CRITICAL REVIEW

Sustainable protocols for direct C-H bond arylation of (hetero)arenes

Gianluigi Albano,[a] Angela Punzi,[a] Maria Annunziata M. Capozzi [a] and Gianluca M. Farinola *[a]

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

Direct C-H bond arylation of (hetero)arenes is a very convenient approach for the synthesis of a wide variety of molecular targets, including compounds of pharmaceutical interest and π-conjugated small molecules and polymers. Compared to traditional transition metal-promoted cross-coupling reactions, direct C-H arylations best fit the *Green Chemistry* criteria, particularly in minimization of waste, use of less hazardous chemicals, atom economy, reduction of unnecessary derivatization steps. Despite the advantages, these reactions still initially suffered from major limitations in terms of sustainable chemistry, *i.e.*, toxic and expensive transition-metal catalysts, toxic and/or hazardous solvents, high temperatures and long reaction times. The increasing attention towards environmentally friendly reaction protocols has boosted studies directed towards the development of sustainable strategies for direct C-H bond arylation of (hetero)arenes. This review offers a critical overview of the research on this topic, focusing on three main aspects: (i) recoverable catalysts; (ii) sustainable solvents; (iii) non-conventional energy sources.

1. Introduction

Organic molecules and polymers containing conjugated (hetero)aryl units have been extensively investigated in recent years. The family spams from simple bi(hetero)aryls, which represent important structural moieties in numerous natural products and many biologically active compounds,[1] to photo/electroactive oligo- and poly(hetero)aryls, used as active materials in organic light emitting diodes (OLEDs), organic field-effect transistors (OFETs), organic photovoltaics (OPVs), and in many other applications of plastic electronics.[2]

Generation of aryl-aryl bonds is the key synthetic step to produce all these compounds, and availability of efficient methods represents a milestone towards their technological development and industrial scalability. The most common and versatile routes to aryl-aryl bond formation are the transition metal-promoted cross-coupling reactions of (hetero)aryl halides or pseudohalides with (hetero)aryl metal derivatives, including boronic acids, organozinc, organotin, organosilicon compounds and Grignard reagents (**Scheme 1**, path a).[3] Despite high yields and good selectivities can be obtained with these methods, and also environmentally benign protocols have been developed,[4] many drawbacks still remain: both coupling partners must be preactivated (*i.e.*, halides and organometallic reagents have to be synthesized), which is wasteful since it requires the installation and the subsequent removal (and disposal) of stoichiometric amounts of the activating agents. Moreover, the generation of a stoichiometric amount of the metal by-products demands for expensive purifications protocols, which are particularly inconvenient in the case of the polymerization processes.[5]

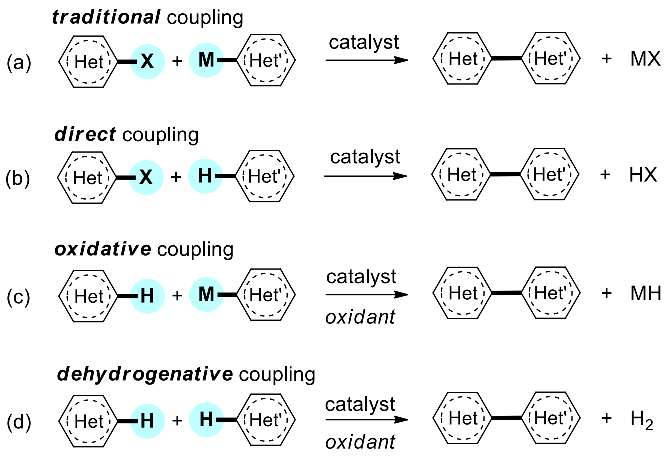
A more recent straightforward approach for the construction of aryl-aryl bonds is the direct arylation of (hetero)aryl C-H bonds with (hetero) aryl halides or pseudohalides (**Scheme 1**, path b): in this case, the pre-activated functionalities (the metal-carbon moiety) of one of the coupling partners (the organometallic reagent) are replaced by the C-H bond of a (hetero)arene, thus reducing the metal waste, simplifying the purification procedure and the number of steps in the synthetic sequence. Although the issue of C-H bond regioselectivity still remains unsolved in some (hetero)aryl systems, in the last two decades the studies have progressed very rapidly: a large variety of efficient direct C-H bond arylations involving five- and six-membered (hetero)arenes have been developed.[6]

The less common oxidative couplings can also be included In the family of direct C-H bond arylation of (hetero)arenes. In this case, the C-H bond of hetero(arene)s can be involved in the reaction with either stoichiometric amounts of organometallic reagents (**Scheme 1**, path c) or with the C-H bond of another simple (hetero)arene (**Scheme 1**, path d). On one hand, oxidative direct C-H arylations of heteroarenes with (hetero)arylmetals suffer the drawback of preliminary synthesis of organometallic reagents as (hetero)arylating reagents and the subsequent production of metal waste, but they are quite efficient and cost-effective, given that (hetero)aryl halides or pseudohalides are not required here (*i.e.*, only one of the reaction partners requires to be activated).[7] On the other, oxidative direct C-H arylations between two different (hetero)arenes, also known as dehydrogenative couplings, can be included among the reactions with the lowest environmental impact. In fact, they allow for superior atom economy transformations, since no preactivation of both coupling partners is required. However, C-H bond regioselectivity issues significantly limit the broad application of these reactions.[7]

---

[a] Dipartimento di Chimica, Università degli Studi di Bari "Aldo Moro", Via Edoardo Orabona 4, 70125 Bari, Italy. E-mail: gianlucamaria.farinola@uniba.it

† Footnotes relating to the title and/or authors should appear here.



Scheme 1. Synthetic methodologies in the (hetero)aryl-(hetero)aryl bond formation: (a) *traditional* transition metal-catalyzed coupling of (hetero)aryl halides or pseudohalides with (hetero)aryl metal derivatives; (b) *direct* C-H bond coupling of (hetero)arenes with (hetero)aryl halides or pseudohalides; (c) *oxidative* direct C-H bond coupling of (hetero)arenes with (hetero)aryl metal derivatives; (d) oxidative direct C-H bond coupling of two different (hetero)arenes (*dehydrogenative* coupling).

Compared to the traditional transition metal-promoted cross-coupling reactions, direct C-H arylations best fit the 12 principles of *Green Chemistry*, particularly in prevention of waste, less hazardous chemical synthesis, atom economy and reduction of unnecessary derivatization. However, there are still aspects of the C-H arylation processes which are scarcely compatible with the green chemistry criteria. Among them, the use of toxic and expensive transition-metal catalysts (in most cases palladium), which eventually contaminate the final coupling product, requiring complex purification procedures, the need of toxic and/or hazardous solvents, which are not available from sustainable or renewable sources. Finally, high temperatures and long reaction times are typically required. More recently, increasing attention towards environmentally friendly protocols has boosted a wide range of studies directed towards the development of green and sustainable protocols for direct C-H bond arylation of (hetero)arenes. Significant efforts have been recently accomplished to face these aspects, including the use of recoverable catalysts, sustainable solvents or non-conventional energy sources.

Several general reviews have been published in the past 15 years on the mechanistic aspects and the synthetic applicability of direct C-H arylation,[8] while only a few and very specific overviews have been reported on the more recent sustainable protocols; the topic of these reviews are more specific, *e.g.* on microwave irradiation-assisted approaches[9] or transition metal-free protocols,[10] on environmentally benign direct C-H arylation of 5-membered ring heteroarenes[11] or sustainable direct (hetero)arylation polymerizations.[12] In other cases, sustainable protocols have been treated as a part of more extended reviews focused on C-H activation reactions.[13] Therefore, we believe that a general, comprehensive and critical overview of the sustainable strategies for direct C-H bond arylation of (hetero)arenes would be timely and useful to overview the present states at this stage of the research in the field.

The review will be organized in three parts, concerning the methods adopted to overcome the three main drawbacks of direct C-H arylation of (hetero)arenes still incompatible with the *Green Chemistry* criteria mentioned above (*i.e.*, toxic and expensive catalysts; not sustainable and hazardous solvents; high temperatures and long reaction times). In the first part we will report an overview of recoverable catalysts used in direct C-H bond arylation of (hetero)arenes; most of them are Pd catalysts supported onto inorganic or organic matrices, but there are also some examples of recoverable catalysts based on other metals. The second part of the review will be focused on the development of direct C-H arylation protocols involving non-toxic and more sustainable solvents: water is definitely the most investigated, but we will also overview studies about other less common sustainable solvents and, finally, the more convenient solvent-free methods. In the third part the application of non-conventional energy sources in direct C-H arylation of (hetero)arenes will be presented: we will mainly focus on the more common photochemical protocols (both in the presence and in the absence of photoredox catalysts) and microwave-assisted protocols, but also the few examples of electrochemical methods, as well as of ultrasound-, mechanical milling- and infrared irradiation-promoted reactions will be considered. Although a complete overview of the existing literature is far from trivial, in each section we will mostly follow a systematic approach as a function of (hetero)arene structure, based on heteroatoms (carbocycles, *N*-heterocycles, *O*-heterocycles and *S*-heterocycles), ring size (five-membered, six-membered and seven-membered) and number of cycles (monocyclic, bicyclic and polycyclic compounds), and also as a function of molecular size of π-conjugated systems, differing between small molecules and oligo/polymers.

2. Recoverable catalysts in direct C-H bond arylation of (hetero)arenes

In the context of direct C-H bond arylation of (hetero)arenes, a broad variety of homogeneous catalytic systems based on transition metal complexes have been investigated, often showing high activity and broad versatility. However, issues related to relatively high costs, low recyclability and contamination of final coupling products are hardly compatible with the *Green Chemistry* criteria. Although many industrial productions still prefer well-established homogeneous methods,[14] with environmental regulations becoming increasingly stringent the need of more sustainable approaches for direct C-H bond arylation is central in the synthesis of bi(hetero)aryl motifs.

The use of heterogeneous catalysts is very attractive for this purpose, although the inertness of the C-H bond of (hetero)arenes made quite difficult their application. However, in some cases heterogeneous catalysis allows to achieve a specific C-H bond regioselectivity, or its switch with respect to the corresponding homogeneous processes, which is highly desirable since the issue of C-H regioselectivity still remains unsolved in some (hetero)aryl systems. Therefore, the study of recoverable and recyclable heterogeneous catalysts in direct C-H bond arylation of (hetero)arenes is highly desirable not only because these systems allow for an easy separation from reaction medium by simple filtration, but also for the development of new selective synthetic protocols.

However, in some cases the actual nature of the catalytic process (heterogeneous *vs.* homogeneous) remains unclear: supported catalysts presented in the literature as merely heterogeneous actually showed a significant loss of their catalytic activities when reused, due to metal leaching occurring during the reaction.[13a,13b] The problem of distinguishing homogeneous from heterogeneous catalysis is far from trivial: careful kinetic studies, hot filtration tests, selective catalysts poisons are very helpful to solve the question of heterogeneity.[15]

In this section we will give a critical overview of all the solid supported metal catalysts applied in direct C-H bond arylation of (hetero)arenes. In particular, in the first part we will consider direct arylation protocols based on supported palladium species, which are most commonly used; then, we will discuss the application of supported catalysts based on the other transition metals.

2.1. Recoverable palladium-based catalysts for direct C-H bond arylation of (hetero)arenes

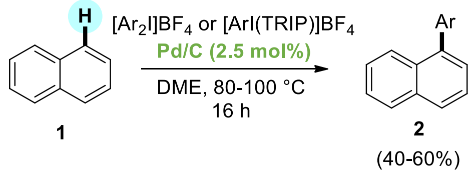
Palladium-based species are definitely the first choice as catalysts for generating C_{sp2}–C_{sp2} bonds. Therefore, it is not surprising that most of direct C-H bond arylation of (hetero)arene protocols are based on Pd catalysts, although not infrequently they are accompanied by a suitable co-catalyst (such as copper).

As we will show below, commercially available Pd/C and $Pd(OH)_2/C$ are among the oldest and the most common recoverable palladium-based catalysts for direct C-H arylations, due to their low cost, high thermal and mechanical stability, broad versatility. However, Pd nanoparticles deposited on other matrices, including mesoporous silica, magnetite, alumina, metal-organic frameworks and also organic polymers, as well as Pd(II) complexes covalently anchored onto solid supports, have been synthesized and successfully tested. Although these catalytic systems are described as reusable and heterogeneous, it is worth emphasizing that only for part of them have actually been tested for recycling and heterogeneity (including palladium leaching determination, hot filtration tests, kinetic studies, etc.).

2.1.1. Recoverable palladium catalysts for direct C-H bond arylation of arenes. In 2011, Matzger and co-workers reported the application of a highly dispersed palladium(II) in a defective metal-organic framework, named Pd(II)@MOF-5(O_h), as efficient catalyst in the direct phenylation of naphthalene with diphenyliodonium tetrafluoroborate.[16] Notably, the use of Pd(II)@MOF-5(O_h) 5 mol% in comparison with homogeneous $Pd(OAc)_2$ 5 mol% resulted in higher yields (*i.e.*, 64% *vs.* 17%) and better stability, although with a lower selectivity for the α isomer over the β isomer (α:β = 3:1 for Pd(II)@MOF-5(O_h) *vs.* 8:1 for $Pd(OAc)_2$). A more general and convenient protocol was then demonstrated by Glorius and co-workers: direct arylation of naphthalene **1** with aryliodonium salts in the presence of Pd/C (2.5 mol%) as catalyst afforded the corresponding arylated products **2** in satisfactory yields and very high α-selectivity (α:β from 95:5 to 97:3) (**Scheme 2**).[17] Interestingly, authors demonstrated a merely heterogeneous mechanism for Pd/C thanks to a standard Hg-poisoning study, a hot filtration test and several three-phase tests using polymer-bound naphthalene, although no recycling tests have been performed. Despite the use of a supported palladium catalyst, it is worth emphasizing that both protocols are actually not of particular convenience from the point of view of *Green Chemistry*: the use of an aryliodonium salt is typically characterized by a low atom economy, as only half of the molecule is involved in the direct arylation process and the other one gives the corresponding aryliodide as a by-product, thus limiting the overall sustainability.

The *ortho*-arylation of substituted benzene cores is a very appealing strategy for the synthesis of highly functionalized biaryl units. In 2014, Srinivasu *et al.* reported the first *ortho*-arylation of benzamides **3** using a supported Pd catalyst: three-dimensional mesoporous silica with highly dispersed palladium nanoparticles composite (named PS-3).[18]

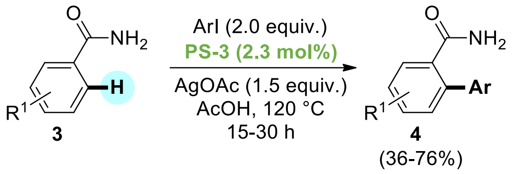
Direct C-H arylations were successfully performed between functionalized benzamides and aryl iodides with different stereo-electronic properties, in acetic acid as solvent and silver acetate as base, affording the *ortho*-arylated products **4** in reasonable yields, 36-76% (**Scheme 3**). Recyclability of PS-3 catalyst was also tested over five different cycles without significant loss of its activity.



Ar = Ph, o-MeC_6H_4, m-MeC_6H_4, p-MeC_6H_4, o-FC_6H_4, p-FC_6H_4, m-NO_2-C_6H_4, p-$MeOC_6H_4$, p-ClC_6H_4, p-$EtOOCC_6H_4$

Scheme 2. Direct C-H bond arylation of naphthalene **1** with aryliodonium salts catalysed by recoverable Pd/C catalyst, developed by Glorius and co-workers in 2015.[17]

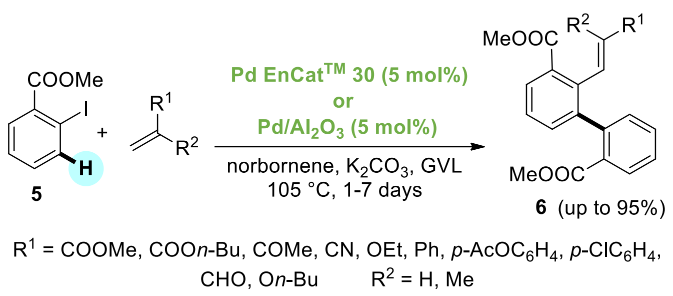
More recently, Glorius and co-workers reported the direct C-H *ortho*-arylation of anilide derivatives with diaryliodonium salts as arylating agents, using Pd nanoparticles supported on magnetite as recoverable catalyst.[19] Kinetic studies revealed the presence of catalytically active soluble species from heterogeneous precursors, also confirmed by a low recyclability after the second cycle and a severe metal leaching in the coupling product. Moreover, the use of diaryliodonium salts as arylating agents with low atom economy further limited the real interest from the point of view of the *Green Chemistry*.



Ar = Ph, m-MeC_6H_4, p-MeC_6H_4, p-COMe-C_6H_4, p-$MeOC_6H_4$
R^1 = H, 4-Br, 2-Cl, 4-Me, 3-OMe

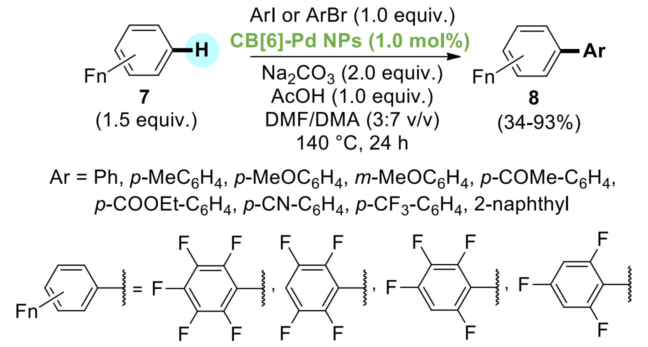
Scheme 3. Direct C-H *ortho*-arylation of benzamides **3** with aryl iodides catalysed by Pd nanoparticles supported on three-dimensional mesoporous silica (PS-3), developed by Srinivasu *et al.* in 2014.[18]

Ackermann and Vaccaro's groups reported in 2016 the first application of heterogeneous palladium catalysts for the Catellani reaction, which is a direct C-H *ortho*-arylation of aryl iodides mediated by norbornene, allowing for a tandem *ipso*-vinylation through a Mizoroki-Heck-type process.[20] Commercial Pd EnCat™ 30 and Pd/Al_2O_3 were successfully applied in the reaction of methyl 2-iodobenzoate **5** with several olefins, affording coupling products **6** from good to excellent yields (**Scheme 4**). The protocol looks highly attractive from a *Green Chemistry* point of view, since the supported palladium catalyst was used in combination with γ-valerolactone (GVL) as a sustainable and environmentally-benign reaction medium (see section 3.3.4). Several mechanistic studies were also performed, revealing the heterogeneous nature of Pd/Al_2O_3 but showing that reactions performed with Pd EnCat™ 30 were actually catalysed by leached homogeneous palladium species.



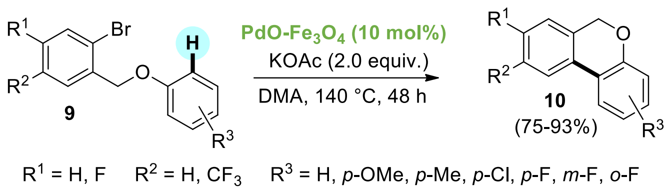
Scheme 4. First application of heterogeneous palladium catalysts (Pd EnCat™ 30 or Pd/Al_2O_3) for the Catellani reaction of methyl 2-iodobenzoate **5**, reported in 2016 by the Ackermann and Vaccaro's groups.[20]

In 2019, Doucet *et al.* showed the potential of Pd/C as catalysts for the direct C-H *ortho*-arylation of (poly)fluorobenzenes with aryl bromides. Reactions were performed at 110-150 °C using KOAc as base and DMA as solvent, affording high yields of coupling products in the case of tri-, tetra- and pentafluorobenzene, whereas mono- and difluorobenzene exhibited poor reactivity.[21] Unfortunately, hot filtration tests provided support for the formation of catalytically active soluble Pd species, thus limiting the sustainability of the protocol due to metal contamination of the final products. A similar protocol for the direct C-H *ortho*-arylation of (poly)fluoroarenes **7** with aryl iodides and bromides was developed by Cao and co-workers, although they used Palladium nanocrystals stabilized by cucurbit[*6*]uril (CB[6]-Pd NPs) as catalyst .[22] In particular, reactions were carried out in the presence of 2.0 equiv. of Na_2CO_3 and 2.0 equiv. of acetic acid, in a DMF/DMA mixture as reaction medium, in the presence of 1 mol% of supported palladium catalyst, at 140 °C for 24 h, affording the corresponding biaryl products **8** from modest to good yields (**Scheme 5**). Although the CB[6]-Pd NPs catalyst showed a better recyclability in comparison with other commercial palladium systems, the overall sustainability of the process appears quite low: the use of harmful solvents (*i.e.*, DMF and DMA), as well as the need of high temperatures for long reaction times make the protocol of limited interest in the context of the Twelve Principles of *Green Chemistry*.



