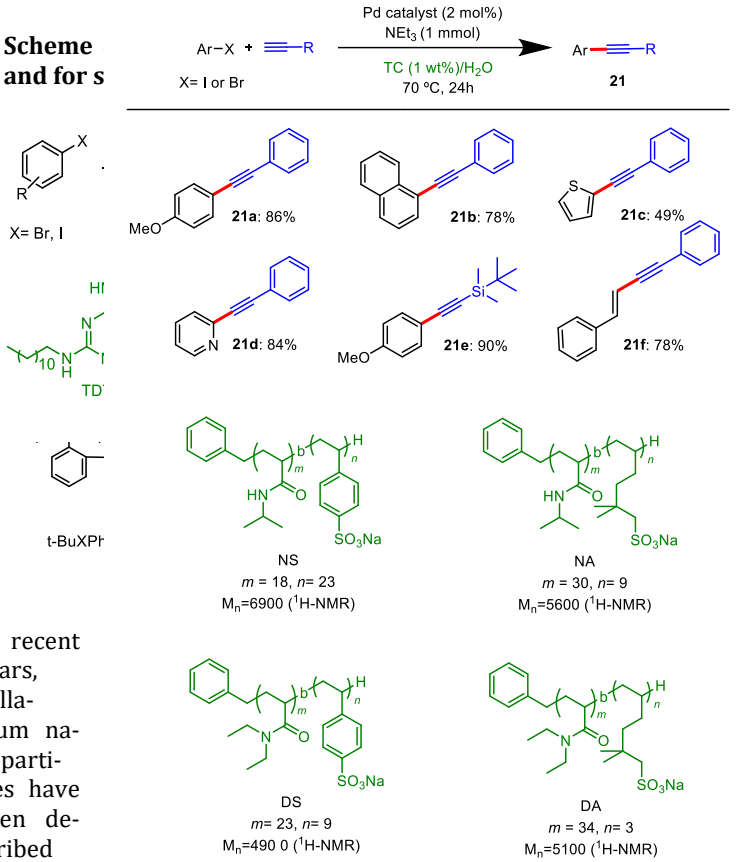
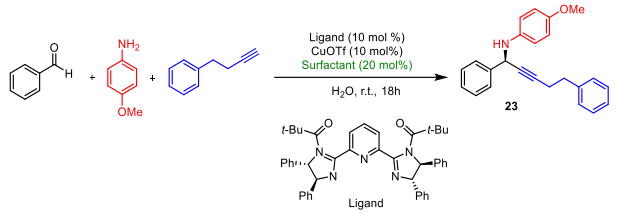


In recent years, palladium nanoparticles have been described as efficient catalysts for Sonogashira couplings under micellar conditions. For example, Panahi described[21] the pseudo-surfactant TDTAT, by 2,4,6-trichloro-1,3,5-triazine (TCT) and dodecylamine, which also stabilized Pd NPs as catalyst for Sonogashira coupling in water. TEM analysis showed that Pd(II) precursors in the presence of TDTAT in water at 80 °C converted into Pd(0) nanoparticles with an average size of~3 nm. Also, emulsion droplets containing Pd NPs operated as effective reactors for the C-C coupling reactions, with higher reaction rates. The recycling of these catalytic was verified for five consecutive runs (Scheme 8).

Lipshutz reported a micellar catalytic system, based on nanoparticles derived from $FeCl_3$ stabilized with the ligand

XPhos and with a Pd loading of 500 ppm coupled to nanomicelles of designer surfactant TPGS-750-M.[22] This catalytic system induced Sonogashira coupling within the rt-45 °C interval with excellent yields between 79-95% (Scheme 9). The success of this system was associated to the "nano-to-nano" effect, which refers to the natural tendency of MPEG units, present on surface of the spheres of TPGS-750-M, to function as a stabilizing ligand of metallic nanoparticles that are also present as catalyst in aqueous solutions.[23] This "nano-to-nano" effect was confirmed by cryo-TEM analyses,

Table 1. Enantioselective three-component reaction using various surfactant types

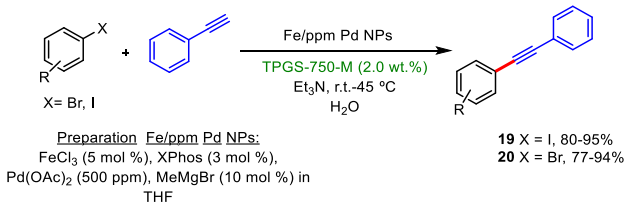


Entry	Surfactant	Yield (%)	ee (%)
1	SDS	99	98
2	CTAB	0	-
3	Triton X-100	17	98
4	SLS	0	-

which showed cluster of nanomicelles around metallic NPs.

In 2021, Suzuki reported a palladium-catalyzed system using different types of thermoresponsive diblock copolymers as surfactants.[24] These copolymers formed micelles at temperatures above 50 °C, which were employed as reaction medium for several Pd-phosphine complexes, at 70 °C,

Scheme 9. Examples of products of the Sonogashira coupling catalyzed by Fe/ppm Pd NPs.



leading to excellent yields in the Sonogashira coupling (Scheme 10).

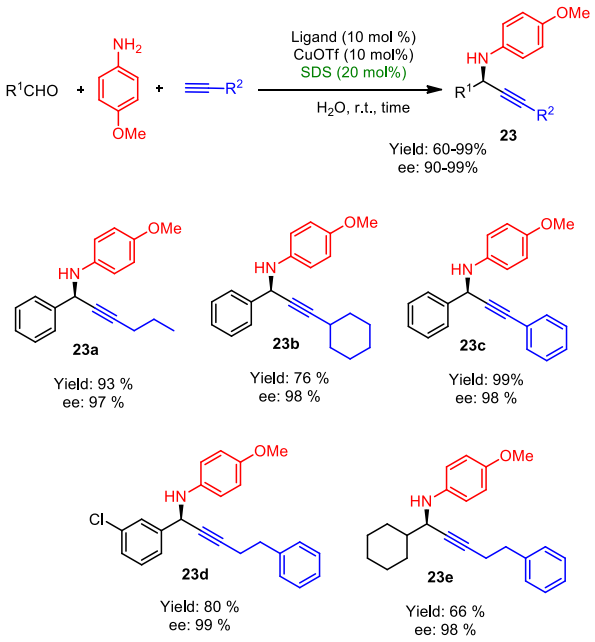
Synthesis of ynamides. Ynamides are terminal active alkynes which have been employed as building blocks for the formation of nitrogen-containing products. The synthesis of ynamines and ynamides has typically involved dry organic solvents because of their moisture-sensitivity and their insolubility in water. However, in the last years, different processes were described employing water as solvent, in the presence of micelles.