Scheme 5. Direct *ortho*-arylation of (poly)fluoroarenes **7** with aryl iodides and bromides catalysed by Palladium nanocrystals stabilized by cucurbit[6]uril (CB[6]-Pd NPs), reported by Cao and co-workers in 2015.[22]

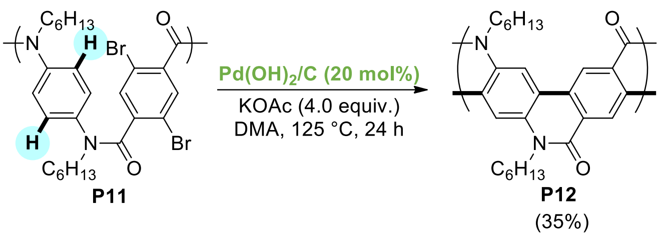
Intramolecular direct C-H *ortho*-arylations of benzene derivatives based on supported palladium catalysts have also been reported in literature, allowing the synthesis of benzofused (hetero)cycles. The first work was reported in 2005 by Fagnou *et al.*: $Pd(OH)_2/C$ (known as Pearlman's catalyst) was used for the synthesis of 6*H*-benzo[*c*]chromenes, 5,6-dihydrophenanthridines and other tricyclic *O*- and *N*-heterocycles via intramolecular direct arylation of suitable haloethers and haloamines.[23] Although the reactions occurred in high yields (69-98%), authors attributed the catalysis to the formation of homogeneous Pd species by leaching from the support. The preparation of 6*H*-benzo[*c*]chromenes **10** through a similar intramolecular direct C-H arylation of haloethers **9** has been then reported by McGlacken and co-workers: they used palladium impregnated on magnetite ($PdO-Fe_3O_4$) as easily removable catalyst, *i.e.* by simply using a magnet, although a complete deactivation was observed after the first cycle (**Scheme 6**).[24] ICP-AES analysis excluded the occurrence of a significant palladium leaching into the solution, as further confirmed by hot filtration test, which testified no reaction progress after filtration; however, substantial changes of both Pd particle distribution and size were observed with the help of TEM microscopy.



Scheme 6. Preparation of 6*H*-benzo[*c*]chromenes **10** through intramolecular direct C-H bond arylation of haloethers **9** catalyzed by the easily removable $PdO-Fe_3O_4$ catalyst, studied by McGlacken and co-workers.[24]

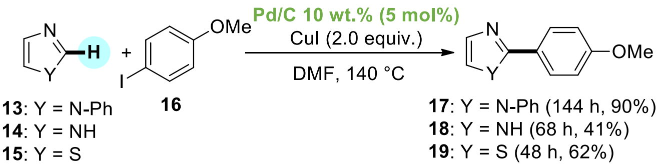
Felpin *et al.* described the preparation of functionalized phenanthrene derivatives via intramolecular direct arylation of *cis*-2-bromostilbenes. Although reactions were first performed under typical homogeneous conditions ($Pd(OAc)_2$, K_2CO_3, DMA, 110 °C), aiming for more sustainable heterogeneous catalysis they were also repeated by adding charcoal to reaction mixture, which afforded a moderate yields improvement (60-94%).[25] However, the effective benefits of the supported catalyst in the context of the *Green Chemistry* (that is, recyclability and heterogeneity) have not been investigated, thus casting serious doubts on the real sustainability of this protocol. Domínguez and SanMartin reported preliminary studies for the application of heterogeneous Pd catalysts in the intramolecular direct C-H arylation of 5-(2-bromophenyl)-1-phenyl-1*H*-pyrazole: interestingly, FibreCat 1000-D7 afforded the pyrazolo[1,5-*f*]phenanthridine product in 53% yield, with respect to 60% yield of the homogeneous $Pd(OAc)_2$.[26] Actually, its application appeared quite limited, due to the modest thermal stability of the polymer support of FibreCat 1000-D7, responsible of a severe palladium leaching into the solution, and subsequent metal contamination of the corresponding product. More recently, Takagi *et al.* applied $Pd(OH)_2/C$ catalyst for the synthesis of amide-bridged ladder poly(*p*-phenylene) polymer **P12** by intramolecular direct *ortho*-arylation of a suitable precursor polymer **P11** (**Scheme 7**); also in this case it was not possible to evalutate the sustainability of the protocol (which was, among other things, limited to a single substrate), as no studies of recyclability and heterogeneity were perfomed.[27]

2.1.2. Recoverable palladium catalysts for direct C-H bond arylation of *N*-heteroarenes. Supported Pd species have found wide application as recoverable and reusable catalysts in the direct C-H bond arylation of both monocyclic and bicyclic *N*-heteroarenes.



Scheme 7. Synthesis of amide-bridged ladder poly(*p*-phenylene) **P11** by intramolecular direct *ortho*-arylation of polymer precursor **P12** catalysed by $Pd(OH)_2/C$, reported in 2015 by Takagi *et al.*[27]

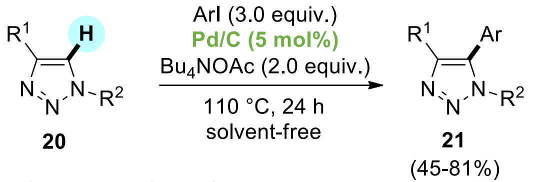
To the best of our knowledge, the first example of direct C-H arylation of (hetero)arenes catalyzed by a supported Pd catalyst was reported in 1982 by Nakamura *et al.* for a monocyclic *N*-heteroaromatic substrate: aiming to synthesize analogues of muscimol, a bioactive product extracted from *Amanita muscaria* fungi, the phenylation of substituted isoxazoles with iodoarenes was performed with commercially available Pd/C, although low yields (43-47.5%) of the final products were obtained.[28] It is worth to emphasize that the use of Pd/C was here tested simply as one of the commercially available palladium catalyst, rather than to a real need of more environmental friendly experimental conditions. A preliminary investigation for evaluating the use of Pd/C in place of homogeneous $Pd(OAc)_2$ in regioselective direct C-2 arylation of azoles **13-15** was performed by Bellina *et al.*: reactions were performed with *p*-iodoanisole **16**, at 140 °C in DMF with 5 mol% of Pd/C (10 wt.%) and 2 equiv. of CuI.[29] Interestingly, if the reaction of 1-phenyl-1*H*-imidazole **13** afforded the corresponding C2-arylated product **17** in high yield (90%), products **18-19** were obtained in lower yields (41-62%) (**Scheme 8**). However, the use of homogeneous Cu(I) iodide as co-catalyst, together with the absence of recyclability tests, reduces the potential sustainability of the protocol.



Scheme 8. Preliminary studies for the use of recoverable Pd/C catalyst in regioselective direct C2 arylation of azoles **13-15** reported by Bellina *et al.*[29]

In 2016, Ackermann and Vaccaro reported an appealing application of Pd/C as reusable heterogeneous catalyst for the direct C-H arylation of 1,2,3-triazoles in biomass-derived γ-valerolactone as environmentally-benign reaction medium: their procedure was successfully applied to a wide range of triazoles and aryl bromides, and Palladium catalyst could be recycled and reused without loss of activity and with very low leaching (3.6-5.5 ppm).[30] The same protocol was efficiently performed in continuous flow conditions, which allowed for an optimal reuse and durability of the Pd/C catalyst.[31] The possibility of combining highly sustainable experimental conditions with the typical facilities of flow chemistry make this study very appealing for synthetic organic chemists working in the field of the *Green Chemistry*: it enabled an optimal reuse and durability of the catalyst, which combined with the simple purification of the products and the recovery of the solvent made such protocol operationally simple and very efficient in terms of waste minimization and a low E-factor.

Very recently, our research group described a solvent-free protocol for direct C-H bond arylation of 1,2,3-triazoles based on commercial Pd/C, performed at 110 °C for 24 h in the presence of Bu_4NOAc as base: 1,4-disubstituted 1,2,3-triazoles **20** were treated with several functionalized aryl iodides, affording 1,4,5-trisubstituted triazoles **21** with yields ranging from 45 to 81% (**Scheme 9**).[32] Recycling tests on Pd/C catalyst showed an unchanged catalytic activity until the third run, while halving of activity was detected at the fourth cycle.



R^1 = Ph, C_5H_{11}, *p*-MeC_6H_4, C_6H_{13}

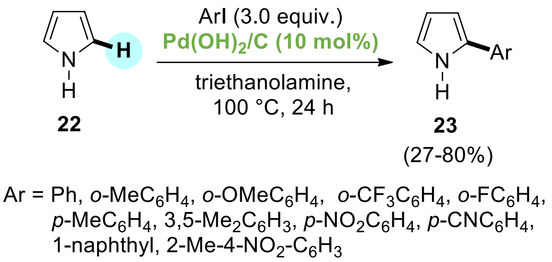
R^2 = $C_{16}H_{33}$, CH_2CH_2Ph, C_8H_{17} *p*-MeC_6H_4

Ar = Ph, *o*-MeC_6H_4, *m*-MeC_6H_4, *p*-MeC_6H_4, 3,5-$Me_2C_6H_3$, *p*-FC_6H_4, *p*-$NO_2C_6H_4$, *p*-$CF_3C_6H_4$, *m*-$OMeC_6H_4$, 3-pyridyl

Scheme 9. Direct C-H arylation of 1,2,3-triazoles **20** with aryl iodides based on commercial Pd/C catalyst, developed very recently by our research group.[32]

Doucet *et al.* reported in 2018 a very extended work, where 1 mol% of heterogeneous catalyst Pd/C promoted very efficiently the direct C-H arylations of many monocyclic *N*-heteroaromatic substrates, *i.e.*, pyrroles, thiazoles, imidazoles, isoxazoles.[33] Reactions were performed using (hetero)aryl bromides as coupling partners, proceeding with high regioselectivity and in moderate to very high yields. However, although authors developed this protocol in combination with the use of green solvents, neither heterogeneity tests nor recyclability studies on the Pd/C were performed. Very recently, the same group applied Pd/C as recoverable catalyst for the C2 regioselective direct C-H arylation of N-substituted pyrroles with functionalized benzenesulfonyl chlorides as non-conventional arylating agents. Although their use in direct C-H bond arylation reactions is still quite limited, benzenesulfonyl chlorides showed many advantages, such as broad availability and easy handling; moreover, the generation of SO_2 as by-product does not represent a severe issue for industrial processes, as it is typically used as additive for some foods.[34]

The Pearlman's catalyst (*i.e.*, $Pd(OH)_2/C$) was also used for direct C-H arylation of five-membered *N*-heteroarenes. Fagnou *et al.* reported its application in few examples of the coupling between thiazole and aryl iodides or bromides,[23] but high metal loading (10 mol%) were required for obtaining the corresponding 5-arylthiazoles in satisfactory yields (71-82%); moreover, the use of harmful DMA as the solvent and high temperature (140 °C) for long reaction times (typically 24 h) made the protocol unattractive from the point of view of the *Green Chemistry*. A more extensive work was instead reported in 2010 by Jafarpour and co-workers, which described the efficiency of Pearlman's catalyst in regioselective C-2 direct arylation of free NH-pyrroles **22** with aryl iodides.[35] Also in this case, reactions were carried out with 10 mol% of $Pd(OH)_2/C$, in triethanolamine as the solvent, for 24 h at 100 °C, giving the corresponding α-arylated pyrroles **23** in good yields (**Scheme 10**); in addition to the high metal loading adopted by the authors, which suggested a only moderate catalytic activity of $Pd(OH)_2/C$ under these conditions, no studies about its potential recyclability were carried out.



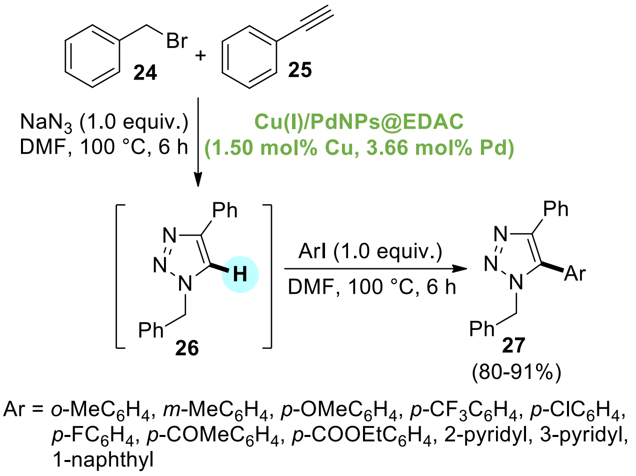
Scheme 10. C2 Regioselective direct C-H arylation of free NH-pyrroles **22** with aryl iodides catalysed by $Pd(OH)_2$/C, developed in 2010 by Jafarpour and co-workers.[35]

Other supported Pd catalysts have only occasionally been used for the direct arylation of this class of *N*-heteroarenes. Hierso *et al.* reported the application of palladium-polypyrrole nanocomposites Pd@PPy for the reaction of pyrroles and imidazoles with bromoarenes, working with a "leaching and re-deposition" mechanism: in other words, the formation of homogeneous palladium species leached into solution occurred during the direct C-H bond arylation process, but at the end of the reaction the polypyrrole support worked as a metal scavenger, thus allowing for their re-deposition.[36] If on one hand this phenomenon was definitely responsible for a severe metal contamination of the coupling products, on the other it also allowed for moderate recycle of Pd@PPy catalyst.

Commercial silica-supported catalyst SiliaCat® DPP-Pd was used in the direct arylation of thiazole with a brominated indoloquinoxaline, as an intermediate step for the synthesis of extended π-conjugated squaraine dyes for optoelectronic applications.[37] This work was only focused on the synthesis and characterization of the π-conjugated dyes, so no studies were carried out in order to evaluate the sustainability of the method in terms of recyclability and/or heterogeneity of SiliaCat® DPP-Pd catalyst.

In 2013, Shaabani and co-worker reported the synthesis of bimetallic copper(I) and palladium nanoparticles supported on ethylenediamine-functionalized cellulose, used as recoverable and reusable catalyst (up to five cycles) for the preparation of 1,4,5-trisubstituted 1,2,3-triazoles through tandem 1,3-dipolar cycloaddition/direct arylation sequence.[38] In particular, reactions were carried out by treatment of benzyl bromide **24** with sodium azide and phenylacetylene **25** in the presence of the Cu(I)/PdNPs@EDAC catalyst (1.50 mol% of Cu, 3.66 mol% of Pd) and Et_3N as base (0.5 equiv.), in DMF at 100 °C; after 2 h, the corresponding 1,4-disubstituted 1,2,3-1*H*-triazole **26** was treated in situ with the aryl halides for further 6 h at 100 °C, affording the final 1,4,5-trisubstituted products **27** in high yields (80-91%) (**Scheme 11**). Cu(I)/PdNPs@EDAC showed a good recyclability, with four consecutive runs with no loss of activity, although its mechanism (homogeneous *vs.* heterogeneous) has not been investigated.

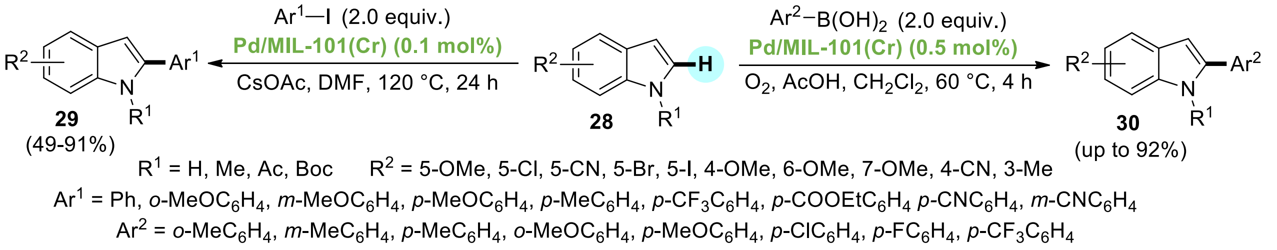
Very recently Li *et al.* described a diimine Pd complex anchored on graphene oxide (named Pd-DI@GO), which acts as an efficient and reusable catalyst for direct C-H arylation of 2,4-dimethylthiazole with a large family of (hetero)aryl bromides, carried out with 0.094 mol% of Pd loading, in the presence of pivalic acid (2.0 equiv.) as additive and in DMA as the solvent, at 120 °C for 12 h, allowing in most cases for high yields (> 85%) of the coupling products.[39]



Scheme 11. Tandem 1,3-dipolar cycloaddition/direct C-H arylation sequence for the synthesis of 1,4,5-trisubstituted 1,2,3-1*H*-triazoles **27** catalysed by Cu(I)/PdNPs@EDAC, developed in 2013 by Shaabani and co-worker.[38]

Moving to bicyclic *N*-heteroarenes, indole is definitely the most investigated substrate in the direct C-H arylation with supported Pd catalysts. The first study was reported in 2006 by Djakovitch *et al.*: two different palladium catalysts, *i.e.*, microporous $[Pd(NH_3)_4]$/NaY and mesoporous Pd/SBA-15, were used in the synthesis of 2-substituted free NH-indoles and their following regioselective C3 arylation with aryl bromides.[40] Although recycling and leaching tests of both Pd catalysts were evaluated only for the step of indole synthesis, results suggested a dissolution-redeposition equilibrium for microporous $[Pd(NH_3)_4]$/NaY and a merely heterogeneous mechanism for mesoporous Pd/SBA-15. Despite its lower performance in process sustainability due to significant metal leaching, $[Pd(NH_3)_4]$/NaY was then used by the same group in direct C3 arylation of 2-substituted free NH-indoles with a larger number of aryl bromides.[41]

Cao *et al.* carried out detailed studies on the application of Palladium supported on metal-organic frameworks as efficient catalysts for the direct C2 arylation of indoles. In 2011, they prepared highly dispersed Pd nanoparticles encapsulated in the mesoporous cages of the metal-organic framework MIL-101(Cr), named Pd/MIL-101(Cr), that exhibited extremely high catalytic activity in the C2 regioselective direct arylation of substituted indoles **28** with aryl iodides, carried out in the presence of CsOAc, in DMF at 120 °C to give the corresponding 2-arylated products **29** in 49-91% yields (**Scheme 12**, path a).[42] More interestingly, the same catalytic system was used in another work for a similar C2 direct arylation of free NH and substituted indoles **28** with aryl boronic acids, performed under mild conditions (acetic acid, CH_2Cl_2, 60 °C, 4 h) and in the presence of O_2 as oxidant, affording 2-arylindoles **30** with yields up to 92% (**Scheme 12**, path b).[43] In both these studies, Pd/MIL-101(Cr) catalyst showed low metal leaching (0.4 ppm and 0.9 ppm in the reactions with aryl iodides and boronic acids, respectively), probably because Pd nanoparticles hardly escape from the mesoporous cages of MIL-101 support, having dimension of 2.9 and 3.4 nm, through microporous windows (with 1.2 and 1.4 nm of diameter). Moreover, Pd/MIL-101(Cr) exhibited good recyclability in the direct arylation reactions of *N*-methylindole: up to five runs with iodobenzene and up to six runs with phenyl boronic acid.



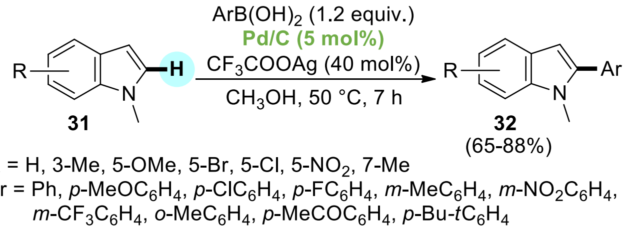
Scheme 12. Application of recoverable Pd/MIL-101(Cr) catalyst to the C2 regioselective direct C-H arylation of substituted indoles **28**: (a) synthesis of 2-arylindoles **29** by reaction with aryl iodides as arylating agents; (b) synthesis of 2-arylindoles **30** by reaction with aryl boronic acids as arylating agents.

Recently, the same group chose the perfluoroalkane-functionalized mesoporous metal-organic framework NU-1000 as a hydrophobic platform to encapsulate ultrafine palladium nanoparticles for direct C-H arylation of indoles with aryl iodides in water: reactions seems to occur in heterogeneous phase, although the authors could not completely exclude the possibility of leached active palladium species redeposited on the support after the coupling reaction.[44]

Although commercial Pd/C catalyst has found several applications in the direct C-H arylation of indoles, it was first examined in some comparative studies with other homogeneous and heterogeneous Pd catalysts. Unfortunately, these works did not investigate its recyclability and heterogeneity: Schmidt *et al.* focused on the different regioselectivity (C2 *vs.* C3) depending on the type of Pd precursor (*i.e.*, soluble *vs.* supported),[45] while Fairlamb *et al.* compared their catalytic activity in the model reaction of *N*-methylindole with diphenyliodonium tetrafluoroborate.[46] It is evident that both protocols were not carried out from the *Green Chemistry* point of view: on one hand, the study of Schmidt *et al.*, involving the use of homogeneous catalytic species, undoubtedly involved a metal contamination of the coupling products; on the other, the investigation of Fairlamb *et al.* was based on the use of an aryliodonium salt as arylating agent, which is far from the typical features required by the atom economy.

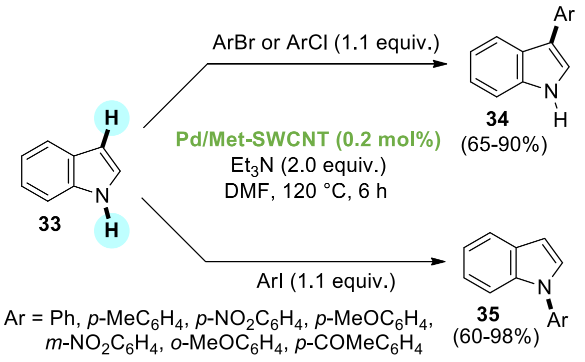
A more consistent investigation was reported only in 2020, when Bora and co-workers described the use of palladium-on-carbon in the C2 regioselective direct C-H arylation of functionalized *N*-methylindoles **31** with various aryl boronic acids: reactions were performed in MeOH at 50 °C for 7 h, using 5 mol% of Pd/C catalyst and 40 mol% of silver trifluoroacetate as oxidant, affording the corresponding 2-aryl *N*-methylindoles **32** in yields ranging between 65 and 88% (**Scheme 13**).[47] Hot filtration test revealed residual Pd level (<0.01 ppm)in the filtrate, suggesting the heterogeneous nature of active catalyst species; moreover, Pd/C catalyst was recycled four times with only a little loss in reactivity, probably due to the physical loss of the catalyst rather than to metal leaching. Despite these invaluable advantages, it is worth to emphasize that the use of boronic acids as arylating agents involved here the production of boron salts as by-products, which could still contaminate the coupling products, although their removal is generally easier with respect to palladium.

Very recently, Pd/C was successfully applied by Vaccaro *et al.* in the C2 direct arylation of free NH indoles with diaryliodonium salts as arylating agents: reactions worked well for 5-substituted indoles (30-93% yields), but it failed with 3-methyl indole.[48] Despite diaryliodonium salts are typically characterized by a low atom economy, such protocol exhibited a great attention to sustainability, corroborated by the use of Polarclean/water as safe and recoverable reaction medium, and by the good recyclability of Pd/C (up to six runs) without lowering the yield and low Pd leaching (≤ 1.0 ppm).



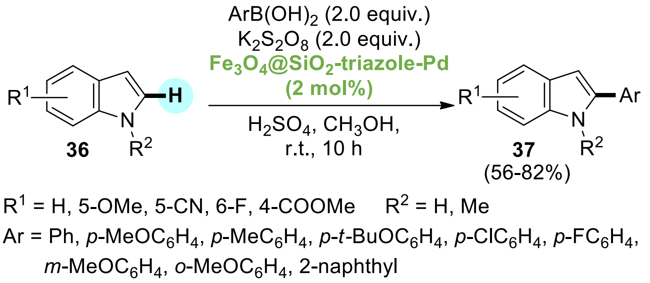
Scheme 13. Pd/C catalysed, C2 regioselective oxidative direct C-H arylation of functionalized *N*-methylindoles **31** with various aryl boronic acids, developed in 2020 by Bora and co-workers.[47]

Veisi and co-workers reported the use of Pd nanoparticles supported on biguanide(metformin)-functionalized single-walled carbon nanotubes (Pd/Met-SWCNT) in the C3 regioselective direct C-H arylation of indole **33** with aryl bromides/chlorides to give β-arylindoles **34**; interestingly, working under the same conditions with aryl iodides, the corresponding C-N coupling occurred to give the *N*-arylated indoles **35** (**Scheme 14**).[49] Reactions were carried out with a low metal loading (0.2 mol%), but at the same time they required DMF as harmful and toxic solvent, and a prolonged thermal heating (120 °C for 6 h), which represented a severe limit to the sustainability of the protocol. Although heterogeneity tests were only performed on a model C-N coupling, ICP-AAS analysis of the filtrate obtained by hot filtration test showed very low Pd leaching (150 ppb).



Scheme 14. Regioselective direct C-H arylation of indole **33** catalysed by Pd/Met-SWCNT, developed in 2015 by Veisi and co-workers:[49] with aryl bromides/chlorides as arylating agents, 3-arylindoles **34** were obtained; with aryl iodides, *N*-arylated indoles **35** were isolated.

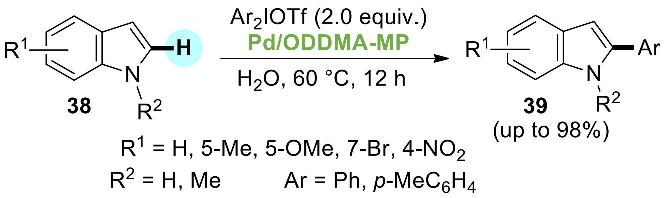
Recoverable palladium catalysts supported on silica-based materials were also applied in the direct C-H arylation of indoles. In 2011, Cai *et al.* reported the preparation of fluorous silica gel-supported palladium nanoparticles (named Pd/FSG) and their application in C2 arylation of *N*-substituted indoles with aryl iodides and bromides.[50] Hot filtration test suggested that reactions may proceed over the catalyst surface in heterogeneous fashion, although they did not exclude the possibility that redeposition of leached active Pd species could occur at the end of reactions (*i.e.*, according to a "leaching and re-deposition" mechanism). A C2 regioselective direct C-H arylation of *N*-methyl and free-NH indoles **36** with aryl boronic acids promoted by triazole-Pd complex anchored on SiO_2-coated magnetic nanoparticles (named Fe_3O_4@SiO_2-triazole-Pd) was described in 2014 by Wang and co-workers: a considerable palladium loading was required (2.0 mol%), but the catalyst showed good sustainability due to its high recyclability (up to 8 runs) and very low leaching (< 0.20 ppm), limiting the possibility of a Pd contamination of the arylated products, although the formation of boron salts as by-products still represented a major issue for the sustainability of the protocol.[51] Reactions were carried out under acid conditions (H_2SO_4, 0.5 equiv.) in the presence of $K_2S_2O_8$ as oxidant, at room temperature in methanol as the solvent, affording the corresponding 2-arylindoles **37** in good yields (**Scheme 15**).



Scheme 15. C2 regioselective oxidative direct C-H arylation of *N*-methyl and free-NH indoles **36** with aryl boronic acids catalysed by Fe_3O_4@SiO_2-triazole-Pd, developed in 2014 by Wang and co-workers.[51]

In the same year, Yamada *et al.* developed a silicon nanowire array-stabilized palladium nanoparticle catalyst (also called SiNA-Pd), which was successfully applied on several Pd-catalyzed reactions, including direct C-H bond arylation of *N*-methyl indoles, performed with a low palladium loading (0.3 mol%); moreover, SiNA-Pd seems to show very high recyclability (10 runs with no loss of activity), although it was only performed on a Mizoroki-Heck coupling as model reaction.[52] In fact, the present study was focused on the synthesis and characterization of the supported material, rather than to the development of a sustainable and green synthetic protocol. Among other Pd catalysts supported on inorganic matrices in the direct C-H arylation of indole, McGlacken *et al.* used PdO-Fe_3O_4: it was easily removable but not recyclable, since it resulted totally deactivated after the first run, due to a substantial changes in both Pd particle distribution and size (observed by TEM microscopy), rather than of a metal leaching into the solution.[24]

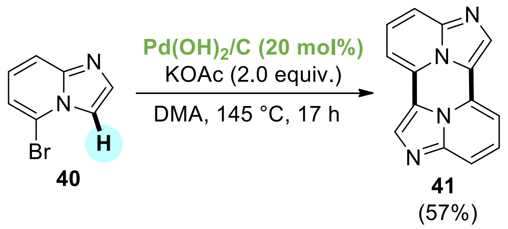
Few examples of direct arylation of indoles catalyzed by recoverable Pd catalysts on organic supports have been also reported. Wan *et al.* described the use of palladium nanoparticles supported on ordered mesoporous hybrid polymer-based materials (called Pd/ODDMA-MP) in a sustainable direct arylation protocol of functionalized *N*-methyl and free-NH indoles **38** with aryliodonium salts: reactions were performed in water as solvent, at 60 °C for 12 h, affording the corresponding 2-arylated indoles **39** almost in all cases with high yields (**Scheme 16**).[53] Pd/ODDMA-MP was recycled eight times without notable activity loss, particle aggregation or structural destruction; moreover, hot filtration and mercapto-functionalized silica poison tests provided evidence of the negligible palladium leaching in the solution.



Scheme 16. C2 regioselective direct C-H bond arylation of *N*-methyl and free-NH indoles **38** with aryliodonium salts using palladium nanoparticles supported on ordered mesoporous hybrid polymer-based materials (Pd/ODDMA-MP).

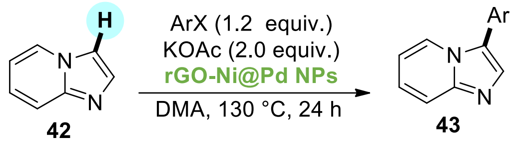
In 2017, Somorjai *et al.* reported the preparation of PolyAMido AMine (PAMAM) dendrimer-stabilized palladium nanoparticles, which were used as excellent catalyst in several synthetic transformations, including preliminary C2 regioselective direct C-H bond arylation of indole with diphenyliodonium tetrafluoroborate.[54] The catalyst was used with 0.75 mol% in water as the solvent at 60 °C, although in our opinion the need of 2.0 equiv. of the iodonium salt (an arylating agent with low atom economy) represents a major drawback for the sustainability of this protocol. Very recently, low cost palladium nanoparticles stabilized by black pepper extract were used by Dateer and co-workers in the direct arylation of indole with aryl iodides, which unfortunately showed low recyclability attributable to severe metal leaching.[55]

Supported Pd species have found successful application as recoverable catalysts also in the direct arylation of other bicyclic *N*-heteroarenes, *i.e.*, imidazopyridines, imidazopyrimidines, adenines and quinolines. In 2013, Lee *et al.* investigated the direct C-H arylation of imidazo[1,2-*a*]pyridine with aryl bromides of different stereo-electronic properties in the presence of bimetallic Pd-Fe_3O_4 heterodimer nanocrystals (1 mol%), affording the corresponding arylated products with complete C3 selectivity: in this case no heterogeneity tests were performed, but Pd-Fe_3O_4 catalyst exhibited high recyclability (10 runs by keeping almost the same product yield).[56] However, the use of very high temperatures (166 °C) for a prolonged time (12 h) could represent a not negligible limitation for the sustainability of this protocol. Gryko and co-workers reported instead the use of Pd(OH)$_2$/C as supported catalyst for the first case of double head-to-tail direct arylation of aromatic compounds: the *bis*-imidazo[1,2-*a*]pyridine **41** was obtained in 57% yield by reaction of 5-bromoimidazo [1,2-a]pyridine **40** (**Scheme 17**);[57] however, since the study was mainly focused on the synthesis and characterization of this material, no studies about recyclability and heterogeneity have been performed.



Scheme 17. Synthesis of *bis*-imidazo[1,2-*a*]pyridine **41** by dimerization of 5-bromoimidazo[1,2-a]pyridine **40** via direct C-H bond arylation reaction promoted by the Pearlman's catalyst Pd(OH)$_2$/C.

More recently, Metin *et al.* described the direct C-H bond arylation of imidazo[1,2-*a*]pyridine **42** with aryl iodides and bromides using Ni@Pd core-shell nanoparticles on reduced graphene oxide (rGO-Ni@Pd) to give the corresponding 3-arylated products **43** in satisfactory yields (77-96%).[58] Reactions were carried out in DMA at 130 °C for 24, in the presence of KOAc as base (**Scheme 18**); however, although the catalyst has been described as reusable and heterogeneous, it actually showed a moderate loss of activity in recyclability tests. Since authors did not perform hot filtration tests and/or metal leaching analysis, we are not able to to establish whether this moderate loss of catalytic activity was really due to a leaching of the metal into the solution, rather than to the aggregation of the metal nanoparticles or to a partial deactivation due to the adsorption of the substrates on the nanoparticles surface.



X = Br, I

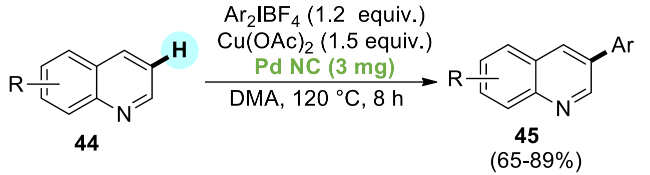
Ar = Ph, *p*-OMeC_6H_4, *p*-MeC_6H_4, *p*-CHOC_6H_4, *p*-COMeC_6H_4, *p*-$NO_2C_6H_4$, *p*-CNC_6H_4, *p*-$CF_3C_6H_4$, 1-naphthyl, 3-pyridyl

Scheme 18. Direct C-H bond arylation of imidazo[1,2-*a*]pyridine **42** with aryl iodides and bromides using rGO-Ni@Pd catalyst, reported in 2018 by Metin *et al.*[58]

A highly sustainable protocol for direct C-H arylation of heteroarenes, including imidazo[1,2-*a*]pyridines and imidazo[1,2-*b*]pyridazines, with *para*-substituted aryl bromides has been developed by Doucet and co-workers in 2018: the use of commercial Pd/C catalyst (at 1 mol% or 10 mol% loading) has been associated to 3-methylbutan-1-ol as a green solvent, affording the corresponding C3 arylated products in excellent yields (90-96%).[33] Fagnou *et al.* reported instead the use of Pearlman's catalyst $Pd(OH)_2$/C in few examples of direct C-H bond arylation of imidazo[1,2-*a*]pyrimidines with aryl bromides, performed with KOAc as base and DMA as a solvent, at 140 °C for 12-24 h.[23]

The same catalyst (*i.e.*, $Pd(OH)_2$/C) was chosen by Alami and co-workers for the of direct C-H arylation of free-(NH_2) adenines. In the first work, aryl iodides were used as arylating agents: in the presence of $Pd(OH)_2$/C (5 mol%), CuI (3.0 equiv.) as co-catalyst, Cs_2CO_3 (2.5 equiv.) as base, NMP as solvent and under microwave irradiation, 8-aryladenines have been obtained in good yields (42-90%) and short reaction times (0.25-1 h).[59] In a following paper, the same authors extended their protocol to aryl chlorides: working under similar conditions but under thermal heating at 160 °C instead of microwave irradiation, the desired 8-aryladenines were synthesized in 54-94% yields.[60] Unfortunately, in both cases no studies on the potential recyclability and heterogeneity of palladium catalyst were performed, casting shadows on the real sustainability of the process.

Finally, in 2020 Yadav *et al.* developed an interesting method for the synthesis of 3-arylquinolines **45** by C3 regioselective direct C-H bond arylation of different quinolines **44** with diaryliodonium salts having electron donating and electron withdrawing groups (1.2 equiv.), in the presence of palladium nanoparticles (named Palladium nanocatalyst, Pd NC) as recoverable catalyst, in DMF at 120 °C for 8 h (**Scheme 19**).[61] The recyclability of Pd NC was shown up to five runs, while hot filtration test revealed a negligible metal leaching (3.389 ppb of Pd by ICP-MS analysis). If the protocol appeared quite sustainable from the point of view of the catalyst, the same is not true for both the reaction medium (due the use of toxic DMF) and the arylating agent (due to the typical low atom economy of aryliodonium salts, affording a large amount of by-products); moreover, the need of 1.5 equiv. of $Cu(OAc)_2$ as oxidant represents definitely a further issue of the procedure, as homogeneous copper species could contaminate the coupling products.

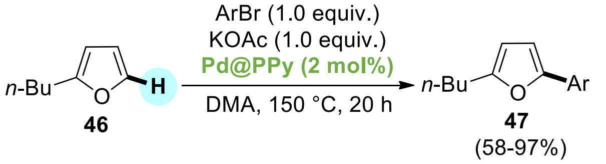


R = H, 6-Me, 8-NO_2

Ar = Ph, *p*-OMeC_6H_4, *p*-ClC_6H_4, *p*-FC_6H_4, *p*-$CF_3C_6H_4$, *p*-CNC_6H_4, *m*-MeC_6H_4

Scheme 19. C3 regioselective direct C-H bond arylation of quinolines **44** with diaryliodonium salts using Palladium nanocatalyst, reported in 2020 Yadav *et al.*[61]

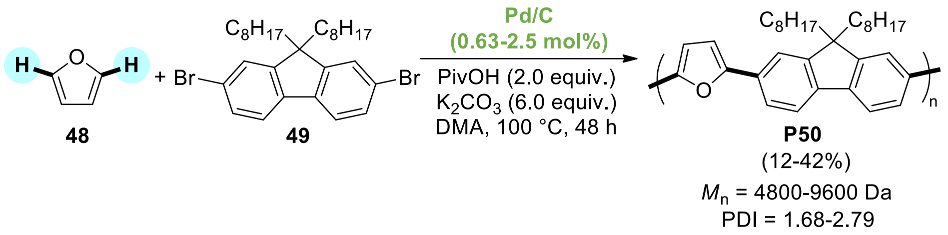
2.1.3. Recoverable palladium catalysts for direct C-H bond arylation of *O*-heteroarenes. The first application of a recoverable Pd catalyst in direct C-H bond arylation of *O*-heteroarenes was reported in 2011 by Hierso *et al.*: palladium-polypyrrole nanocomposites Pd@PPy were successfully applied in the direct arylation reactions of 2-*n*-butylfuran **46** with bromoarenes, affording the α-arylated products **47** in 58-97% yields (**Scheme 20**).[62] Recycling tests and post-catalysis characterization of Pd@PPy in the reaction of 2-*n*-butylfuran with 4-bromobenzonitrile supported the hypothesis of a “leaching and re-deposition” mechanism, which unfortunately does not exclude a potential metal contamination in the coupling products.



Ar = Ph, *p*-CNC_6H_4, *p*-COMeC_6H_4, *m*-MeC_6H_4, 2,4,6-$Me_3C_6H_2$, 3-quinolinyl

Scheme 20. Direct C-H arylation of 2-*n*-butylfuran **46** with bromoarenes using palladium-polypyrrole nanocomposites Pd@PPy, reported in 2011 by Hierso *et al.*[62]

More recently, Koizumi and co-workers used commercial Pd/C as solid-supported catalyst for the direct C-H arylation polycondensation of furan **48** with 2,7-dibromo-9,9-dioctylfluorene **49** under ligand-free conditions: working in DMA at 100°C, in the presence of K_2CO_3 as base and pivalic acid as additive, alternating co-polymers **P50** were obtained in 12-42% yields and molecular weight M_n of 4800-9600 (**Scheme 21**).[63] Although a comparison between homogeneous $Pd(OAc)_2$ and supported Pd/C reactivity has been explored, no studies of recyclability and/or heterogeneity have been taken into account. This represent a very critical point from the point of view of the method sustainability, since the purification procedures of polymers from metal traces are typically more complicated than those of small molecules.