In 2021, Zhao reported[25] the synthesis of ynamides and arylynamines by Sonogashira coupling between ynamines and aryl iodides in water using $Pd(Ph_3)_4$ as catalyst, Cs_2CO_3 as base and CTAB as surfactant. The authors found that this system was tolerant to a broad range of aryl iodides and ynamines featuring both electron-donating and electron-withdrawing groups, affording a wide variety of ynamines **22** in good to excellent yields (Scheme 11). These results suggested that in micellar media, ynamides could be protected from hydrolysis by location at the hydrophobic core of micelles, thus retarding decomposition in water.

A³ coupling reactions

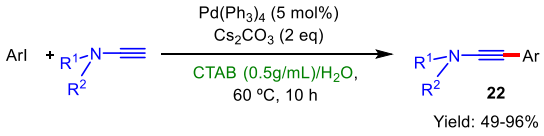
The aldehyde-alkyne-amine (A^3) coupling reaction constitutes a useful synthetic strategy for alkyne functionalization via activation of C-H bonds toward the synthesis of propargylamines. Several contributions have appeared in the last decade for the development of this reaction under micellar conditions.

Scheme 12. Enantioselective three-component reaction



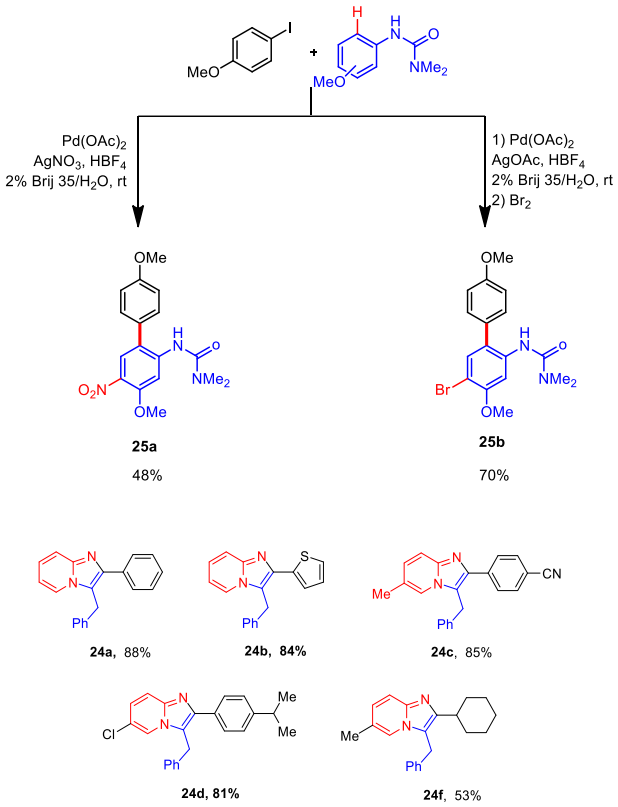
In 2014, an enantioselective three component reaction of aldehydes, amines and alkynes in water using bis-(imidazoline)Cu^I species as catalysts and SDS as surfactant was

Scheme 11. Synthesis of ynamines by Sonogashira coupling under micellar conditions



reported by Nakamura (Scheme 12).[26] The reaction took place, in the presence of SDS, with excellent yields, whereas the use of other anionic, cationic or neutral surfactants such as SLS, CTAB or Triton X-100 did not provide good results (Table 1). A broad range of aldehydes and alkynes was tested to give optically active propargylamines with excellent yields (60-99%) and enantiomeric excess (90-99%).

Scheme 15. Tandem C-H arylation/electrophilic trapping



Banerjee later disclosed an efficient synthesis of imidazo[1,2-*a*]pyridine derivatives by A^3 coupling reaction catalyzed by Cu(II)-ascorbate in aqueous micellar media (Scheme 13) in the presence of SDS.[27] This system showed a high tolerance for both electron-withdrawing and electron-donating substituents on 2-aminopyridine and benzaldehyde substrates. A wide variety of imidazo[1,2-*a*]pyridine with good yields between 50-89% were obtained. The reaction was very slow in absence of surfactant yielding only 14% of **24a** at 80 °C after 24 h. This suggested that the micellar "nanoreactors" were necessary to bring together water-insoluble components in their hydrophobic core, thus favoring the reaction to proceed.

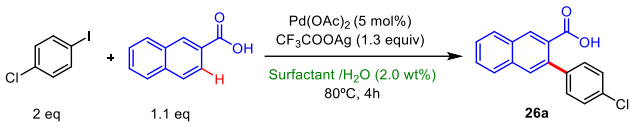
2. C(sp^2)-H BOND FUNCTIONALIZATION

Arylation reactions

One of most useful synthetic strategies to achieve the functionalization of aromatic C(sp^2)-H bonds is the arylation reactions employing aryl halides and (hetero)arenes. The relative inertness of such bonds requires the use of hard conditions, including high temperatures and/or strong acidic media, with subsequent drawbacks such as tolerance to functional groups. The use of directing groups has been used as an alternative strategy, albeit it does not always solve the problems. Recent studies have shown that micellar catalysis may provide high yields and selectivities under mild conditions.

In 2010, Lipshutz reported[28] the first mono C(sp^2)-H arylation reaction under mild conditions in water. Arylation reactions of aniline derivatives with aryl iodides catalyzed by

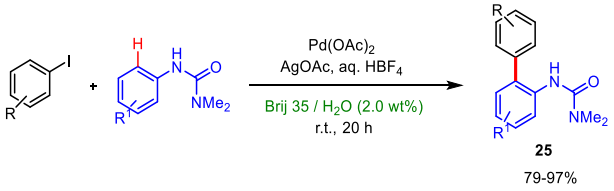
Table 2. Scope of surfactant for Pd-catalyzed carboxylate-directed C-H arylation in water



Entry	Surfactant	Conversion (%)
1	None	0
2	Tween 80	82
3	Tween 20	87
4	Tween 40	77
5	Tween 60	55
6	Brij 35	67
7	SDS	10
8	HTAB	40

$Pd(OAc)_2$ was performed in the presence of AgOAc and HBF_4 in 2 wt% surfactant/water solutions at room temperature. Several common and designer surfactants were tested. The best results were reached using Brij 35, which led to yields between 79-97% under optimal reaction conditions (Scheme 14). Also, they found that the micellar conditions improved selectivities, since aniline derivatives lacking ortho- or meta-substitutions, which have previously shown to be prone to double arylation, formed products exclusively from mono-arylation reaction under these conditions. The limitation of these reactions in water was the use of sterically hindered substrates or electron-deficient ureas. Likewise, a series of tandem processes, like C-H activation/electrophilic trapping, were described under these mild conditions: bromide and nitrate biaryl products were isolated with good yields (Scheme 15).

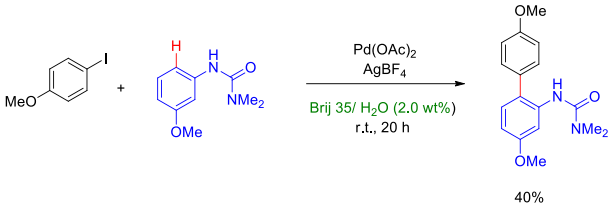
Scheme 14. C-H arylation process in micellar media



The mechanistic studies showed that the presence of active cationic palladium species was essential for the arylation reaction to proceed at room temperature. When the catalytic system, Pd(OAc)2-AgOAc-HBF_4, was replaced by commercially available palladium complex, $[Pd(MeCN)_4](BF_4)_2$, the reaction was inhibited. However, when the catalytic system was substituted by the system Pd(OAc)-$AgBF_4$, biarylated products were obtained with moderate yields around 40% without the assistance of any acid or coordinated ligand (Scheme 16).

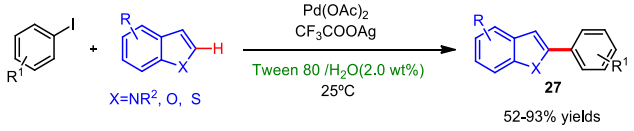
Ren reported[29] an efficient Pd-catalyzed carboxylate-directed C-H arylation reaction of aryl carboxylic acids with iodobenzenes in 2 wt% surfactant/water solutions where different commercial surfactants were used. The presence of these surfactants improved the solubility of the starting materials in reaction media and allowed carrying out this type of reactions at a lower temperature (80 °C) than those previously reported (> 100 °C), using conventional organic solvents. The desired products were isolated with yields between 62-92% (Scheme 17).

Scheme 16. Acid-free C-H bond arylation in micellar media



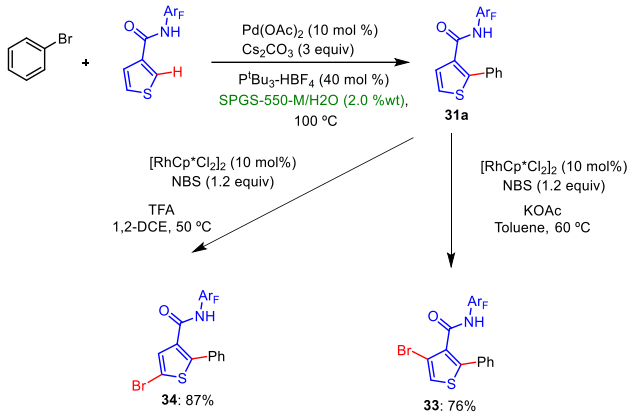
The effect of the nature of surfactants in the reaction outcome is illustrated in Table 2. For example, the neutral surfactants such as Brij 35, Tween 80 or Tween 20 were effective for the C-H arylation of aryl carboxylic acids, whereas ionic surfactants such as SDS or CTAB led to low conversions. The best results were achieved using Tween 20 as the micelle precursor.

Scheme 18. C2-arylation of indoles, benzofuranes and benzothiophenes at room temperature in the presence of Tween 80



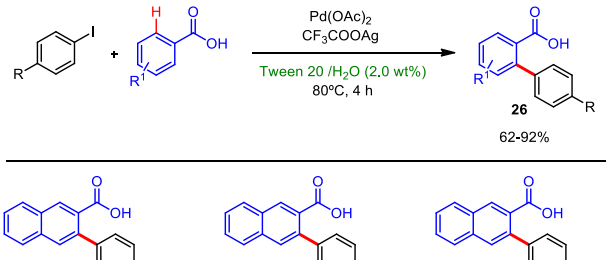
The C-H activation/arylation reactions of indoles, benzofuranes, and benzothiophenes is also of interest, albeit most of the reported methods have generally showed regioselectivities issues unless directing groups, high temperatures (100-150 °C) or acid co-solvents are employed. In 2015, Ren reported[30] the mild, efficient and C2 selective palladium-catalyzed arylation reaction of indoles, benzofurans and benzothiophenes with iodobenzenes at room temperature in the presence of Tween 80 as surfactant. The products were synthetized with good yields, and in a selective manner toward that position, with no detection of the C3 arylation derivatives (Scheme 18).