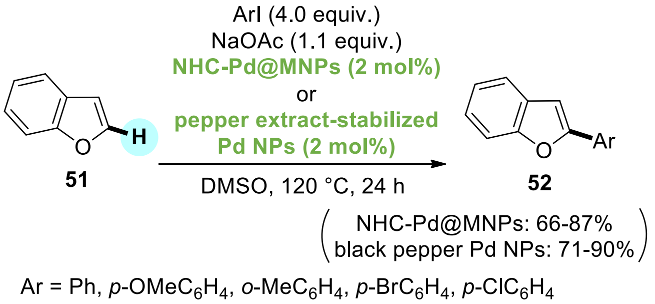


Scheme 21. Application of recoverable Pd/C catalysts to the direct C-H arylation polymerization of furan **48** with 2,7-dibromo-9,9-dioctylfluorene **49** under ligand-free conditions for the synthesis of alternating co-polymers **P50**.

Commercial Pd/C was also applied in few other examples of direct C-H arylation of furans and benzofurans in the framework of more extensive works: Fairlamb *et al.* compared its performance with those of other palladium catalysts (*i.e.*, $Pd_2(dba)_3$, $Pd(OAc)_2$ and PVP-Pd) in the reaction with diphenyliodonium tetrafluoroborate;[46] Doucet *et al.* studied the reaction with selected aryl bromides in different solvents,[33] and very recently also with benzenesulfonyl chlorides as alternative arylating agents.[34] Therefore, commercial Pd/C proved to be a robust and very versatile catalyst, with successful application to arylating agents having different features and chemical reactivity: from the poorly sustainable iodonium salts to the highly environmental benign sulfonyl chlorides.

In 2016, McGlacken and co-workers described a C2 regioselective direct C-H arylation of benzofurans with diaryliodonium salts catalyzed by Pd impregnated on magnetite (PdO-Fe_3O_4), which was found to be an efficient, cheap and easily accessible system.[24] Although reactions required high palladium loading (10 mol%), 2-arylbenzofurans were obtained in good yields (55-84%); unfortunately, PdO-Fe_3O_4 was easily removable (by simply using a magnet) but not recyclable, since it was totally deactivated after the first run. This phenomenon was due to a substantial changes in both Pd particle distribution and size (observed by TEM microscopy), rather than of a metal leaching into the solution. However, a major drawback in the present protocol was the use of diaryliodonium salts as arylating agents, characterized by a low atom economy and thus producing a large amount of co-products, requiring tedious purification procedures.

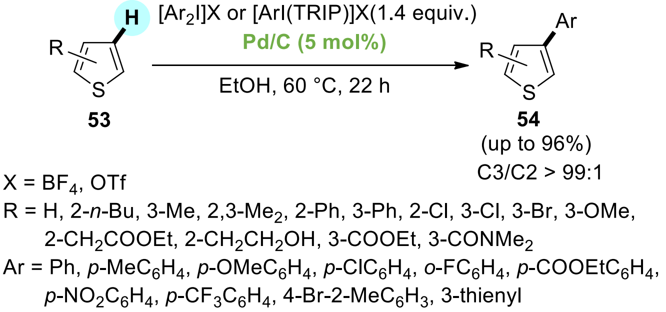
Recently, a comparison between *N*-heterocyclic carbene-palladium magnetic nanoparticles (NHC-Pd@MNPs) and black pepper extract-stabilized palladium nanoparticles in the C2 regioselective direct C-H bond arylation of benzofuran **51** with aryl iodides was reported by Dateer *et al.*[55] In both cases, reactions were carried out with 2 mol% of the palladium catalyst, with 1.1 equiv. of sodium acetate as base, in DMSO at 120 °C for 24 h, affording the corresponding 2-arylbenzofuran **52** in good yields: 66-87% with NHC-Pd@MNPs; 71-90% with black pepper extract-stabilized Pd nanoparticles (**Scheme 22**). On one hand, NHC-Pd@MNPs catalyst could not be recycled due to its high solubility in the reaction medium; on the other, the pepper extract-stabilized Pd nanoparticles are definitely more interesting from the point of view of *Green Chemistry* as based on economically cheap and environmental friendly materials, but actually they showed only modest recyclability attributable to a severe metal leaching. However, a severe issue of both protocols is the need of a large excess (*i.e.*, 4.0 equiv.) of the aryl iodide, thus producing also a significant amount of organic waste.



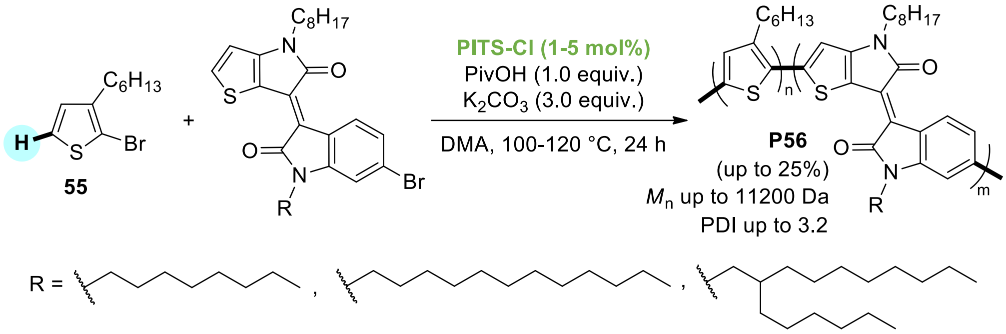
Scheme 22. Direct C-H bond arylation of benzofuran **51** with aryl iodides promoted by NHC-Pd@MNPs and black pepper extract-stabilized palladium nanoparticles.

2.1.4. Recoverable palladium catalysts for direct C-H bond arylation of *S*-heteroarenes. Among *S*-heteroarenes, thiophene ring is definitely one of the most investigated substrates in direct C-H arylation with supported palladium catalysts, not only for the synthesis of π-conjugated small molecules, but also to obtain polythiophenes and thiophene-based co-polymers.

Pd/C catalyst has been widely used for this purpose. The first work was reported by Glorius *et al.* in 2014: a wide range of monofunctionalized thiophenes **53** were treated in EtOH at 60 °C with diaryliodonium salts (1.4 equiv.) as arylating agent and Pd/C(5 mol%) as catalyst, affording β-arylthiophenes **54** through C3 regioselective direct arylation reaction (**Scheme 23**).[64] Interestingly, authors performed several studies (three-phase test, hot filtration test, Hg-poisoning test) in order to identify the active species: although Pd/C is often reported to act as a reservoir for Pd species in solution, all the experiments suggested a heterogeneous mechanism, showing a marked sustainability of the protocol. The same protocol was used by Fairlamb *et al.* in the model reaction of 2-*n*-butylthiophene with diphenyliodonium tetrafluoroborate, in order to compare its performance with those of $Pd_2(dba)_3$ and $Pd(OAc)_2$.[46]



Scheme 23. C3 regioselective direct C-H bond arylation of functionalized thiophenes **53** with aryliodonium salts catalysed by Pd/C, developed by Glorius *et al.* in 2014.[64]



Scheme 24. Palladium immobilized on thiol-modified silica gel chloride counter anion (PITS-Cl) as efficient and recoverable catalyst for the direct C-H bond arylation polymerization of 2-bromo-3-hexylthiophene **55** with unsymmetrical monothienoisoindigo units.

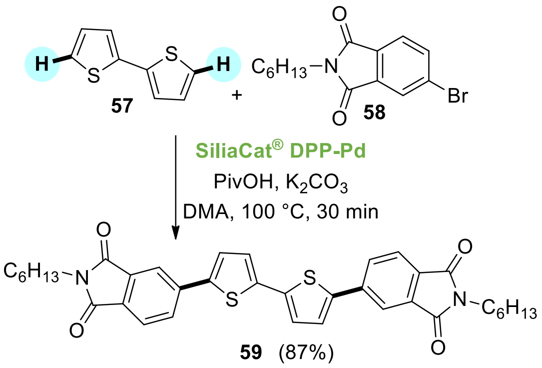
Doucet *et al.* reported the reaction of 2-functionalized thiophenes with aryl bromides, which were carried out in DMA at 150 °C using 1 mol% of Pd/C and KOAc (2 equiv.) as the base: in this case, C2 regioselective arylation occurred, giving the corresponding α-arylthiophene as the only product.[33] Some representative reactions were also repeated in green solvents (*e.g.*, alcohols, diethylcarbonate, cyclopentyl methyl ether) in order to improve the process sustainability, but recyclability and/or heterogeneity of the catalytic system were not investigated. In 2020 the same research group used Pd/C catalyst in the reaction of 2-methylthiophene with benzenesulfonyl chlorides as non-conventional arylating agents: interestingly, in this case a C3 selective direct arylation was observed, with the formation of β-arylthiophenes in modest to good yields (21-79%).[34] As already mentioned above, the use of benzenesulfonyl chlorides as arylating agents showed many advantages in the context of the *Green Chemistry*, in particular broad availability and easy handling; moreover, the generation of SO_2 as by-product does not represent an issue, as it is typically used as additive for some foods.

Koizumi and co-workers showed the use of Pd/C for the synthesis of thiophene-based polymers via direct C-H arylation reactions. In 2015, they reported the homo-polymerization of 2-bromo-3-hexylthiophene using Pd/C (2.5 mol%), in the presence of K_2CO_3 (3.0 equiv.) and pivalic acid (1.0 equiv.), at 100 °C in DMA or NMP as the solvent: the resulting poly(3-hexylthiophene)s were obtained in good yields (34-91%), good head-to-tail regioregularity (94-97%) and high molecular weights (M_n = 5000-16300).[65] In the same work preliminary direct C-H arylation co-polymerization of thiophene with 2,7-dibromo-9,9-dioctylfluorene was also described, but a more detailed investigation was performed in a following paper: yields up to 72% and molecular weights M_n up to 8600 were obtained.[63] The same authors also reported the direct C-H arylation polymerization of 2-bromo-3-hexylthiophene catalyzed by the Pearlman's catalyst ($Pd(OH)_2/C$): the resulting polymers showed properties similar to those obtained with Pd/C, but polymerization was faster (*i.e.*, 8-18 h for $Pd(OH)_2/C$ *vs.* 48 h for Pd/C).[65] Although these studies emphasized the benefits of using a supported catalyst, authors did not investigate its reusability and heterogeneity, which leaves open the question of the real sustainability of these protocols. Moreover, such direct C-H bond arylation polymerizations were typically carried out in DMA as reaction medium and at high temperatures for long reaction times, i.e., experimental conditions which hardly fit with the Twelve Principles of the *Green Chemistry*.

Palladium species deposited on other inorganic matrices were synthesized and tested as catalysts in different reactions, including a few representative examples of direct arylation of thiophenes. Xi and Jia's groups developed a Pd(II) salt on the surface of functional reduced graphene oxide (named Pd(II)-FRGO), which was applied to the direct α-arylation of 2-ethylthiophene with aryl bromides bearing different stereo-electronic properties, carried out in DMF at 140 °C and in the presence of cesium acetate as the base, affording 2-arylthiophenes in 67-85% yields.[66] Yamada and co-workers reported the α-arylation of 2-methyl- and 2-ethylthiophene with iodobenzene catalyzed by SiNA-Pd, *i.e.*, silicon nanowire array-stabilized palladium nanoparticle catalyst; reactions were carried out with a low palladium loading (0.3 mol%); SiNA-Pd showed here a very high recyclability (10 runs with no loss of activity), although it was only performed on a Mizoroki-Heck coupling as model reaction.[52] In fact, the study was mainly focused on the synthesis and characterization of the material, rather than to the development of a sustainable and green synthetic protocol.

McGlacken *et al.* described few examples of regioselective β-arylation of thiophenes promoted by Palladium impregnated on magnetite (PdO-Fe_3O_4).[24] It was found to be an easily removable catalyst, *i.e.* by simply using a magnet, but not recyclable, with a complete deactivation was observed after the first cycle , due to a substantial changes in both Pd particle distribution and size observed by TEM analysis. Hayashi and co-workers used PITS-Cl, that is, Pd immobilized on thiol-modified silica gel chloride counter anion for the polymerization via direct arylation of 2-bromo-3-hexylthiophene **55** with monothienoisoindigo units, to synthesize the donor-acceptor regioregular random copolymers **P56** (**Scheme 24**).[67] As with most direct C-H bond arylation polymerization investigations, here authors were primarily interested in the synthesis and characterization of the material, rather than in a real and concrete interest in the development of a green and sustainable polymerization protocol.

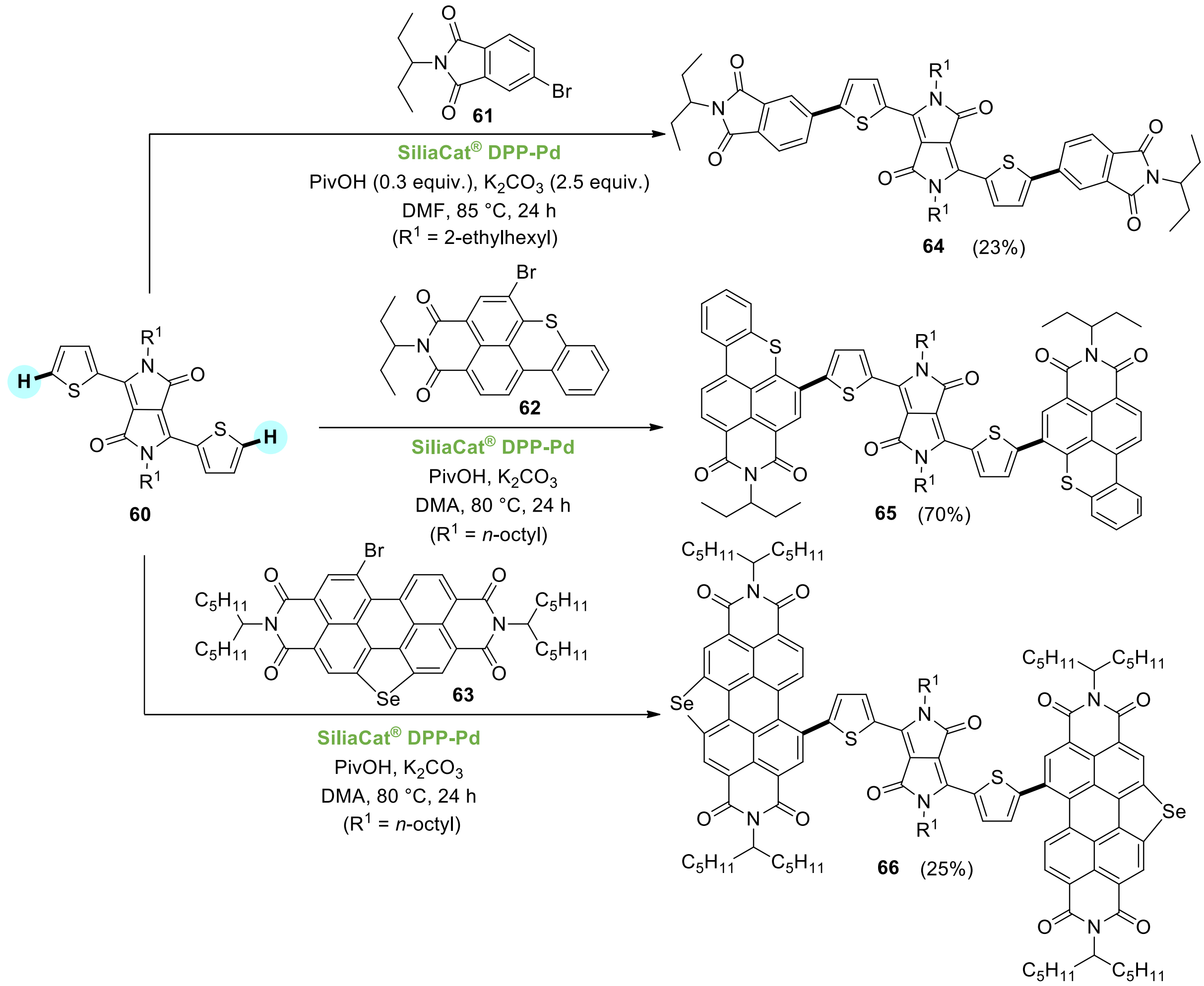
However, one of the most important supported palladium catalyst used in the last few years for the direct C-H arylation of thiophene systems is commercial SiliaCat® DPP-Pd, *i.e.*, a diphenylphosphine palladium(II) complex covalently anchored to silica through a linear alkyl spacer. It was applied for the first time in 2015 by the Welch's research group for the synthesis of a thiophene-phthalimide molecular semiconductor **59**: bithiophene **57** was treated with 4-bromo-*N*-hexylphthalimide **58** at 100 °C under microwave irradiation, using K_2CO_3 as the base, pivalic acid as additive and DMF as the solvent (**Scheme 25**).[68] Interestingly, **59** was obtained after 30 min in 87% yield, significantly higher than that observed using homogeneous $Pd(OAc)_2$ under the same conditions (67%).



Scheme 25. Synthesis of thiophene-phthalimide molecular semiconductor **59** via direct C-H bond arylation catalysed by commercial SiliaCat® DPP-Pd catalyst, reported in 2015 by Welch and co-workers.[68]

The authors successfully used the same catalytic system for the preparation of diketopyrrolo[3,4-c]pyrrole[69] (DPP)-based small molecules **64-66** for organic electronics, by direct C-H arylation of the thiophene rings of *bis*-thienylDPP derivatives **60** with brominated phthalimides **61**,[70] benzothioxanthenes **62**[71] and perylene diimides **63** (**Scheme 26**).[72] More recently, SiliaCat® DPP-Pd was also used by Welch *et al.* in the direct C-H arylation polymerization of a *bis*-thienylDPP derivative with 2,7-dibromo-9,9'-spirobifluorene, affording the corresponding co-polymer in good yield (88%) and molecular weight (M_n = 10900),[73] as well as in the synthesis of a borane-containing non-fullerene acceptor by direct arylation of the thiophene rings of a bisthienylborane with a brominated perylene diimide derivative.[74] It is worth emphasizing that also in this case the works focused on the synthesis of π-conjugated materials, rather than on the development of a general direct arylation protocol: therefore, a complete evaluation of the recyclability and heterogeneity of SiliaCat® DPP-Pd in these reaction is missing, although authors have repeatedly highlighted all the advantages of its use compared to other homogeneous Pd catalysts.

Palladium catalysts supported on organic matrices were hardly used in direct C-H bond arylation of thiophenes. In 2011 Hierso *et al.* described the application of palladium-polypyrrole nanocomposites (Pd@PPy), in representative reactions of 2-*n*-butylthiophene with bromoarenes.[62] The catalyst worked through a "leaching and re-deposition" mechanism: the formation of homogeneous palladium species leached into solution occurred during the direct C-H bond arylation process, but at the end of the reaction the polypyrrole support worked as a metal scavenger, thus allowing for their re-deposition.



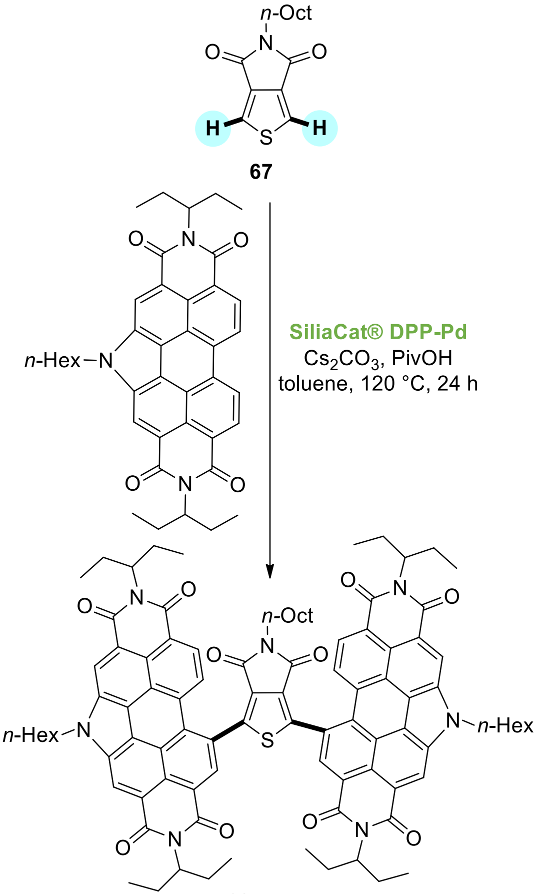
Scheme 26. Synthesis of several DPP-based small molecules **64-66** for organic electronics by direct C-H arylation of the thiophene rings of *bis*-thienylDPP derivatives **60** with brominated phthalimides **61**, benzothioxanthenes **62** and perylene diimides **63** catalysed by commercial SiliaCat® DPP-Pd catalyst.