Scheme 21. Sequential regioselective functionalization of thiophenes

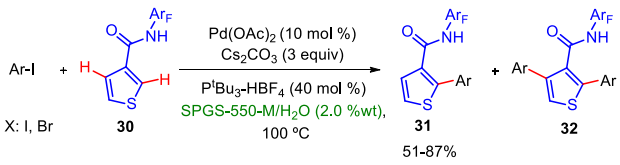


Subsequently, Kumar described[31] a selective C3/C2 arylation of indoles using the designer surfactant SPGS-550-M (Nok) in the presence of [cinnamyl)]$PdCl_2$]/phosphine ligand, as catalyst in water at 80 °C. The micellar medium allowed this process to be carried out under mild conditions with high yields, and outstanding regio- (C3 vs C2) and chemoselectivity (C vs N) control. A high functional group

Scheme 17. Arylation reaction of carboxylic acids derivatives under micellar conditions

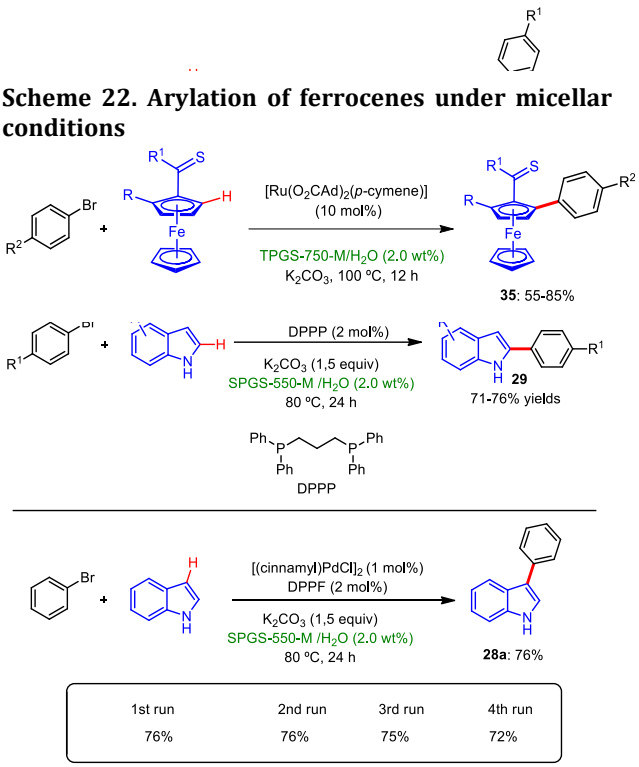


Scheme 20. Arylation of thiophenes in micellar medium.



tolerance was also observed. It is the nature of the phosphine ligand that displays the key role for achieving site-selectivity. DPPF and DPPP ligands were the most effective in promoting the arylation at C3-H and C2-H, respectively. Also, the surfactant solutions could be recycled and reused without compromising products yields (Scheme 19).

Scheme 19. Selective C3/C2-arylation of (NH)-indoles in the presence of SPGS-550-M (top). Reusability of the surfactant solutions (bottom)



Tan described a Pd-catalyzed arylation of 3-substituted thiophenes in a regioselective manner when performed in water/surfactant media (Scheme 20).[32] These conditions provided the desired C2-arylated thiophene derivatives with high yields and selectivities. The phosphine ligand, P^{t}Bu$_3$, performed a key role in selectivity control toward mono-arylation products, limiting the functionalization to the 4-position. In this work, it was found that the starting material and desired product showed a greater stability in water than in the previously used organic solvents. The addition of different types of surfactants improved the efficacy and led to better yields. The best results were reached with SPGS-550-M (N0k). Whereas electron-withdrawing substituted aryl halides led to excellent yields and selectivities, those bearing electron-donating groups showed lower oxidative addition reaction rates, increasing the ratio of the bisarylated products. Moreover, the functionalization of positions C4 and C5 was achieved with high regioselectivities. The formation of 2,3,4-substituted thiophenes was only found when the arylation reaction was tested using a rhodium catalyst and KOAc as a weak base under basic conditions. On the other hand, in the presence of a strong acid such as TFA, only the functionalization of position 5 was observed. The 2,4,5-substituted thiophenes were obtained with the best yields under these conditions (Scheme 21).

In 2019, Ackermann described[33] the first example of chemoselective arylation of ferrocenes catalyzed by a ruthenium complex in water

Scheme 23. Alkenylation reactions in micellar media

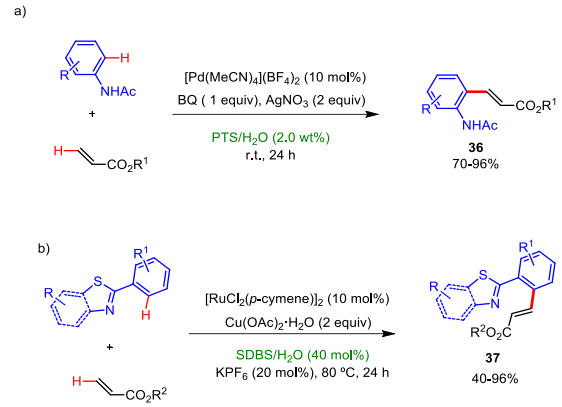
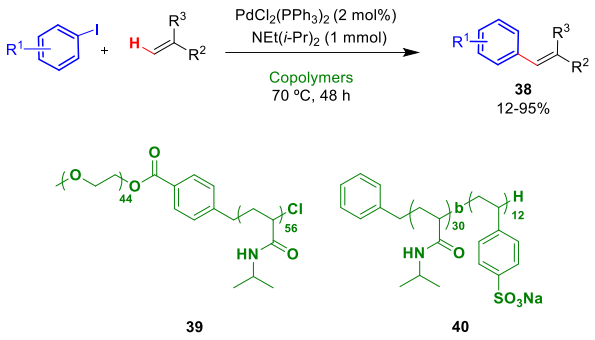
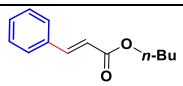
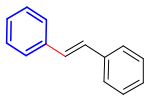
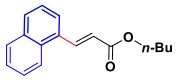
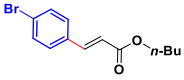
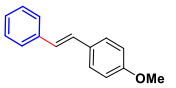
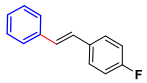
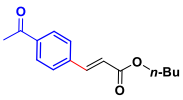


Table 3. Representative examples of Mizoroki-Heck reactions with various aryl halides and alkenes in water



Entry	Copolymer	Product	Yield (%)
1	**39**		96
2	**40**		99
3	**39**		62
4	**40**		98
5	**39**		93
6	**39**		73
7	**40**		80
8	**40**		56
9	**40**		79

through micellar catalysis. The presence of a single component ruthenium catalyst and K_2CO_3 as base gave the optimal results, in a process assisted by weakly coordinating thiocarbonyls in an aqueous solution of surfactant, TPGS-750-M (Scheme 22). This reaction showed fully tolerance with valuable functional group such as chloro, bromo, ester, ketone or aldehyde, with a wide variety of mono and bis-substituted ferrocenes. Also, the designer surfactant could be recycled up to four times without affecting to reaction yields.