Recently, Patil and co-workers reported the preparation of palladium nanoparticles dispersed in cellulose, isolated from agriculture residue (sugarcane bagasse), as dip catalyst for the α-arylation of 2-substituted thiophenes with aryl iodides and bromides as arylating agents.[75] The catalytic system showed a moderate recyclability (3 runs without loss of activity), although Pd content of the dip catalyst was found to be 3.86% w/w after the 3rd cycle, with respect to the starting 4.12% w/w loading. However, the use of cellulose from agriculture waste as a catalyst support is definitely very attractive from the point of view of the global sustainability of the process.

Few examples of recoverable palladium catalysts have been reported also for the direct C-H arylation of bicyclic *S*-heteroarenes, including 3,4-ethylenedioxythiophene (EDOT), thieno[3,4-*c*]pyrrole-4,6-dione and benzothiophene. Hayashi *et al.* studied in detail the EDOT scaffold: in 2016, they designed a Pd catalyst immobilized on thiol-modified silica gel (named PITS), which was successfully applied in the direct arylation of EDOT with bromo- and dibromo-(hetero)arenes for the synthesis of small molecules and polymers;[76] in 2017, they focused on commercial Pd/C for the preparation of alternating co-polymers by direct arylation polycondensation of EDOT with various dibromoarenes.[77] Very recently, Vellayan *et al.* instead proposed the use of a Pd catalyst supported on montmorillonite clay, which was found to be effective for the synthesis of EDOT-based small molecules by direct arylation of EDOT with aryl bromides.[78] Interestingly, this catalytic system (named MPd500 by the authors) worked through a substantially heterogeneous mechanism, as confirmed by hot filtration (no Pd leaching was found) and recyclability tests (3 cycles without loss of yields). In our opinion, such system seems quite convenient from the point of view of the *Green Chemistry*, but the synthetic protocol still needs of further investigations, since it was carried out on a quite limited family of aryl bromides.

Concerning thieno[3,4-*c*]pyrrole-4,6-dione (TPD), the only example was reported in 2018 by Welch and co-workers: symmetric perylene diimide-TPD-perylene diimide **68** non-fullerene acceptors for organic solar cells were synthesized by direct C-H arylation of TPD derivatives **67**.[79] In particular, if the reaction of *N*-(2-ethylhexyl)-TPD worked only by using homogeneous Herrmann-Beller Pd catalyst, with *N*-*n*-octyl-TPD they successfully used SiliaCat® DPP-Pd supported catalyst, which allowed for easy metal separation from the reaction media and its possible reuse, although no recycling tests were performed there. (**Scheme 27**).

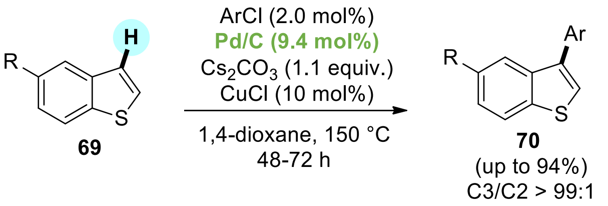
Glorius *et al.* reported in 2013 the first application of a heterogeneous palladium catalyst, *i.e.*, commercial Pd/C, on direct C-H bond arylation of benzo[*b*]thiophenes **69**: working with aryl chlorides as arylating agents, in the presence of 9.4 mol% of Pd/C and 10 mol% of CuCl as a dual catalytic system, Cs_2CO_3 as the base, at 150 °C in 1,4-dioxane as the solvent, a completely regioselective C3-arylation was observed, with the formation of 3-arylbenzo[*b*]thiophenes **70**, in most cases in good yields (**Scheme 28**).[80] If the protocol scalability was demonstrated by repeating representative reactions on a 3 mmol scale, unfortunately efficient recycling of Pd/C was not established. A similar β-regioselectivity was also observed by McGlacken *et al.*, using PdO-Fe_3O_4 as an easily removable catalyst in direct C-H bond arylation of benzothiophenes with diaryliodonium salts.[24] However, compared to the study of Glorius *et al.*, this method for C3 regioselective arylation of benzo[b]thiophene is in our opinion less convenient in the frame of the *Green Chemistry*, due to the low atom economy of the diaryliodonium salts, as well as to the complete deactivation of PdO-Fe_3O_4 after its first use, making no possible its recycling.



68 (46%)

Scheme 27. Symmetric perylene diimide-TPD-perylene diimide **68** non-fullerene acceptor for organic solar cells synthesized by direct C-H bond arylation of TPD derivative **67**.

C2 arylation of benzo[*b*]thiophenes with aryl iodides was described by Dateer *et al.*: they compared the performance of black pepper extract-stabilized palladium nanoparticles, showing a modest recyclability due to a severe metal leaching, and *N*-heterocyclic carbene-Pd magnetic nanoparticles (NHC-Pd@MNPs), which could not be recycled due to their high solubility in the reaction medium.[55] However, the pepper extract-stabilized Pd nanoparticles can be considered more interesting from the point of view of *Green Chemistry*, since they were based on economically cheap and environmental friendly materials.



R = H, Ph, OMe
Ar = Ph, *p*-MeC_6H_4, *m*-MeC_6H_4, *o*-MeC_6H_4, 2,6-$Me_2C_6H_3$, *p*-$COOMeC_6H_4$, *p*-$MeOC_6H_4$, *m*-$MeOC_6H_4$, *m*-$NO_2C_6H_4$, *m*-FC_6H_4, *m*-$CF_3C_6H_4$, 1-naphthyl

Scheme 28. First application of a heterogeneous palladium catalyst, *i.e.*, commercial Pd/C, on direct C-H arylation of benzo[b]thiophenes **69**: efficient protocol for the synthesis of 3-arylbenzo[*b*]thiophenes **70** developed by Glorius *et al.* in 2013.[80]

In 2020, Doucet and co-workers reported a C3 regioselective direct C-H bond arylation of benzo[*b*]thiophenes with benzenesulfonyl chlorides as arylating agents.[34] As already mentioned above, benzenesulfonyl chlorides are definitely interesting starting substrates for direct C-H bond arylation of heteroarenes, due to their broad availability and easy handling; however, in the present protocol their attempts of catalyst recycling failed, with a significant decrease in the product yield after the second run.

Finally, for completeness we also need to mention very briefly the use of commercial SiliaCat® DPP-Pd by Welch *et al.* as supported catalyst in the direct C-H bond arylation reactions of other more complex *S*-heteroarenes: indacenodithienothiophene,[81-82] dithienophosphole,[83] and cyclooctatetrathiophene[84] derivatives. It is worth pointing out that, despite the use of supported SiliaCat® DPP-Pd catalyst, all these works were actually performed under experimental conditions far from sustainability, with the use of toxic and harmful solvents (DMA or DMF) and a prolonged thermal heating; in fact, the studies were only focused on the development of π-conjugated materials for optoelectronic applications. In this context, it is clear that the potential heterogeneity and recyclability of the SiliaCat® DPP-Pd catalyst were not specifically investigated here.

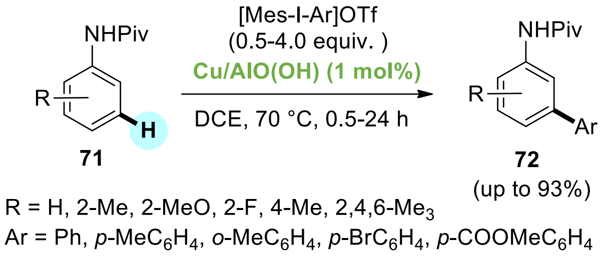
2.2. Other recoverable catalysts for direct C-H bond arylation of (hetero)arenes

If palladium-based species represent the first choice as supported and recoverable catalysts for direct C-H arylation of (hetero)arenes, the use of other metal catalysts is not unusual: they generally operate through different mechanistic pathways, often resulting in alternative regioselectivity of the coupling products. Supported copper species are definitely the most common, due to their lower cost and good compatibility with environmentally friendly conditions, but few examples of iron, nickel, ruthenium, zirconium, aluminium, cerium and titanium-based recoverable catalytic systems have been also reported.

It is worth emphasizing that in this case, besides the classic metal species deposited on inorganic or organic matrices, a further possibility is the use of metal oxides or metal-organic frameworks (MOFs) acting themselves as catalysts, which have lower chances of metal leaching and therefore they could be considered as purely heterogeneous catalysts.

Finally, there are also very few examples of direct C-H arylation of (hetero)arenes promoted by recoverable non-metal catalysts, such as graphitic carbon nitride, fullerene or black phosphorus, most of them working by photocatalytic processes.

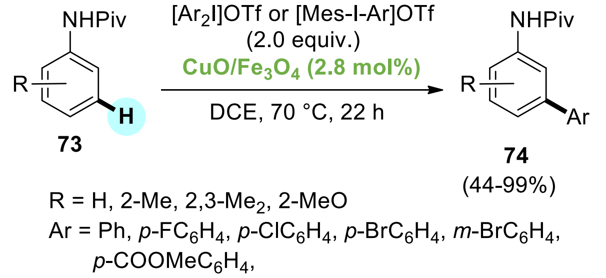
2.2.1. Recoverable copper catalysts for direct C-H bond arylation of (hetero)arenes. Interestingly, supported copper catalysts have found appealing application in direct *meta*-arylation of substituted benzene cores, a synthetic process which is far from trivial. In 2011, Park and Lee reported the first report of a direct *meta*-arylation of anilides **71** with diaryliodonium salts catalyzed by a recoverable copper catalyst, that is, Cu/AlO(OH): working with 0.5-4.0 equiv. of diaryliodonium salt, 1 mol% of copper loading, at 70 °C in dichloroethane, the corresponding *meta*-arylated products **72** were obtained in most cases with yields higher than 60% (**Scheme 29**).[85] A recycling test of Cu/AlO(OH) showed good reusability for 3 runs, after that a slow decrease in product yield was observed. The authors did not investigate the cause of this drawback (probably attributable to metal leaching or issues in the catalyst recovery), but they rather emphasized that the reaction mechanism was different from that of homogeneous copper species.



Scheme 29. Direct C-H bond *meta*-arylation of anilides **71** with diaryliodonium salts catalyzed by recoverable copper catalyst Cu/AlO(OH) developed in 2011 by Park and Lee.[85]

More recently, other supported copper catalysts were tested for similar direct *meta*-arylation reactions. In 2016, Hong *et al.* described the use of inside Cu-exchanged zeolites (with mid- or large-pore framework, *i.e.*, β-type, Y-type and mordenite) in the direct C-H arylation of pivanilides with diphenyliodonium salts: a combination of computational studies, showing well-fitted copper-aryl complexes inside zeolite frameworks, and experimental analyses, testifying no leaching of catalytically active Cu species during reactions, proved their behaviour as heterogeneous catalysts.[86] In a following paper, authors extended the use of Cu(II)/β-type zeolite system to a wider family of substrates, improving the previous protocol with the assistance of microwave irradiation (see section 4.2.1).[87]

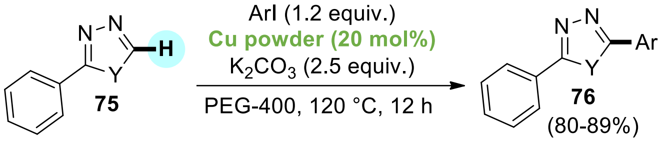
Glorius *et al.* proposed copper oxide on magnetite (CuO/Fe_3O_4) as easily removable catalyst, by simply using a magnet, for the direct *meta*-arylation of anilide derivatives **73**: very interestingly, if the Pd/Fe_3O_4 used in the same work for *ortho*-arylation showed a low recyclability after the second cycle (see section 2.1.1), CuO/Fe_3O_4-promoted *meta*-arylation reactions proceeded successfully to give the corresponding meta-arylated products **74** in five consecutive cycles without loss of activity, although a lower degree of leaching was still observed (**Scheme 30**).[19]



Scheme 30. Direct C-H *meta*-arylation of anilide derivatives **73** promoted by CuO/Fe_3O_4 catalyst, reported in 2017 by Glorius *et al.*[19]

All the above mentioned copper-catalyzed *meta*-regioselective direct C-H bond arylation reactions of benzene cores represent definitely very appealing synthetic strategies in Organic Chemistry, but there are still some severe issues which limit their concrete interest In the field of the *Green Chemistry*: the use of diaryliodonium salts as arylating agents with low atom economy and of dichloroethane (DCE) as a toxic reaction medium, that in our opinion need to be addressed in order to improve such protocols towards a better sustainability.

Moving to *N*-heteroarenes, Vidavalur *et al.* described the use of copper powder as heterogeneous catalyst for the direct C-H arylation of 3,4-diaryl-1,2,4-triazoles and 2-aryl-1,3,4-oxadiazoles **75** with aryl iodides in PEG-400 as sustainable reaction medium: the corresponding products **76** were obtained in high yields (80-89%), but no tests of reusability and/or hot filtration were performed (**Scheme 31**).[88] The procedure is experimentally simple and free from addition of external chelating ligands or co-catalysts, but no studies of Cu leaching into the solution at the end of the reaction, in order to rule out the occurrence of a possible solubilization of copper species during the direct C-H arylation reaction, were performed.

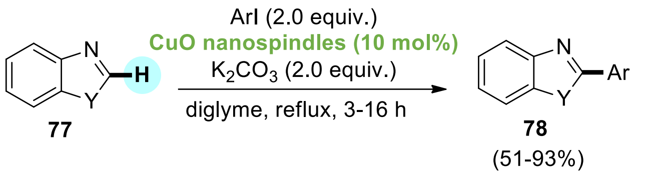


Y = N-Ph, N-(p-ClC_6H_4), N-(m-ClC_6H_4), N-(p-MeC_6H_4), O
Ar = Ph, p-MeC_6H_4, p-$MeOC_6H_4$, o-$MeOC_6H_4$, p-BrC_6H_4, p-$NO_2C_6H_4$, m-ClC_6H_4, 3,4,5-$(MeO)_3C_6H_2$

Scheme 31. Direct C-H arylation of 3,4-diaryl-1,2,4-triazoles and 2-aryl-1,3,4-oxadiazoles **75** with aryl iodides catalysed by copper powder, reported in 2015 by Vidavalur *et al.*[88]

In 2016, Wang and co-workers used a three-dimensional porous $Cu_{2-x}S$-MoS_2 framework as recoverable and efficient photocatalyst for the C2 regioselective direct C-H bond arylation of pyridine with aryldiazonium salts as arylating agents, performed for 1 h at room temperature under irradiation with a Xenon lamp (see also section 4.1.1).[89] However, it is worth to emphasize that the use of aryldiazonium salts as arylating agents in direct C-H arylation reactions is highly desirable in the context of the *Green Chemistry*, in particular in terms of waste prevention, since they generate N_2 as by-product, which moves away from the reaction mixture as a gas.

Direct C-H bond arylation reactions promoted by supported Cu species are more common on benzo-fused *N*-heterocycles. Wang *et al.* focused their attention on copper oxide as efficient catalyst for direct C-H bond arylation of benzimidazoles, benzoxazoles and benzothiazoles. In a first study, they reported the use of CuO nanospindles: working in diglyme as reaction medium and K_2CO_3 as a more environmentally friendly base, the direct arylation of benzo-fused azoles **77** with iodoarenes afforded the corresponding 2-arylated products **78** in good yields (51-93%) after 3-16 h (**Scheme 32**).[90] The recyclability of CuO nanospindles was also tested in the reaction of benzoxazole with iodobenzene, showing no significant decrease in the catalytic activity after 3 runs; moreover, XRD and SEM of CuO nanospindles after reaction demonstrated that the catalysts did not change during the coupling process. In a following paper, they also studied the application of CuO nanoparticles (having average size of 6.5 nm) in the direct C-H arylation of the same azoles **77** with bromo(hetero)arenes, under similar conditions although in the presence of PPh_3 as ligand. Recyclability (3 runs without loss of catalytic activity) and hot filtration tests (< 1 ppm Cu leaching) proved that they worked through a merely heterogeneous mechanism.[91] The good performance of CuO nanospindles, in combination with the quite mild and sustainable experimental conditions required, makes in our opinion these protocols highly appealing for scientists working in the field of the *Green Chemistry*, and their extension to other classes of heteroarenes would be highly desirable



Y = O, S, NMe
Ar = Ph, p-MeC_6H_4, p-$MeOC_6H_4$, o-$MeOC_6H_4$, p-$COOEtC_6H_4$, p-ClC_6H_4, p-CNC_6H_4

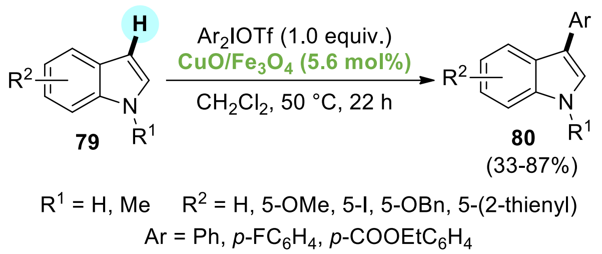
Scheme 32. CuO nanospindles-catalyzed C2-regioselective direct C-H bond arylation of azoles **77** with aryl iodides reported by Wang *et al.*[90]

In the same year, Nageswar *et al.* reported instead the use of copper ferrite nanoparticles (named $CuFe_2O_4$ NPs) as magnetically separable catalyst for the direct arylation of benzothiazole with aryl iodides under sustainable conditions (K_3PO_4, PPh_3, DMSO, 10 h, 110 °C).[92] The Cu catalyst was perfectly recyclable for 4 runs: TEM and SEM studies showed that $CuFe_2O_4$ nanoparticles were intact in size and shape, as well as in morphology, after the 4th cycle.

Phan and co-workers studied two Cu-based crystalline porous metal-organic framework, $Cu_2(BPDC)_2(BPY)$[93] and $Cu_2(OBA)_2(BPY)$,[94] in the direct C-H arylation of benzoxazoles with aryl halides: they exhibited significantly higher activity than that of common copper salts, as well as good reusability; moreover, leaching tests indicated no contribution from homogeneous catalysis of active species leaching into reaction solution, thus avoiding the tedious metal contamination of the final coupling products. In 2015, Wu *et al.* developed a redox-active Cu-based metal-organic framework working through single-crystal-to-single-crystal (SCSC) structural transformations, which produced a redox switchable catalyst for selective direct C-H bond arylation reactions of benzimidazoles, benzoxazoles and benzothiazoles with (hetero)aryl iodides and bromides.[95] It is worth to emphasize that the reactions (carried out in the presence of 2.5 mol% of Cu catalyst, 2.0 equiv. of K_2CO_3, in DMF at 140 °C for 10 h) were only tested on a quite limited family of iodides and bromides: more than the development of a sustainable synthetic protocol on a wide range of substrates, the authors presented this work as a proof-of-concept.

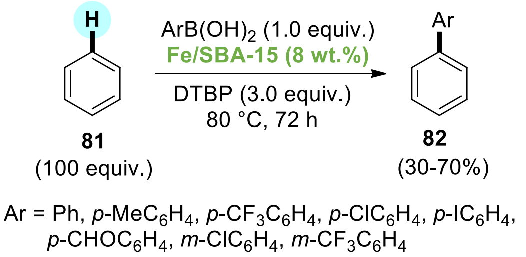
More recently, Glorius *et al.* have reported the use of copper oxide impregnated on magnetite (CuO/Fe_3O_4) as reusable catalyst for the direct arylation of electron-rich heteroarenes, including free NH and substituted indoles **79** with diaryliodonium salts: reactions generally occurred with C3 selectivity affording β-aryl indoles **80** in good yields, although the formation of α-arylated products was also observed in the presence of 3-substituted indoles (**Scheme 33**).[96] An extended mechanistic study was carried out, including kinetic measurements, mass spectrometry analysis, heterogeneity tests, poisoning experiments and also several catalyst characterizations, in order to elucidate the active catalytic species: indicating the generation of soluble copper nanoparticles leached from the amorphous heterogeneous precursor, acting as catalytic species in solution.

In the context of *O*- and *S*-heteroarenes, few examples of supported Cu catalysts have been reported to date: the above mentioned three-dimensional porous $Cu_{2-x}S$-MoS_2 framework of Wang *et al.*[89] and the CuO/Fe_3O_4 developed by the Glorius' research group,[96] have been also applied in the reaction of furans and thiophenes.