Alkenylation reactions

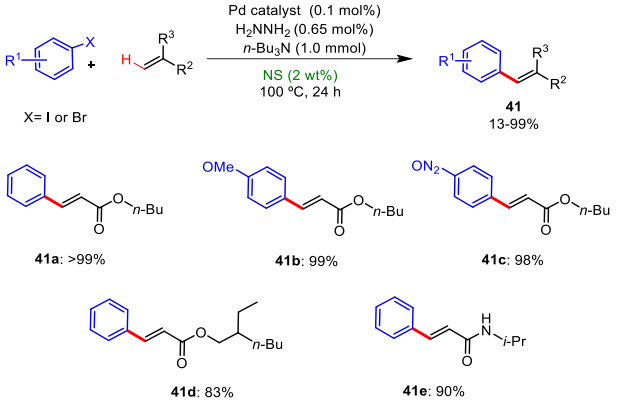
Another useful synthetic method for the formation of C-C bonds from C(sp^2)-H aryl bonds is the alkenylation of arenes. Examples reported in the literature in conventional media usually need elevated temperature, anhydrous acidic conditions, as well as high pressures of CO or O2 as the oxidant. Also, these studies showed the pernicious effect of water as an inhibitor reagent. Only very recently it has been demonstrated that micellar catalysis can be employed toward the alkenylation reaction of C(sp^2)-H bonds in water.

In 2010, Lipshutz and Nishikata reported[34] the first example of an efficient catalytic Fujiwara-Moritani alkenylation reaction of C-H bonds between anilide and acrylate ester. The complex $[Pd(MeCN)_4](BF_4)_2$ was employed as catalyst and $AgNO_3$ and 1,4-benzoquinone as additives without an external acid at room temperature in surfactant/water solutions as reaction media. The surfactant PTS led to the best results, with high yields and regioselectivities (Scheme 23a). Later, Ding developed[35] an efficient ruthenium (II) catalyzed regioselective *ortho*-oxidative C-H bond alkenylation of substituted 2-arylbenzo[d]thiazoles and 2-aryltihiazoles with diverse acrylates using Cu(OAc)2 as oxidant in water in the presence of catalytic amounts of SDBS at 80 °C (Scheme 23b). In the case of 2-arylbenzo[d]thiazoles, the alkenylation reaction afforded the desired products with excellent yields and regioselectivities in the presence of both electron-rich as well as electron-deficient derivatives. However, the alkenylation of 2-aryltihiazoles gave alkylated products with high yields but moderate selectivities.

Mizoroki-Heck reactions

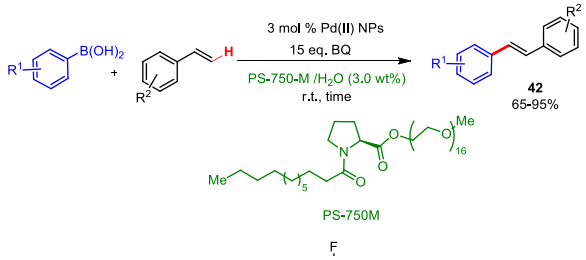
In 2019, Suzuki and Tsai described a Pd-catalyzed Mizoroki-Heck reactions between aryl iodides and alkenes terminals in water at 70 °C using thermoresponsive block copolymers **39** and **40** as surfactants (Table 3).[36] A broad variety of aryl iodides and alkenes with electron-donating and electron-withdrawing substituents were tested, affording a wide range of products in good and excellent yields. They found that like conventional surfactants, the nature of these copolymers also affected to efficiency of the reactions. The reactions carried out using the copolymer **39**, which presents an anionic tail, were more efficient than those with

Scheme 24. Mizoroki-Heck reactions in micellar media with thermoresponsive copolymers as micelle precursor (see Scheme 10 for NS)

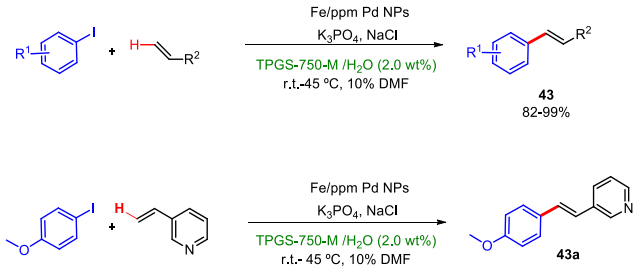


40, lacking such tail, as surfactant (Table 3). The use of thermoresponsive block copolymers shown in Scheme 10 was also described.[24] A number of Pd complexes were examined, the Mizoroki-Heck reaction giving the corresponding products in excellent yields (Scheme 24), with low palladium loadings (0.1 mol%).

Scheme 25. Coupling reactions between styrenes and aryl-boronic acids under micellar conditions



Scheme 26. Arylation reaction of alkenes catalyzed by Fe/ppm Pd NPs



1st run	2nd run	3rd run	4th run
93%	92%	94%	90%

Handa reported the development of stable, phosphine ligand-free and catalytically active Pd(II) nanoparticles gener-

ated from $Pd(OAc)_2$ and coupled to micelles with last generation surfactant PS-750M. The Pd NPs were efficient catalysts for the coupling reactions of styrene and aryl-boronic acids in an aqueous solution of PS-750M at room temperature, unusual conditions for these coupling reaction types (Scheme 25).[37]

Subsequently, Lipshutz described a new catalytic system, formed by Fe nanoparticles derived from $FeCl_3$ containing ppm levels of Pd ligated by P^tBu_3, capable of efficiently performing the arylation reaction of alkenes in 2 wt % TPGS-750-M/ water solution using DMF as co-solvent between room temperature and 45 °C. Excellent yields (82- 99%) of a variety of products with different functional groups were thus obtained (Scheme 26).[38] This group found that micellar conditions were necessary to carry out efficiently these catalytic reactions since the aqueous conditions altered the morphology of NPs, transforming inactive spherical NPs to rod-shape, catalytic active NPs. Moreover, the catalytic system could be recycled leading to similar yields after four consecutive cycles.