Scheme 33. Direct arylation of free NH and substituted indoles **79** with diaryliodonium salts catalysed by CuO/Fe_3O_4, reported in 2016 by Glorius *et al.*[96]

2.2.2. Other recoverable metal catalysts for direct C-H bond arylation of (hetero)arenes. Iron grafted over mesoporous silica (*i.e.*, Fe/SBA-15) was used by Satishkumar *et al.* as an efficient supported catalyst for the oxidative direct C-H arylation of benzene **81** with aryl boronic acids as arylating agents, performed in the presence of di-*tert*-butyl peroxide (DTBP) as the oxidant, affording the corresponding biaryl products **82** in good yields (**Scheme 34**).[97] One of the most fascinating point of this protocol is that aryl halides did not react under these conditions: by using chloro-, bromo- and iodo-functionalized aryl boronic acids, the direct C-H arylation of benzene occurred selectively on the carbon atom bound to the boronic group. The recyclability of Fe/SBA-15 was tested in the reaction of benzene with 4-bromophenylboronic acid: the iron catalyst was used five times without loss of activity, with a slight decrease of Fe loading from 8 wt.% to 7.8 wt.% (ICP-OES analysis). Such procedure is not without criticisms: the formation of boron salts as by-product of the oxidative direct arylation coupling, and above all the need of a large excess (100 equivalents) of benzene (used as both solvent and reagent) represent strong limitations to the real sustainability of this synthetic method.



Scheme 34. Direct C-H bond arylation of benzene **81** with aryl boronic acids as arylating agents catalysed by Fe/SBA-15, reported in 2017 by Satishkumar *et al.*[97]

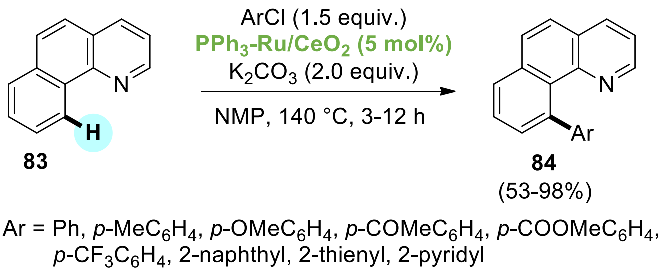
Phan *et al.* reported the use of an Fe-based metal organic framework (named $Fe_3O(BDC)_3$) for the C2 regioselective direct C-H bond arylation of benzothiazoles with benzaldehydes as arylating agents, carried out in *N*-methyl-2-pyrrolidone as a solvent and DTBP as oxidant.[98] One of the most intriguing aspect of this catalyst is its recyclability: it was used for 9 runs without loss of activity; moreover, hot filtration test excluded the presence of homogeneous iron species able to catalyse the direct C-H bond arylation reaction. Interestingly, the $Fe_3O(BDC)_3$ system is one of the most efficiently recyclable supported catalysts reported to date in the field of direct C-H bond arylation of (hetero)arenes.

Sun and co-workers reported in 2012 a bimetallic iron-nickel nanoalloy as catalyst for the direct arylation of benzene with iodoarenes: working with an excess of benzene (acting as both reagent and solvent) in the presence of *N*,*N'*-dimethylethane-1,2-diamine (DMEDA) and potassium *tert*-butoxide as base, the corresponding biaryl products were obtained in good yields (in most cases, ≥ 90%).[99] The sustainability of Fe-Ni alloy catalyst is related to its recoverability (by simply using a magnet) and its good recyclability (up to 8 runs with no loss of catalytic activity), although the large excess of benzene is a major drawback of the procedure.

Truong *et al.* developed nickel-base metal organic frameworks, *i.e.*, $Ni_2(BDC)_2(DABCO)$[100] and Ni-MOF-74.[101] The first one was used in the oxidative direct arylation of benzoxazoles with aryl boronic acids; unfortunately, hot filtration test demonstrated that the reaction still proceeded to higher conversion after removing $Ni_2(BDC)_2(DABCO)$ from the reaction mixture, thus demonstrating a contribution from leached active Ni species to the catalysis process. The second catalyst was used in the direct arylation of thiazoles with aryl iodides; in this case, the hot filtration test performed on a representative reaction indicated that homogeneous catalysis via leached active nickel species in solution is unlikely.

A few other examples of direct C-H arylation catalysed by metal organic frameworks based on other metals have also been reported. On the one hand, the aluminium-based MOF-253, *i.e.*, Al(OH)(bpydc), used in the reaction of benzene with (hetero)aryl iodides/bromides, which showed a good reusability, although no studies of metal leaching were performed, in order to clarify the reaction mechanism (homogeneous *vs.* heterogeneous) and possibly rule out the occurrence of leaching in the solution.[102] On the other, the zirconium-based UiO-66, applied in the C2 regioselective direct arylation of furan and thiophene with aryl diazonium salts.[103] The use of diazonium salts as arylating agents is here highly desirable in terms of *Green Chemistry*, in particular in the context of waste prevention, with the generation of N_2 as by-product, which easily moves away from the reaction mixture as a gas.

A very interesting work was reported by Wada *et al.*: a PPh_3-modified ruthenium catalyst supported on ceria (PPh_3-Ru/CeO_2) was successfully applied in the C10 regioselective direct arylation of benzo[*h*]quinoline **83** with (hetero)aryl chlorides, performed at 140 °C in the presence of potassium carbonate as the base and *N*-methyl-2-pyrrolidone as the solvent, giving the corresponding 10-(hetero)arylbenzo[*h*]quinoline **84** in very good yields (**Scheme 35**).[104] The sustainability of PPh_3-Ru/CeO_2 catalyst was fully confirmed by recycling and hot filtration tests, which supported the hypothesis of an heterogeneous mechanism. Moreover, the use of (hetero)aryl chlorides in organic synthesis is more favourable than other typical arylating agents, because they are less expensive and readily available compared to the corresponding aryl bromides and iodides.

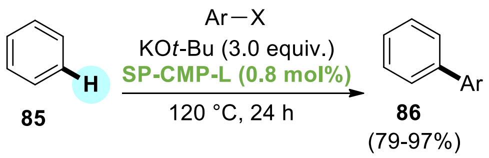


Scheme 35. C10 regioselective direct C-H arylation of benzo[*h*]quinoline **83** with (hetero)aryl chlorides, catalysed by recoverable PPh_3-Ru/CeO_2 catalyst.

Finally, recoverable metal oxide-based catalysts were occasionally used in direct C-H arylation reactions: in 2015, Nagarkar *et al.* reported the application of nano-ceria supported on Fe_3O_4 (CeO_2-Fe_3O_4) in the direct arylation of benzoxazoles or benzothiazoles with aryl iodides, bromides and diazonium salts, carried out in dimethyl sulfoxide or water as the solvent;[105] in the same year Rueping *et al.* described a C2 regioselective, photocatalytic direct arylation of pyridine, furan and thiophene with aryldiazonium salts, catalysed by easily accessible and recyclable TiO_2 used as catalyst.[106]

2.2.3. Recoverable metal-free catalysts for direct C-H bond arylation of (hetero)arenes. The use of recoverable non-metal catalysts in direct C-H bond arylation of (hetero)arenes has only been reported in the last five years. These systems are starting to attract significant interest: in fact, one of their main advantages in terms of sustainability is the total absence of metal contamination in the coupling products, thus making their purification procedures easier and cheaper. This class also includes some examples of organocatalysts, which in recent years are playing an increasingly central role in the *Green Chemistry*.

A salen-porphyrin-based conjugated microporous polymer (named SP-CMP-L) was proposed by Qiaolin and co-workers to serve as metal-free organocatalyst for direct C-H arylation of unactivated arenes **85** with aryl halides under base-mediated conditions: in particular, the reaction of benzene (used as both solvent and reagent) with functionalized aryl iodides, in the presence of SP-CMP-L (0.8 mol%) and potassium *tert*-butoxide (3.0 equiv.), after 120 °C at 24 h afforded the corresponding biaryl products **86** in good to excellent yields, 79-97% (**Scheme 36**).[107] This catalytic system is very appealing from a *Green Chemistry* perspective: in addition to the lack of tedious metal leaching, it showed a very good recyclability, working for 6 cycles with no loss of activity. However, on the other hand the need of a large excess of benzene is a major drawback of the procedure.

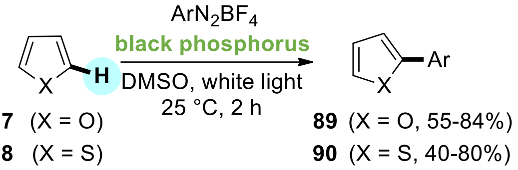


Ar = Ph, p-MeC_6H_4, p-$MeOC_6H_4$, p-CNC_6H_4, p-$NO_2C_6H_4$

Scheme 36. Direct C-H bond arylation of unactivated arenes **85** catalysed by the SP-CMP-L organocatalyst.

However, recoverable non-metal catalysts were most commonly used in the direct C-H arylation of furan and thiophene, in combination with photochemical processes (see section 4.1.1). In 2017, Wang and co-workers reported two very interesting works based on the use of graphitic C_3N_4 (g-C_3N_4): in one case, a g-C_3N_4 catalyst supported onto reduced graphene oxide was prepared by impregnation-chemical reduction strategy and applied up to five runs in the direct arylation of furan and thiophene with *para*-functionalized aryl diazonium salts under visible light irradiation;[108] in the other, a 3D aligned heterojuction aerogel of g-C_3N_4 with polypyrrole was applied as robust and highly recyclable (up to eight cycles) photocatalyst for the direct arylation of furan with aryl diazonium salts.[109] Very recently, Yadav *et al.* proposed a graphitic carbon nitride-based fluorescein isothiocyanate (called g-C_3N_4–FITC) thin film as excellent photocatalyst for the direct arylation of furan and thiophene, which was used up to four times with no significant loss of activity.[110] These three protocols are in our opinion very appealing in the frame of the *Green Chemistry*: in fact, the use of a recoverable and recyclable catalytic system was here coupled with the use of a photocatalytic method as non conventional energy source, aryl diazonium salts as highly environmental friendly arylating agents (due to the formation of N_2 as by-product), and in some cases also a quite sustainable reaction medium.

A different appealing approach was used in 2020 by Metin *et al.*: black phosphorus was used for the first time as heterogeneous and recoverable photoredox catalyst for the C2 regioselective direct C-H bond arylation of furan **87** and thiophene **88** with aryl diazonium salts, performed in DMSO as a solvent under white light, at 25 °C for 2 h (**Scheme 37**): the corresponding 2-arylfurans **89** and 2-arylthiophenes **90** were obtained in fair to satisfactory yields (55-84% and 40-80%, respectively).[111] The sustainability of this protocol is limited by the moderate recyclability of the non-metal catalyst: the decrease in the product yield after each run was attributed to the loss of a certain amount of thin black phosphorous nanosheets, that are highly dispersed in DMSO solvent and cannot be precipitated by simple centrifugation.



Ar = Ph, p-MeC_6H_4, p-$MeOC_6H_4$, p-BrC_6H_4, m-BrC_6H_4, o-BrC_6H_4, p-$NO_2C_6H_4$, m-$NO_2C_6H_4$, o-$NO_2C_6H_4$

Scheme 37. Black phosphorus as heterogeneous and recoverable photoredox catalyst for C2 regioselective direct arylation of furan **87** and thiophene **88** with aryl diazonium salts.

3. Sustainable solvents for direct C-H bond arylation of (hetero)arenes

Direct C-H bond arylation of (hetero)arenes typically requires high temperatures: this is due to the inertness of the (hetero)aryl C-H bonds, which often need a significant amount of thermal energy to be activated. Therefore, for a long time these reactions were carried out in most cases in high boiling point polar aprotic solvents, such as 1,4-dioxane, *N*-methyl-2-pyrrolidone (NMP), *N*,*N*-dimethylformamide (DMF) and especially *N*,*N*-dimethylacetamide (DMA). However, all these solvents are classified as undesirable for green chemistry,[112] since they are corrosive, flammable, explosive, irritant, toxic, harmful and/or (suspected) carcinogen.[113] Furthermore, it is well established that most of the waste generated in organic synthesis derives from organic solvents used as reaction media:[114] solvents undoubtedly represent the main element for environmental concerns in industrial synthetic processes.[115]

It is not surprising that Principle 5 of *Green Chemistry* ("Safer Solvents and Auxiliaries") has challenged fundamental studies in synthetic organic chemistry. Recently, this topic has acquired large interest also in the direct C-H bond arylation of (hetero)arenes: new protocols based on the use of more sustainable and environmental friendly reaction media have been developed. Water is definitely the most accessible and investigated solvent, given its immediate availability at almost zero cost. Unfortunately, organic compounds used as coupling partners of direct C-H bond arylation reactions often show only limited solubility in water, and hence biphasic mixtures water/organic solvent are often used, thus limiting the real sustainability of the process. The same issue of poor reagents solubility is also typical of alcohols, in particular ethanol and methanol (the latter is also characterized by the further issue of its moderate toxicity). A valid alternative is represented by biomass-derived solvents, such as cyclopentyl methyl ether (CPME), diethyl carbonate (DEC), 2-methyltetrahydrofuran (2-MeTHF), γ-valerolactone (GVL) and polyethylene glycol (PEG):[116] all these materials are easily available from renewable feedstocks, including agricultural and urban wastes and aquatic biomasses, showing in most cases low toxicity and high biodegradability.[117] Ionic liquids (ILs) and deep eutectic solvents (DES) are often associated with the class of sustainable reaction media, although there is often a lack of information on their real toxicity, thus limiting their use as solvents in the field of direct C-H bond arylation of (hetero)arenes. Solvent-free protocols are the most convenient approaches to pursue highly sustainable direct C-H bond arylation of (hetero)arenes, although the absence of a reaction medium could generate some issues, *e.g.* difficult mixing of reagents.

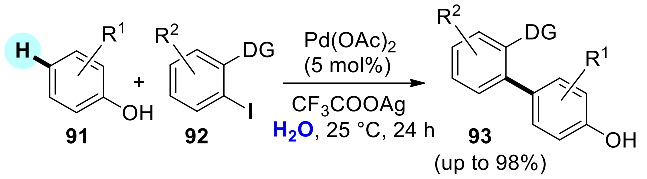
Following the above-mentioned summary, in this section we will give a critical overview of the main sustainable solvents applied in direct C-H bond arylation of (hetero)arenes, describing the advantages and any limitations associated with their use, including reactions performed in solvent-free conditions.

3.1. Direct C-H bond arylation of (hetero)arenes in water

Among all the solvents considered sustainable, water is definitely the most common: it is very cheap, non-flammable and non-toxic, it does not require special care when handled, and waste generated from its use as a reaction medium usually have lower disposal costs, although its recycling is generally quite expensive.[118]

Although water became quite popular as a solvent in organic synthesis from the 1990s,[119] one of the main drawbacks related to its use is the limited solubility of non-polar organic compounds, which is a frequent case in the direct C-H bond arylation of (hetero)arenes. Therefore, these reactions can be performed "on-water", or alternatively in a biphasic mixture water/organic solvent (sometimes in the presence of a phase transfer catalyst), which undermines the protocol sustainability. However, in some examples the use of amphiphiles and water-soluble ligands circumvented these solubility issues.

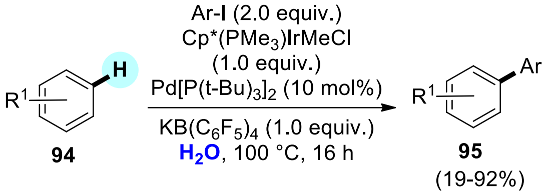
3.1.1. Direct C-H bond arylation of arenes in water. In 2013, Zhou and co-workers studied the direct C-H bond arylation of phenols **91** with aryl iodides **92** in H_2O: the reactions were carried out under mild conditions, with $Pd(OAc)_2$ (5 mol%) as catalyst and silver trifluoroacetate as base, at 25 °C for 24 h, affording the corresponding arylated phenols **93** in good yields and complete *para*-regioselectivity.[120] However, this protocol was successfully applied only to iodides **92** bearing an *ortho*-coordinating group: -COOH, $-CONH_2$, -CONHMe, $-CONMe_2$, -COMe, -COPh (**Scheme 38**). This protocol is very appealing in the frame of the *Green Chemistry*, since it required very mild experimental conditions, and in particular no need of thermal heating, thus minimizing the energy requirements. In a following paper, the same group extended their investigation to a broader family of *ortho*- and *meta*-functionalized aryl iodides, although in this case quite different experimental conditions were required (*i.e.*, $Pd(OAc)_2$ as catalyst, silver acetate as base, TsOH as additive, at 70 °C for 48 h) and a H_2O/acetic acid mixture (1:1 v/v) as reaction medium.[121] In fact, when few preliminary tests were performed in pure water, no reaction occurred: acetic acid could play an active role (*i.e.*, more than a simple solvent) in the mechanism, although it made the protocol less appealing from a sustainability point of view compared to the previous one.



DG = COOH, $CONH_2$, CONHMe, $CONMe_2$, COMe, COPh
R^1 = 2-Me, 2-I, 2-Br, 2-Ph, 2-*t*-Bu, 2-Cl, 2-CHO, 2-$COCH_3$,
2-NO_2, 2-COOH, 2,5-Me_2, 3-F
R^2 = 2-F, 2-Me, 3-Me, 3-OMe, 3-Cl, 3-Br, 3-CF_3

Scheme 38. Direct C-H bond arylation of phenols **91** with aryl iodides **92** in H_2O reported in 2013 by Zhou and co-workers.[120]

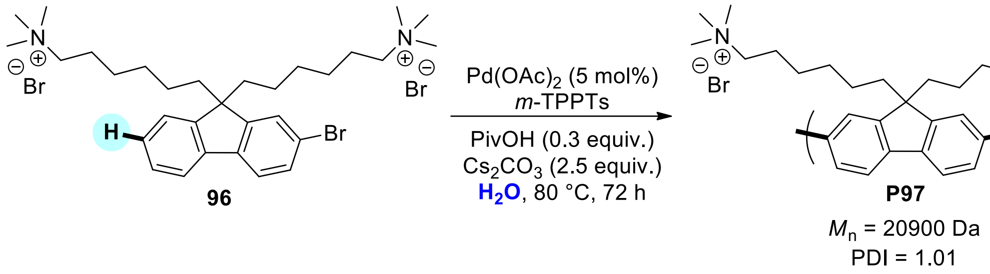
In 2014, Lewis *et al.* reported a different approach for the direct C-H bond arylation of unactivated arenes **94** in water: they discovered that $Cp^*(PMe_3)IrMeCl$ complex is able to activate C-H bonds on arenes, that undergo a subsequent cross-coupling with aryl iodides catalysed by $Pd[P(t\text{-}Bu)_3]_2$ to give biaryl products **95**.[122] Reactions were performed for 16 h in refluxing water not only on benzene, but also on methyl- and/or chloro-functionalized arenes, showing a good *para*- or *meta*-regioselectivity resulting from steric rather than electronic effects. A similar performance was also observed using a water/toluene mixture, used in order to improve the reagents solubility (**Scheme 39**). On one hand, such protocol appears quite appealing since it was carried out in a sustainable reaction medium and, unlike many other direct C-H bond arylation procedures of unactivated arenes, it did not require a large excess of arene; on the other, the need of a stoichiometric amount of the expensive $Cp^*(PMe_3)IrMeCl$ complex is hardly compatible with the typical canons of the *Green Chemistry*.



R^1 = H, 3,5-Me_2, 3,4-Me_2, 3-Me, 3,5-Me_2-4-Cl, 3,4-Cl_2, 3-CF_3
Ar = *p*-$OMeC_6H_4$, *p*-MeC_6H_4, 3,4-$Me_2C_6H_3$, 2-naphthyl

Scheme 39. Direct C-H bond arylation of unactivated arenes **94** in water as the solvent, promoted by the $Cp^*(PMe_3)IrMeCl$ complex, reported in 2014 by Lewis *et al.*[122]

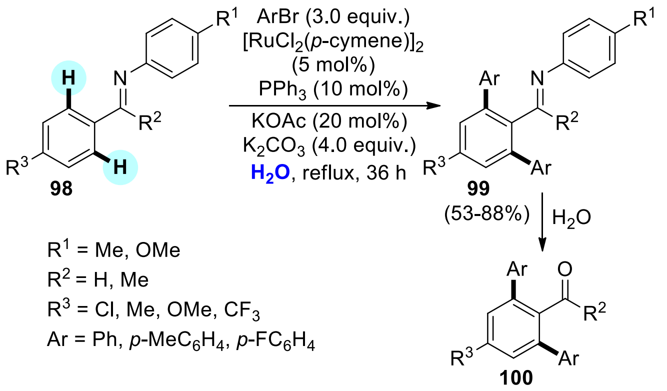
Very recently, Lai and co-workers reported the use of deionized water as solvent for the Pd-catalyzed direct C-H arylation polymerization of 2-bromofluorene monomer **96**, bearing two hexyltrimethylammonium bromide chains, to give the corresponding homopolymer **P97** (**Scheme 40**), showing relatively high M_n (20900 g mol^{-1}) and at the same time narrow polydispersity (1.01).[123] However, the use of water as reaction medium was here due in order to solubilize the cationic monomer **96**, rather than to a real interest of the authors in developing a sustainable polymerization protocol.



Scheme 40. Palladium-catalyzed direct C-H bond arylation polymerization of 2-bromofluorene monomer **96** performed in deionized water as the reaction medium: synthesis of the polyfluorene **P97**.

The direct C-H bond *ortho*-arylation of substituted benzenes in aqueous conditions has been widely investigated. To the best of our knowledge, the first study on this topic was reported in 1975 by McKillop *et al.*: a tandem *ortho*-arylation/lactonization of 2-bromobenzoic acid with resorcinol, performed with $CuSO_4$ as catalyst and basic H_2O as a solvent, affording 3-hydroxy-6*H*-benzo[*c*]chromen-6-one.[124] This work is of relevance only from an historical point of view, since at that time there was not yet a real interest of the scientific community towards a green and sustainable organic synthesis.

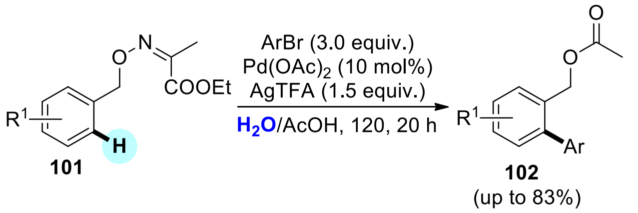
The carbonyl moiety and its derivatives represent an excellent *ortho*-directing group in the direct arylation reactions. In 2014, Darcel and co-workers described the *ortho*-diarylation of aryl ketimines **98** with aryl bromides, performed with [RuCl$_2$(*p*-cymene)]$_2$ (5 mol%), PPh_3 (10 mol%), KOAc (20 mol%), K_2CO_3 (4 equiv.) in refluxing H_2O for 36 h, affording the corresponding *ortho*-diarylated products **99** in good yields (**Scheme 41**).[125] Although reactions could be also performed in NMP as organic solvent, water enabled to produce a more active Ru catalyst, as well as to increase the process sustainability. Moreover, the direct *ortho*-diarylation of imines in water allowed the access to *ortho*-diarylated benzaldehydes **100** after the subsequent hydrolysis, as under these conditions benzaldehydes and aryl ketones gave no arylation. In 2015, Murai, Takai *et al.* reported the multi-step preparation of highly π-conjugated systems, *i.e.*, 3,11-dialkyl[6]phenacenes,[126] 3,10-disilyl[5]phenacenes and 3,12-disilyl[7]phenacenes,[127] including a direct *ortho*-arylation of suitable naphthyl aldimines under the same above mentioned conditions of Darcel and co-workers, thus demonstrating the broad synthetic interest and versatility of this protocol in the synthesis of highly functionalized organic compounds.



R^1 = Me, OMe
R^2 = H, Me
R^3 = Cl, Me, OMe, CF_3
Ar = Ph, *p*-MeC$_6$H$_4$, *p*-FC$_6$H$_4$

Scheme 41. Direct C-H *ortho*-diarylation of aryl ketimines **98** with [RuCl$_2$(*p*-cymene)]$_2$, developed in 2014 by Darcel and co-workers;[125] the *ortho*-diarylated imine products **99** allowed the access to the corresponding benzaldehydes **100** after the subsequent hydrolysis.

In 2018, a H_2O/acetic acid mixture was used as reaction medium for the cascade Pd-catalyzed direct C-H *ortho*-arylation/C-O bond solvolysis of pyruvate *O*-benzyloxy ketoximes **101** for the synthesis of biaryl 2-methyl acetates **102**.[128] In particular, reactions were carried out with aryl iodides (3.0 equiv.) as arylating agents, Pd(OAc)$_2$ (10 mol%) as catalyst, silver trifluoroacetate (1.5 equiv.) as additive, in H_2O/acetic acid at 120 °C for 20 h, affording of biaryl 2-methyl acetates **102** in good yields (**Scheme 42**). The protocol is highly interesting from a merely synthetic point of view as it showed a broad substrate, but we cast serious doubts about its sustainability: the use of acetic acid as the co-solvent, the need of a stoichiometric amount of a silver salts and the request of a prolonged thermal heating are features hardly compatible with most of the Twelve Principle of the *Green Chemistry*.

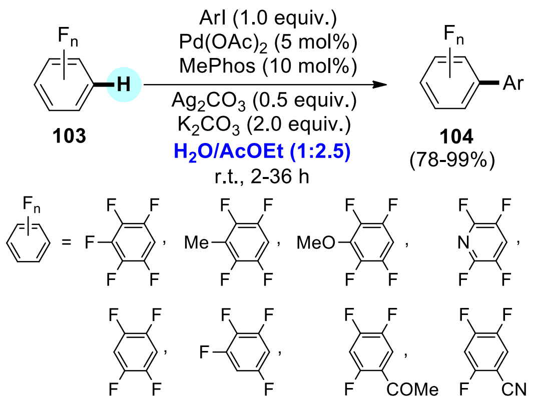


R^1 = 2-OMe, 2-Ph, 2-F, 2-I, 2-CF$_3$, 2-NO$_2$, 3-OMe, 3-Me, 3-Cl, 3-Br, 4-Me, 4-i-Pr, 4-F, 2,4-Cl$_2$, 2-Me-4-Cl
Ar = Ph, *p*-MeC$_6$H$_4$, *p*-OMeC$_6$H$_4$, *p*-FC$_6$H$_4$, *p*-ClC$_6$H$_4$, *p*-BrC$_6$H$_4$, *p*-IC$_6$H$_4$, *p*-COOMeC$_6$H$_4$, *m*-MeC$_6$H$_4$, *m*-OMeC$_6$H$_4$, *m*-ClC$_6$H$_4$, *m*-BrC$_6$H$_4$, *m*-CF$_3$C$_6$H$_4$, *o*-OMeC$_6$H$_4$, 3,5-Me$_2$C$_6$H$_3$, 3,5-Cl$_2$C$_6$H$_3$, 2-naphthyl, 6-CF$_3$-2-pyridyl, 6-chloro-3-pyridyl

Scheme 42. Pd-catalyzed direct C-H *ortho*-arylation/C-O bond solvolysis of pyruvate *O*-benzyloxy ketoximes **101** for the synthesis of biaryl 2-methyl acetates **102** performed in water as the solvent.

The first direct C-H bond *ortho*-arylation of (poly)fluorobenzenes in aqueous conditions was described in 2010 by Fagnou and co-workers: in this work, polyfluoroarenes **103** were treated with functionalized aryl iodides in water/ethyl acetate (1:2.5 v/v) mixture under mild conditions (that is, Pd(OAc)$_2$ 5 mol%, MePhos 10 mol%, $AgCO_3$ 0.5 equiv + K_2CO_3 2 equiv., 2-36 h, room temperature), affording the corresponding biaryl products **104** in 78-99% yields (**Scheme 43**).[129] The use of water was fundamental, as in a preliminary solvent screening low yields were obtained without adding water; however, a biphasic aqueous/organic mixture was preferred in order to allow a complete solubilization of all components of the system. In continuation with this study, Zhang and co-workers developed a more appealing protocol for the direct *ortho*-arylation of (poly)fluorobenzenes with iodoarenes: working with Pd(OAc)$_2$ (5 mol%) as catalyst, PPh_3 (10 mol%) as ligand and $AgCO_3$ (0.75 equiv.)

as base, reactions were carried out in only water (70°C for 24h).[130] Despite the higher temperature, authors highlighted their improvements towards sustainability, due to the use of fully aqueous conditions.



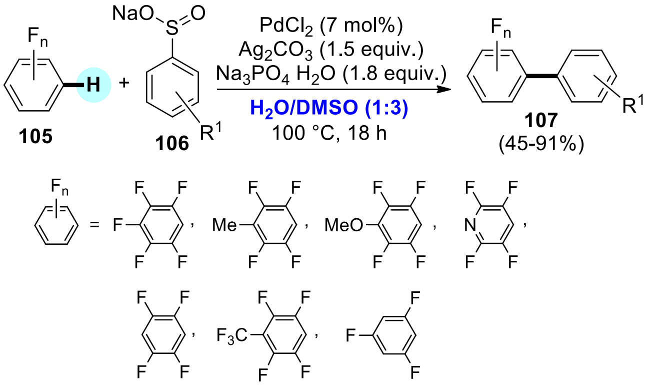
Ar = Ph, p-MeC_6H_4, p-$OMeC_6H_4$, p-$COMeC_6H_4$, p-$COOMeC_6H_4$, m-$OMeC_6H_4$, o-$OMeC_6H_4$, o-MeC_6H_4, m-$CF_3C_6H_4$, 1-naphthyl

Scheme 43. Direct C-H bond arylation reactions of polyfluoroarenes **103** with functionalized aryl iodides in water/ethyl acetate (1:2.5 v/v) mixture as the solvent under mild conditions, developed in 2010 by Fagnou *et al.*[129]

Beverina *et al.* reported a representative example of sustainable direct C-H bond *ortho*-arylation of octafluorobiphenyl with an aryl bromide, performed in Kollifor 2% in H_2O/toluene (9:1 v/v) mixture.[131] One of the most appealing features of the protocol is definitely the application of a micellar catalysis: the use of Kolliphor, which is a FDA-approved surfactant obtained by the reaction of castor oil with ethylene oxide, allowed for the development of micellar catalytic systems within direct arylation reactions may occur. The key concept of micellar catalysis is related to the preferential accumulation of organic compounds within the lipophilic pockets formed by the self-assembly of surfactants in H_2O. Therefore, thanks to the high concentration and local polarity effects, reactions are very efficient and often selective even at the ppm level of catalyst loading. It is clear that such protocol was developed giving a central role to the sustainability,as confirmed by the application of the micellar catalysis strategy, and by the low E-factors (*i.e.*, the mass ratio between organic wastes and product) of these reactions, in all cases in the order of 10^{-2}.

Wang and co-worker described a Pd-catalyzed direct C-H bond *ortho*-arylation of electron-poor fluorobenzenes **105**, based on the use of sodium arenesulfinates **106** as non-conventional arylating agents in DMSO/water (3:1 v/v) mixture.[132] This desulfitative protocol, catalyzed by $PdCl_2$ and in the presence of silver carbonate and trisodium phosphate, afforded biaryl products **107** with yields up to 91% (**Scheme 44**). Similarly to benzenesulfonyl chlorides, sodium arenesulfinates are very appealing arylating agents from the point of view of the *Green Chemistry*, since they generate SO_2 as by-product, which easily moves away from the reaction mixture as a gas. However, the use of an high loading of palladium (7 mol%), in combination with 1.5 equiv. of a silver salts, is a major issue that need to be addressed in order to improve the global sustainability of the method.

N-heteroaryl moieties, such as pyrazoles and pyridines, is a very good class of *ortho*-directing group in direct arylation of functionalized benzenes, especially under ruthenium catalysis. In this context, water has been investigated as reaction medium in the *ortho*-arylation of 1-phenylpyrazoles and 2-phenylpyridines. In 2012, Ackermann *et al.* reported the use of a ruthenium(II) carboxylate catalyst for the *ortho*-arylation of 1-phenylpyrazoles with phenols or diarylsufates as arylating agents, performed in refluxing water.[133] Starting from these interesting results, Dixneuf and co-workers described the use of a chelate Ru(II) complex, able to catalyze the direct C-H bond *ortho*-arylation of both 1-phenylpyrazoles and 2-phenylpyridines with aryl bromides and chlorides in water,[134] and more recently also the application of a family of ruthenium(II)-NHC catalysts in the direct C-H bond *ortho*-arylation of 2-phenylpyridines with (hetero)aryl chlorides.[135]



R^1 = H, 4-Me, 3-Me, 4-*t*-Bu, 4-OMe, 4-F, 4-Cl, 4-Br, 4-NO_2, 2-Me

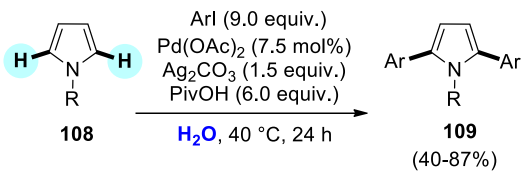
Scheme 44. Direct C-H bond ortho-arylation of electron-poor fluorobenzenes **105** with sodium arenesulfinates **106** as non-conventional arylating agents in DMSO/water solvent mixture.

The *ortho*-arylation of 2-phenylpyridines with (hetero)aryl chlorides in water was also studied by Singh and co-workers, using a series of *ad hoc* synthesized troponate/ aminotroponate Ru(II)-arene complexes as catalyst,[136] and by Gimeno *et al.*, which instead used commercially available $RuCl_3 \cdot n\ H_2O$ in the presence of zinc powder.[137] It is worth to emphasize that in almost all of these studies the use of water as the reaction medium was mainly due to allow the solubility of ruthenium catalysts, rather than for a real need of developing highly sustainable protocols. However, on the other hand the use of (hetero)aryl chlorides in organic synthesis is more favourable than other typical arylating agents, because they are less expensive and readily available compared to the corresponding aryl bromides and iodides.

Finally, intramolecular direct C-H *ortho*-arylation reactions of arenes in aqueous conditions were reported by Würthner *et al.*: a tandem Pd-catalyzed Suzuki-Miyaura cross-coupling/intramolecular direct *ortho*-arylation annulation of *peri*-dibromonaphthalimide with aryl boronic esters (*i.e.*, pyrene, phenantrene and naphthalene pinacol esters) was performed in a biphasic water/toluene mixture, giving *pseudo*-rylene bisimides[138] and polycyclic aromatic dicarboximides[139] which were then optically and electrochemically characterized. Also in these two studies, the need of an aqueous reaction medium as mainly related to the use of an aryl boronic ester in the starting Suzuki-Miyaura step of these tandem proceses, but for the sake of completeness we have still decided to mention them here.

3.1.2. Direct C-H bond arylation of *N*-heteroarenes in water. Water has found wide application as a solvent in the direct C-H bond arylation of *N*-heteroarenes, both monocyclic and bicyclic.

Starting our overview from five-membered monocyclic *N*-heteroarenes, pyrroles are among the most investigated. Chung *et al.* reported in 2015 a very interesting protocol for the direct bis-arylation of *N*-substituted pyrroles **108** with aryl iodides in water: reactions were performed under mild conditions (Pd(OAc)$_2$ 7.5 mol% as the catalyst, Ag_2CO_3 1.5 equiv. as the base, pivalic acid 6 equiv. as additive, for 24 h at 40 °C), affording the corresponding α,α-diarylated products **109** with high regioselectivity and good yields (**Scheme 45**).[140] Authors pointed out the sustainability of their protocol, due not only to the use of H_2O as the reaction medium but also to the PPh_3-free conditions. However, although quite mild experimental conditions were used, the need of 7.5 mol% of palladium and, above all, of a large amount of a silver salt represents a major issue for the real sustainability of the process, since these two metals could contaminate the corresponding coupling products.



R = CH_2Ph, $CH_2(p\text{-}ClC_6H_4)$, $CH_2(p\text{-}BrC_6H_4)$, $CH_2(p\text{-}OMeC_6H_4)$, $CH_2(p\text{-}Bu\text{-}t\text{-}C_6H_4)$, $CH_2(m\text{-}FC_6H_4)$, $CH_2(o\text{-}MeC_6H_4)$, Me, Et, TIPS
Ar = Ph, $p\text{-}MeC_6H_4$, $p\text{-}OMeC_6H_4$, $p\text{-}BrC_6H_4$, $p\text{-}CF_3C_6H_4$, $p\text{-}ClC_6H_4$, $3,5\text{-}MeC_6H_4$, $m\text{-}OMeC_6H_4$, $m\text{-}CHOC_6H_4$

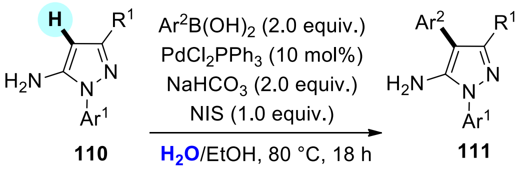
Scheme 45. Direct bis-arylation of *N*-substituted pyrroles **108** with aryl iodides in water developed in 2015 by Chung *et al.*[140]

Štefane and co-workers proposed a tandem Suzuki-Miyaura/direct C-H arylation of *N*-methyl pyrroles in 1,4-dioxane/water solvent mixture for the synthesis of polyaryl substituted pyrroles. The direct C-H bond arylation step was carried out by addition of the suitable aryl bromides and Pd(OAc)$_2$, keeping then the mixture at 120 °C for 24 h. Although such protocol was appealing for the synthesis of highly functionalized heteroaromatic compounds, aqueous conditions were used here in order to perform the starting Suzuki-Miyaura step.[141]

Direct arylations of pyrroles in aqueous reaction medium are quite common under photochemical conditions. It is worth to emphasize that the use of aqueous conditions here is definitely beneficial, but the most innovative aspect of these studies for sustainability is the use of UV-Vis irradiation as a non-conventional energy source (see section 4.1 below). In this context, a first study was reported in 2015 by Zhang *et al.*, who used a H_2O/acetonitrile 1:1 v/v mixture in the reaction of NH-free and *N*-methyl pyrrole with 5-iodouracil or 5-iodouridine under irradiation with a Hg lamp.[142] Despite the substrate scope was quite limited, the strategy appeared quite interesting in terms of sustainability due to the absence of any catalyst.

In 2017, König and co-workers described the C2 regioselective direct C-H arylation of NH-free and *N*-substituted pyrroles with chlorinated or brominated nucleobases in DMSO/water, performed in the presence of rhodamine 6G as photoredox organocatalyst. As well known, the use of organocatalytic system is definitely more appealing than conventional metal catalysts in the context of *Green Chemistry* protocols.[143] In 2021, Beverina *et al.* reported for the first time the application of a micellar catalysis approach in a microfluidic reactor, thanks to the use of castor oil derivative Kolliphor EL as a surfactant in water as a solvent for the direct α-arylation of *N*-methyl pyrroles with (hetero)aryl bromides, performed under 365 nm light irradiation (see also section 4.1.1).[144]

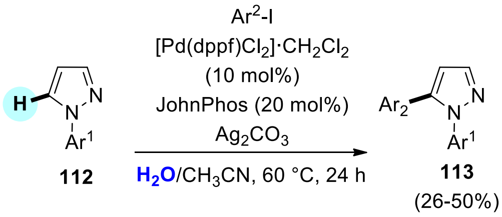
A sustainable water/ethanol solvent mixture was chosen by Zhong and co-workers for the Palladium-catalyzed oxidative direct C-H arylation of pyrazoles: 1,3,5-trisubstituted pyrazoles **110** were treated with aryl boronic acids as arylating agents, in the presence of $PdCl_2(PPh_3)_2$ (10 mol%) as catalyst, $NaHCO_3$ (2.0 equiv.) as base and *N*-iodosuccinimide (1.0 equiv.) as sacrificial oxidant, affording good yields (≤ 88%) the corresponding 4-arylated products **111**, which are fipronil derivatives showing a potential biological activity (**Scheme 46**).[145]



R^1 = CN, Me
Ar^1 = Ph, $2\text{-}Cl\text{-}4\text{-}CF_3\text{-}C_6H_3$, $2,6\text{-}Cl_{2\text{-}4}\text{-}CF_3\text{-}C_6H_2$
Ar_2 = Ph, $p\text{-}MeC_6H_4$, $p\text{-}MeOC_6H_4$, $p\text{-}EtC_6H_4$, $p\text{-}ClC_6H_4$, $p\text{-}FC_6H_4$, $p\text{-}CF_3C_6H_4$, $o\text{-}MeC_6H_4$, $o\text{-}MeOC_6H_4$, $o\text{-}ClC_6H_4$, $2\text{-}MeO\text{-}4\text{-}ClC_6H_4$

Scheme 46. Oxidative direct C-H arylation of 1,3,5-trisubstituted pyrazoles **110** with aryl boronic acids performed in a water/ethanol solvent mixture, reported in 2012 by Zhong and co-workers.[145]

In 2015, Fuse *et al.* reported the sequential synthesis of 1,3,4,5-tetrasubstituted pyrazoles from pyrazole, consisting of four orthogonal direct C-H arylation reactions, each of them performed in different conditions (including solvents). In particular, in the second step 1-arylpyrazoles **112** were treated with aryl iodides in H_2O/acetonitrile 9:1 (v/v) at 60 °C, in the presence of 10 mol% $[Pd(dppf)Cl_2]\cdot CH_2Cl_2$, 20 mol% JohnPhos and Ag_2CO_3, affording with high C5 regioselectivity and good yields (53-93%) the corresponding 1,5-diarylpyrazoles **113** (**Scheme 47**).[146] Despite the high synthetic interest for this protocol, such experimental conditions seem not of particular interest in the frame of *Green Chemistry*, due to the need of a high catalytic loading (*i.e.*, 10 mol% of Pd and 20% of the ligand) and of a large amount of silver carbonate as the base.