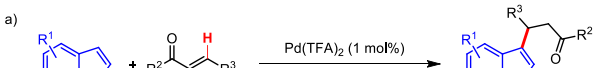
Heteroarene alkylations

The transition-metal catalyzed alkylation reactions of indoles with alkenes constitutes a well-established synthetic tool for $C(sp^2)$-$C(sp^3)$ bond formation. In 2015, Kobayashi group reported a selective C3-alkylation of 1H-indoles with α,β-unsaturated compounds catalyzed by an electrophilic palladium(II) complex in a micellar media at room temperature (Scheme 27a).[39] The alkylated products were obtained with yields between 50-85% and excellent regioselectivities under optimal reaction conditions. Moreover, they found that the presence of an anionic surfactant, such as SDS o SBDS, was essential to induce the alkylation reaction in good yields: non-ionic or cationic surfactants did not facilitate the transformation. The authors suggested that the cationic Pd(II) species was stabilized inside of micelles generated by anionic surfactants, therefore inhibiting the Pd(II) degradation to inactive catalytic Pd(0).

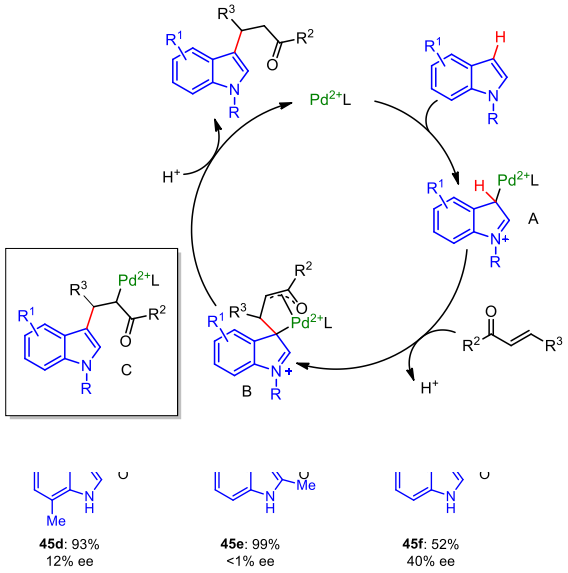
The same group later described the enantioselective version, employing palladium/bipyridine (**L1**) as chiral ligand, SDS as surfactant and PhNMe2 as additive at room temperature (Scheme 27b).[40] Phosphine-based sterically hindered bidentate ligands were found useless for this reaction in the micellar medium, SDS/H_2O. However, when chiral 2,2'-bipyridines (**L1**) were used along with different palladium(II) salts such as $PdCl_2$, $Pd(OAc)_2$, $PdBr_2$ and $PdCl_2(MeCN)_2$, the desired products were achieved with yields between 52-99%, whereas enantiomeric excesses were dispersed (1-91%).

Kobayashi proposed a mechanism for this transfor-

Scheme 27. Alkylation of indoles under micellar conditions



Scheme 28. Proposed catalytic cycle of electrophilic C-H functionalization with cationic Pd(II)

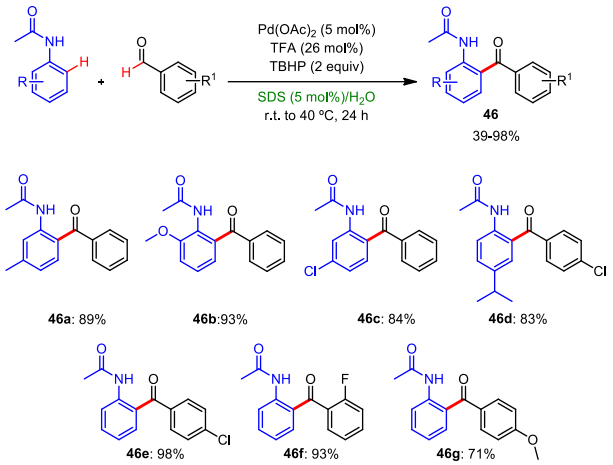


mation in micellar media (Scheme 28),[40] involving electrophilic palladation with an electron-deficient palladium(II) species to generate an indolyl-palladium intermediate (**A**), which reacted with α,β-unsaturated compounds to form C-bonded palladium(II) enolates (**B** or **C**). Despite the intrinsic propensity of **C** to undergo β-hydrogen elimination, they proposed **B** to be stabilizes in the micellar surface.

Arene acylations.

In 2013, Novák developed a new and efficient palladium-catalyzed C-H bond activation method for the synthesis of aryl ketones from anilides and aldehydes in micellar medium.[41] This oxidative coupling was performed in an aqueous solution of SDS using TBHP as oxidant and TFA as additive at temperatures between 25-40 °C. The system worked for an array of combinations (Scheme 29), including substituted anilides as well as aldehydes bearing electron donating or electron withdrawing substituents, leading to the corresponding aryl ketones with good and excellent yields). Also, the authors found that the micellar conditions were essential for the success. The use of conventional solvents such as CH_3Cl, CH_2Cl_2 and toluene gave conversions between the range 22-30%, at variance with those observed with the SDS-water system (63-93%).

Scheme 29. *Ortho*-C-H acylation reaction under micellar conditions



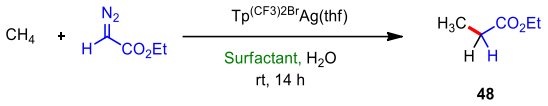
Later, Deng and Xiao succeeded in expanding the field of direct C-H acylation with aromatics aldehydes in micellar medium (Scheme 30).[42] They described the synthesis of diaryl ketones by a palladium-catalyzed *ortho*-C-H acylation reaction between aromatic aldehydes and aromatic oximes, azo aromatics compounds and aryl pyridines using TBHP as oxidant in an aqueous solution of SDS at temperatures between 50-80 °C. The diaryl ketones were isolated with good yields between 50-85% under optimal reaction conditions (Scheme 30). Furthermore, they found that these acylation reactions exhibited excellent regioselectivity and a wide tolerance towards both electron-rich as well as electron-deficient functional groups.

3. C(sp³)-H BOND FUNCTIONALIZATION

The direct formation of C-C bonds via C(sp³)-H activation bonds remains one of the most challenging research topics nowadays. The low reactivity and high thermodynamics stability of C(sp³)- H bonds are the main drawbacks to circumvent. In last decade, several research groups have developed different catalytic systems capable of carrying out the direct formation of C-C bonds from C(sp³)-H moieties under micellar conditions.

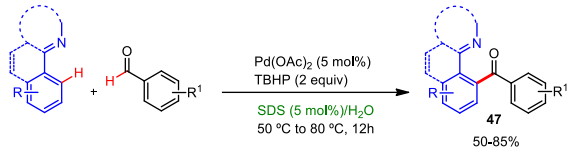
Alkane functionalization by carbene insertion

Table 4. Methane functionalization in water-surfactant mixtures.

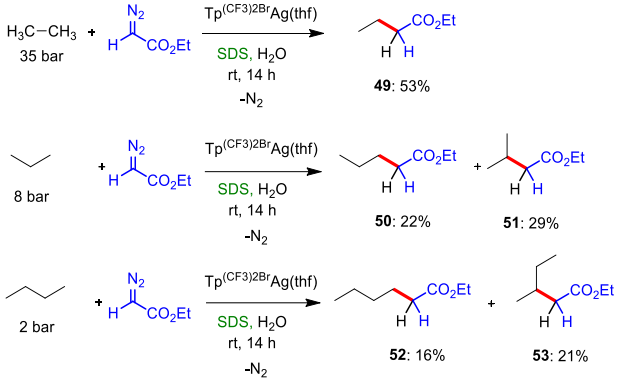


Entry	Surfactant	Yield
1	None	0
2	Triton X-100	0
3	DTAC	0
4	TPGS-750-M M	2
5	SDS	10
6	PFOS	14

Scheme 30. Expansion of the acylation reaction under micellar conditions.



Scheme 31. C2-C4 gaseous alkanes functionalization in water at room temperature



In 2019, our group reported the first example of functionalization of methane in water at room temperature employing micellar catalysis.[43] We employed a silver-based catalyst, $Tp^{(CF3)2Br}Ag(thf)$, capable of performing the formation of ethyl propionate from methane (160 bar) and ethyl diazoacetate (EDA) at room temperature in the presence of the surfactants SDS and PFOS. Ethyl propionate was afforded in 10% and 14% of yields, respectively (Table 4). When SDS was used as surfactant, part of the ethyl diazoacetate initially added led to functionalization of the hydrocarbon chains of the surfactant as well as to the formation of ethyl glycolate ($HOCH_2CO_2Et$) from H2O. On the other hand, the use of fluorinated surfactant avoided the functionalization of the fluorinated chains. Other gaseous alkanes such as ethane, propane and butane were also functionalized following the similar methodology, reaching EDA –based yields in the range of 37-53% (Scheme 31).

Monoarylation reactions of C(sp³)-H bonds

In 2011, Rossi described the highly selective direct C-H α-monoarylation reaction between 4-chromanones, ketones or aldehydes with aryl halides in the presence of $Pd_2(dba)_3/P^tBu_3/HBF_4$ as catalyst and $KHCO_3$ as base in 15 wt% surfactant/water solution at 100 °C (Scheme 32).[44a] The best results were reached using PTS and the optimal conditions led to the desired isoflavanones with yields within 60-90% values. A decrease in yields and selectivities was observed, when the α-monoarylation reactions was performed with aldehydes or ketones as substrates. However, these results surpassed those previously reported in

Scheme 32. Pd-catalyzed α-arylation of carbonyl derivates with aryl halides in PTS/H2O

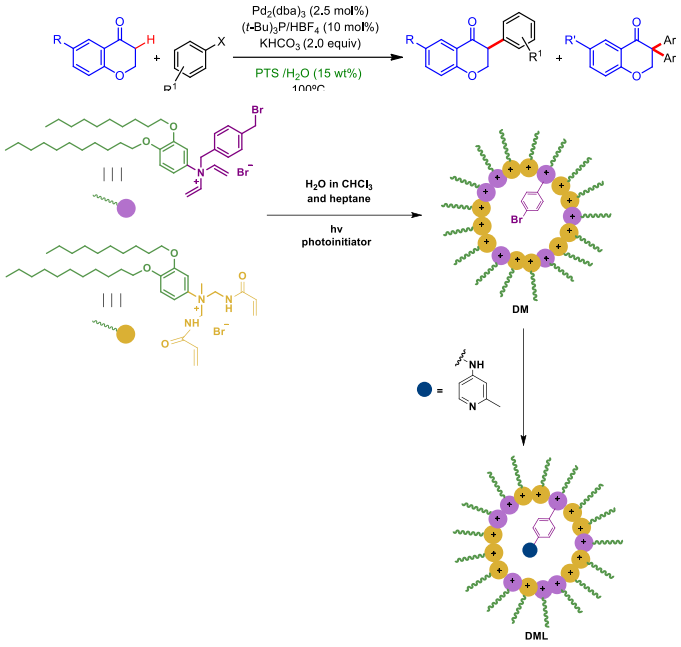
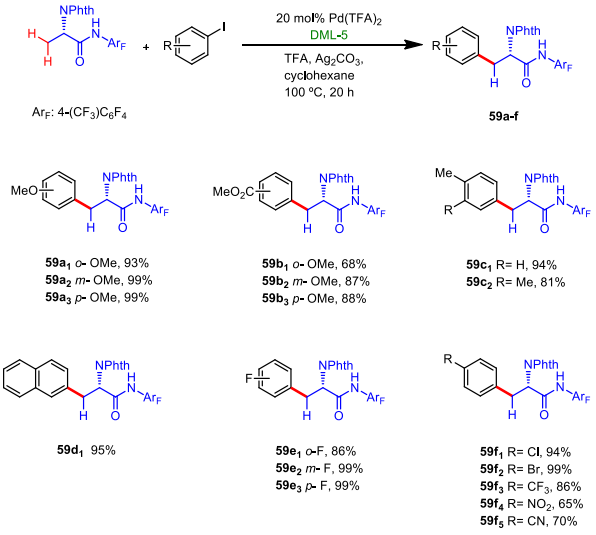


Figure 1. General synthesis of cross-linked micelle-supported ligand.

Scheme 33. Pd-catalyzed C(sp³)-H arylation using DML-5

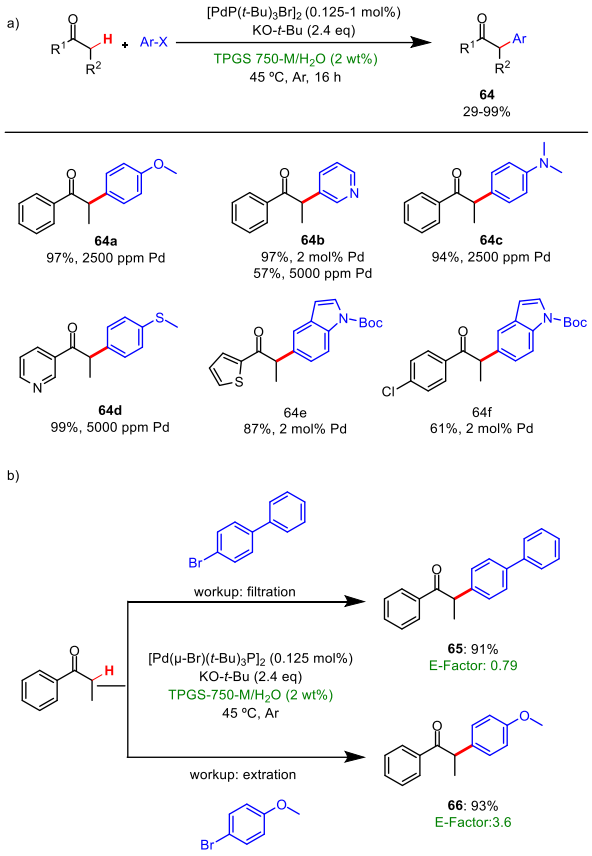


non-micellar media, using dioxane/H2O as reaction medium.[44b]

Jones later reported the first example of C(sp³)-H monoarylation catalyzed by a cross-linked reverse micelle supported palladium(II) catalyst.[45] Reverse micelles were designed to promote selectivity trends influenced by the steric and electronics effects inside the micelle core (Figure 1). They showed that in this new catalytic system both micelles and supported palladium catalyst exhibited a high toler-

ance and compatibility with electron-donating and electron-withdrawing substituents of the aryl iodides located in *ortho*-, *meta*- and *para*-positions (Scheme 33), leading to a series of products with high yields (70-99%) and selectivities (74-99%). DML-5 led to the best results, where DML stands for Double-tail Micelle with Ligands, being five the number of core size.

Scheme 34. a) C(sp³)-H α-arylations under aqueous micellar conditions (catalyst loadings giving in ppm or percentage). b) E-factors calculated for selected examples



In 2021, Lipshutz and co-workers described a new methodology for the α-arylation of aryl and heteroaryl ketones in an aqueous solution of the surfactant TPGS-750-M using a highly active and commercially available pre-catalyst, [Pd(μ-Br)P(t-Bu)$_3$]$_2$.[46] The reactions were performed with a broad range of aryl halides and ketones (Scheme 34a). Altering the aryl halides shown that electron-rich and neutral substrates afforded arylated products with yields 73-99% using Pd loading lower than 0.5 mol%. However, electron-poor halides were not that effective, and they required higher catalyst loading (2 mol%). When the arylation reactions was carried out using aryl methyl ketones and dialkyl ketones, as starting materials, good yields were also reached, although furan or thiophene led to double α-arylation products for most aryl halides. The E-factors calculated for two examples are shown in Scheme 34b, showing the high degree of *greenness* that these transformations display in comparison with the counterparts carried out in conventional reaction media.

The beneficious effect of micellar catalysis in residual metal. One important feature of the use of micellar catalysis is the observance of a significant decrease of the residual metal in the products. This is crucial in terms of the usage of the products for pharma industry. For example, the system shown in Scheme 34b led to a residual metal level of 6.6 ppm of Pd.[46] This value is below the FDA maximum value of 10 ppm of such metal on a daily dose. The same behavior has been reported for copper-free, Sonogashira couplings (Scheme 7), where the amounts of palladium were an order of magnitude below those reported for experiments carried out with 1-5% catalyst loading.[19a,b] A last, representative example corresponds to Mizoroki-Heck coupling catalyzed by metal nanoparticles, that led to the lack of detection of metal (below the detection limit) in the products,[38] making the route suitable for the synthesis of a precursor of galipinine.

CONCLUSIONS

In the context of the search for sustainable and environmentally-benign strategies within the area of transition-metal-catalyzed C-H bond functionalization, micellar catalysis has emerged as an alternative to conventional methods. The addition of surfactants to water generates micelles which accommodate catalyst and reactants in the inner region in such a way that the high local concentration usually triggers the kinetic of the reaction, therefore decreasing temperature and reaction times when compared with the corresponding reactions in conventional (usually organic) reaction media. Alkyl, aryl, alkenyl or alkynyl C-H bonds have been modified upon translating the known reactions in organic solvent to micellar media, in most cases with a significant shift towards greener conditions. The advances achieved in the last two decades point toward a significant value of this strategy in the incoming years.

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Notes

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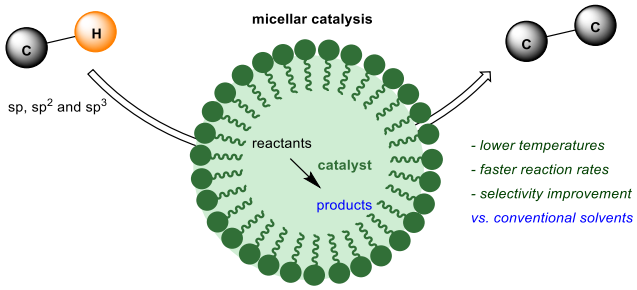
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