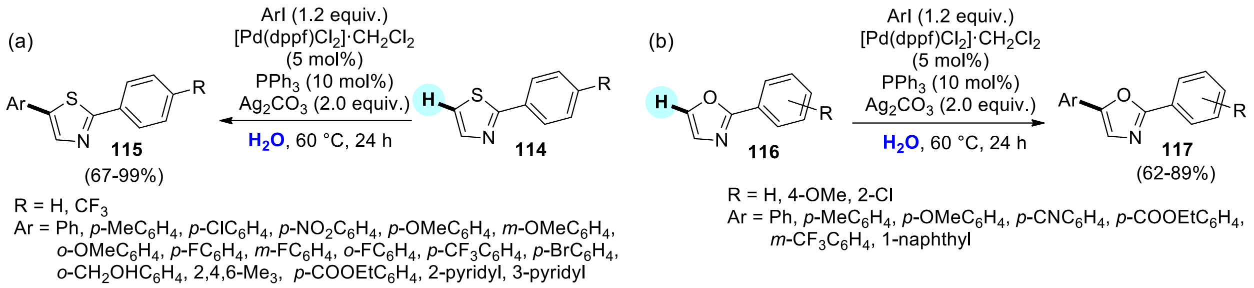


Ar^1 = $p\text{-}F\text{-}C_6H_4$, $p\text{-}MeC_6H_4$, $p\text{-}MeOC_6H_4$
Ar^2 = $p\text{-}CF_3\text{-}C_6H_4$, $p\text{-}NO_2C_6H_4$, $p\text{-}MeOC_6H_4$

Scheme 47. Direct C-H bond arylation of 1-arylpyrazoles **112** with aryl iodides performed in H_2O/acetonitrile 9:1 (v/v), reported in 2015 by Fuse *et al.*[146]

Only one example of direct C-H arylation of imidazoles under aqueous conditions has been reported to date: a C2 regioselective oxidative arylation of the imidazole scaffold of *L*-histidine derivatives with aryl boronic acids, performed with silver nitrate as catalyst, ammonium persulfate as sacrificial oxidant and trifluoroacetic acid as additive, in a biphasic H_2O/CH_2Cl_2 (1:1 v/v) mixture.[147] The role of the solvent was deeply studied: reactions carried out in biphasic organic/aqueous were more efficient than that in pure organic or pure H_2O solvent, suggesting a synergistic effect in the solubilization of all reagents.

The first direct arylation of thiazoles in water was described in 2007 by Greaney *et al.*: a family of 2-substituted thiazoles **114** were efficiently

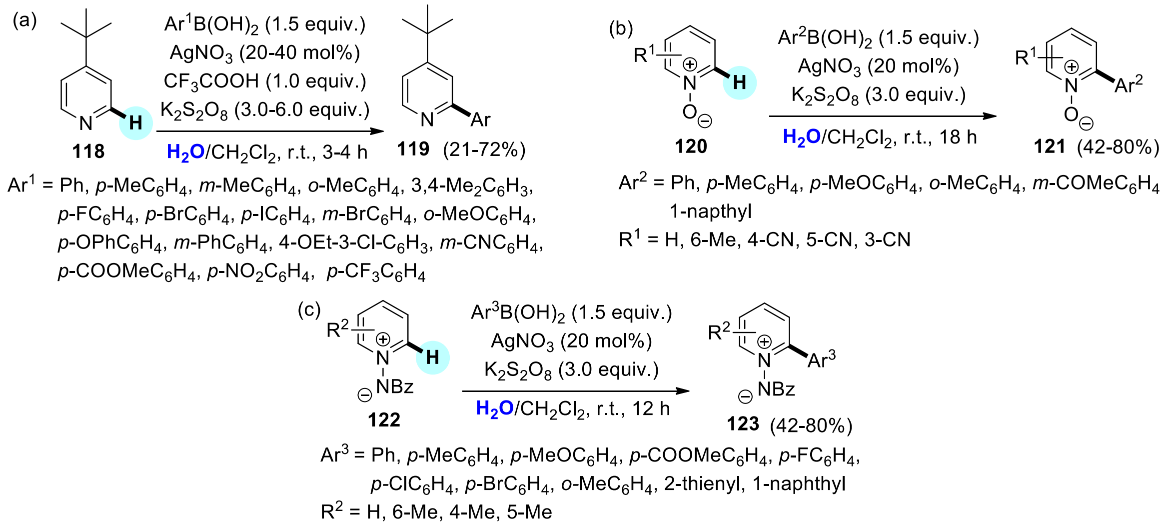


Scheme 48. Direct C-H bond arylation reactions of azoles in water described by Greaney and co-workers:[148-149] (a) C2 regioselective arylations on thiazoles **114**; (b) C2 regioselective arylations on oxazoles **116**.

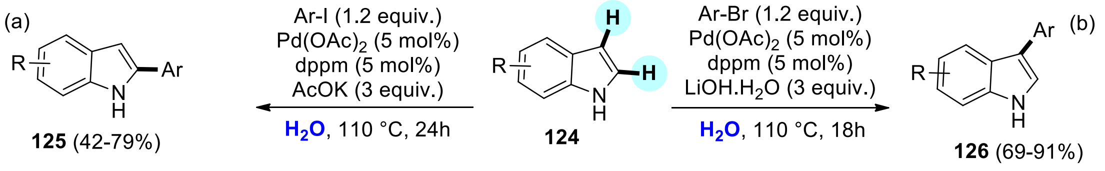
arylated at the C5 position with (hetero)aryl iodides in H_2O under mild conditions, *i.e.*, in the presence of $PdCl_2(dppf)$ (5 mol%), Ag_2CO_3 (2.0 equiv.) and PPh_3 (10 mol%) at 60 °C, affording the corresponding 2,5-disubstituted thiazoles **115** in excellent yields (in many cases > 99%) after 24 h (**Scheme 48a**).[148] The same authors then explored the possibility of direct arylation of 5-substituted oxazoles **116**: very interestingly, using the same aqueous conditions many 2,5-disubstituted oxazoles **117** were obtained in 48-89% yields(**Scheme 48b**).[149] The good sustainability and versatility of this protocol was then applied in a subsequent study for the synthesis of balsoxin and texaline, two bioactive 2,5-diaryloxazoles isolated from *Amyris* plant of Caribbean,[150] while more recently Pyne *et al.* used the same aqueous conditions for the preparation of highly functionalized oxazole and thiazole peptidomimetic.[151] In 2016, Wünsch and co-workers further improved the sustainability of this protocol with the use of microwave irradiation, which allowed to reduce reaction time to 1.5 h in the synthesis of a bioactive thiazole derivative showing high σ_1 receptor affinity (see section 4.2.2).[152] It is clear that the use of water as a solvent appears particularly convenient in direct C-H bond arylation of oxazoles and thiazoles, allowing the synthesis of highly functionalized compounds through procedures of low environmental impact, in compliance with many *Green Chemistry* criteria.

Moving on to the six-membered monocyclic *N*-heteroarenes, direct C-H bond arylation reactions of pyridines are definitely the most investigated in aqueous conditions. A common approach is the straightforward Minisci reaction, that is a Ag(I)-catalyzed radical coupling of pyridine scaffolds with aryl boronic acids, performed in biphasic water/CH_2Cl_2 (1:1 v/v) mixture and in the presence of a suitable oxidizing agent. The first study was described in 2010 by Baran *et al.*, who used $AgNO_3$ as catalyst, $K_2S_2O_8$ as oxidant and trifluoroacetic acid as radical precursor: working at room temperature, 4-*t*-butylpyridine **118** was converted into aryl pyridines **119** with good C2 regioselectivity and yields in 3-24 h (**Scheme 49a**).[153] Interestingly, a similar C2 arylation through Minisci reaction can occur with pyridine *N*-oxides **120**[154] or *N*-iminopyridinium ylides **122**[155] under almost the same experimental conditions, affording products **121** and **123** in satisfactory yields (**Scheme 49b-c**). More recently, Baxter *et al.* proposed a more sustainable version for the direct arylation of pyridine via Minisci reaction, performed in a H_2O/DCE (1:1 v/v) mixture but involving the use of Selectfluor as a mild organic oxidant.[156] For the sake of completeness, it is worth to emphasize that a Minisci reaction of pyridines in a H_2O/CH_2Cl_2 (1:1 v/v) mixture has been also performed with aryl triazenes as arylating agents, although their use in the frame of the *Green Chemistry* is quite limited due to their low atom economy and waste prevention.[157]

More recently, a first step towards sustainability was the use of less expensive Fe salts (instead of silver catalysts) in the same reactions: stoichiometric amounts of FeS,[158] Fe(II) oxalate[159] and $FeSO_4 \cdot 7H_2O$[160] were tested by keeping all the other conditions ($K_2S_2O_8$, CF_3COOH, H_2O/CH_2Cl_2 1:1 v/v, room temperature), although lower C2 selectivity was generally observed with respect to the use of $AgNO_3$ as catalyst. A



Scheme 49. Application of the Minisci reaction to the C2 regioselective direct C-H arylation of pyridine scaffolds through in H_2O/CH_2Cl_2 solvent mixture: (a) arylation of 4-*t*-butylpyridine **118**; (b) arylation of pyridine *N*-oxides **120**; (c) arylation of *N*-iminopyridinium ylides **122**.



R = H, 5-Br, 5-OCH_3, 5-COOMe
Ar = H, *m*-$OMeC_6H_4$, *m*-ClC_6H_4, *m*-$COMeC_6H_4$, *o*-ClC_6H_4, *p*-BrC_6H_4, 1-naphthyl

R = H, 4-OMe, 5-OMe, 5-Cl
Ar = H, *p*-$OMeC_6H_4$, *p*-ClC_6H_4, *p*-$CF_3C_6H_4$

Scheme 50. Direct C-H bond arylation reactions of NH-free indoles **124** under "on water" conditions: the C2 arylation was performed using aryl iodides as arylating agents (path a), while the C3 arylation was carried out using aryl bromides (path b).

further step forward in terms of sustainability was performed in 2020 by Kozak *et al.*, who coupled the $FeSO_4 \cdot 7H_2O$-promoted procedure with the use of microwave irradiation as non-conventional energy source (see section 4.2).[161] In all these works, although the presence of a chlorinated organic solvent limits their sustainability in the frame of the *Green Chemistry*, the use of water as a reaction medium was fundamental for achieving a good solubilization of silver(I) and iron(II) salts. Other major drawbacks of all these protocols are the following: (a) the need of large amounts (sometimes even stoichiometric) of the metal catalysts, which definitely contaminated the desired coupling products, thus requiring tedious purification procedures; (b) the use of boronic acids as the arylating agents, which produce large amounts of boron salts as by-products.

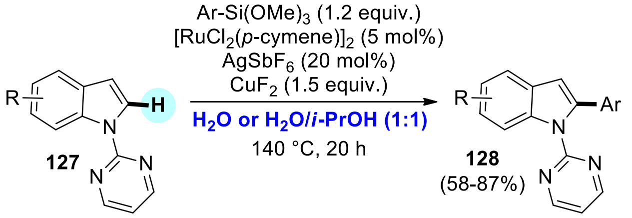
A totally different approach for the direct C-H arylation of pyridines was proposed by Xue and co-workers: aryldiazonium salts were used as arylating agents of functionalized pyridines at the C2 position, working with water as the only solvent at room temperature, in the presence of $[Ru(bpy)_3]Cl_2 \cdot 6H_2O$ as photocatalyst under irradiation with a 45 W bulb lamp.[162] Unlike aryl boronic acids, aryldiazonium salts as arylating agents in direct C-H arylation reactions are highly desirable towards the development of highly sustainable conditions, in particular in terms of waste prevention, thanks to the generation of N_2 as by-product, which moves away from the reaction mixture as a gas.

The direct arylation of other six-membered monocyclic *N*-heteroarenes, such as pyrazines and pyrimidines, has been less investigated under aqueous conditions. The only papers on this topic concern the direct oxidative coupling with aryl boronic acids promoted by $FeSO_4 \cdot 7H_2O$, under thermal heating[160] or microwave irradiation,[161] in a H_2O/CH_2Cl_2 (1:1 v/v) mixture, for which the same considerations as above apply.

Given their interest as scaffolds of many biologically active compounds, indoles have been widely studied as substrates for direct C-H arylation reactions under aqueous conditions. The first, very attractive study was reported in 2010 by Djakovitch and co-workers: they described the use of $[Pd(OAc)_2/dppm]$ as catalyst that worked "on water" in the direct C-H arylation of NH-free indoles **124** without the need of protecting and/or directing groups.[163] In particular, the control of regioselectivity was achieved by small changes in the experimental conditions: C2 arylation was performed using aryl iodides as arylating agents, in the presence of $Pd(OAc)_2$ (5 mol%), dppm (5 mol%) and AcOK (3 equiv.), at 110 °C for 24 h, affording the corresponding 2-arylindoles **125** (**Scheme 50a**); instead, C3 arylation was achieved using aryl bromides as arylating agents, in the presence of $Pd(OAc)_2$ (5 mol%), dppm (5 mol%) and $LiOH{\cdot}H_2O$ (3 equiv.), at 110 °C for 24 h, affording 3-arylindoles **126** (**Scheme 50b**).

This "on water" method was then further investigated by Larrosa *et al.*, who worked on *N*-substituted indoles: by using $Pd(OAc)_2$ (5 mol%) as the catalyst under ligand-free conditions and silver cyclohexanoate (1.5 equiv.) as the base, C2 arylated products were obtained in 16 h working at room temperature, thus improving the relevance of this protocol in the context of the *Green Chemistry*.[164] More recently, Cao and co-workers adopted the same "on water" experimental conditions of Djakovitch for the C2 regioselective direct C-H bond arylation of NH-free indoles, but changing the $[Pd(OAc)_2/dppm]$ catalytic system with ultrafine Pd nanoparticles encapsulated into the perfluoroalkane-functionalized mesoporous metal-organic framework NU-1000 (see also section 2.1.2).[44]

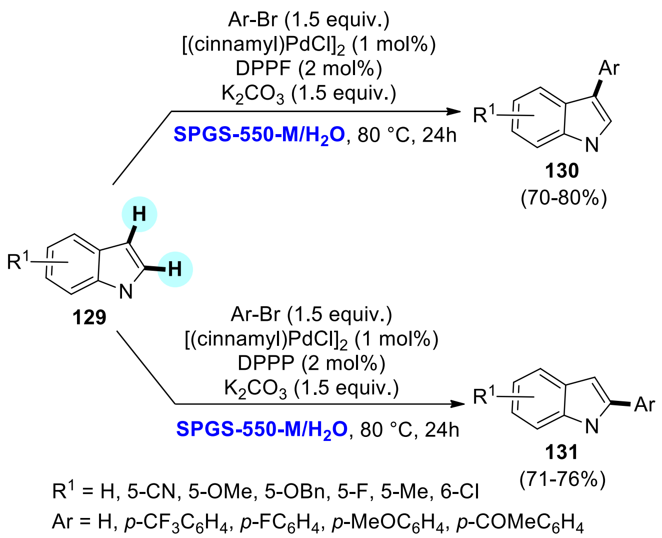
A "on water" strategy was also described in oxidative direct arylations of indoles: Szostak *et al.* reported a ruthenium(II) catalysed protocol, performed with arylsilanes as environmentally benign arylating agents.[165] More in details, *N*-(2-pyrimidyl)indoles **127** were treated with $[RuCl_2(p\text{-cymene})]$ (5 mol%) as catalyst, $AgSbF_6$ (20 mol%) as co-catalyst, CuF_2 (1.5 equiv.) as oxidant, affording the corresponding α-arylated products **128** in good yields (58-87%) after 20 h (**Scheme 51**). Authors pointed out the high sustainability of their method, consisting in the use of water as a green solvent, silanes as benign reactants and ruthenium species as inexpensive catalysts.



R = H, 5-OMe, 5-F, 5-Cl, 4-Br, 5-Br, 4-Br, 6-Br, 3-Me, 7-Me, 4-COOMe, 6-NO_2
Ar = Ph, *p*-MeC_6H_4, *p*-$OMeC_6H_4$, *p*-$CF_3C_6H_4$, *p*-FC_6H_4, *p*-ClC_6H_4, *p*-BrC_6H_4, *m*-$OMeC_6H_4$, *o*-MeC_6H_4, 3-thienyl

Scheme 51. "On water" oxidative direct C-H arylations of indoles **127** reported by Szostak *et al.*[165]

The above mentioned "on water" strategies has opened, in the last few years, to the development of direct C-H bond arylation of indoles based on a micellar catalysis. In fact, working in a aqueous reaction in the presence of a suitable surfactant, their self-assembly into micellar structures may occur; in this way, the preferential accumulation of organic compounds within the lipophilic pockets of micelles allowed for high concentration and local polarity effects, thus making reactions in a very efficient and selective way even at the ppm level of catalyst loading. Therefore, the development of micellar catalysis strategies is highly favourable in the context of the *Green Chemistry*. An appealing micellar catalysis strategy of indoles **129** was reported very recently by Kumar *et al.* using the surfactant SPGS-550-M in the presence of only 1 mol% of [(cinnamyl)PdCl]$_2$ catalyst under mild conditions.[166] In particular, they found that the direct arylation of indoles **129** with aryl bromides could be performed with very high C2 or C3 regioselectivity by simply changing the ligand: DPPF allowed for the β-arylation, thus affording the 3-arylated indoles **130**; on the contrary, using DPPP the α-arylation occurred, thus affording 2-arylated indoles **131** (**Scheme 52**).The combination of micellar catalysis and mild experimental conditions, together with the high capability of controlling the reaction regioselectivity, makes in our opinion this protocol very interesting for scientists working in the field of the *Green Chemistry*.



R^1 = H, 5-CN, 5-OMe, 5-OBn, 5-F, 5-Me, 6-Cl

Ar = H, *p*-$CF_3C_6H_4$, *p*-FC_6H_4, *p*-$MeOC_6H_4$, *p*-$COMeC_6H_4$

Scheme 52. Highly regioselective direct C-H arylation of of indoles **129** with aryl bromides based on a micellar catalysis approach, reported in 2019 by Kumar *et al.*[166]

A quite different approach was proposed by Wan and co-workers, where a sustainable direct arylation protocol of functionalized *N*-methyl and free-NH indoles in H_2O as the only solvent was performed in the presence of a recoverable catalyst (Pd nanoparticles supported on ordered mesoporous hybrid polymer-based materials, Pd/ODDMA-MP) using aryliodonium salts as alternative arylating agents: regioselective C2 arylation occurred, affording the corresponding 2-arylindoles in high yields.[53] Despite the use of water as a solvent is highly desirable for a sustainability point of view, the need of iodonium salts as the arylating agents is instead poorly appealing due to their modest atom economy.

In addition to all the above mentioned "on water", micellar and "in water" protocols, direct C-H arylation of indoles were also performed in biphasic aqueous/organic solvent mixtures. In 2012, Correia *et al.* described the C2 arylation of *N*-methylindole with aryldiazonium salts, performed in H_2O/diisopropyl ether 2:1 (v/v) under very sustainable conditions, *i.e.*, simply in the presence of $Pd(OAc)_2$ as catalyst at room temperature.[167] As pointed out in other points of our manuscript, the aryldiazonium salts are among the most appealing arylating agents in the context of direct C-H bond arylation reactions, since they produced gaseous N_2 as the only by-product, thus avoiding the contamination of the reaction mixture with the production of organic waste.

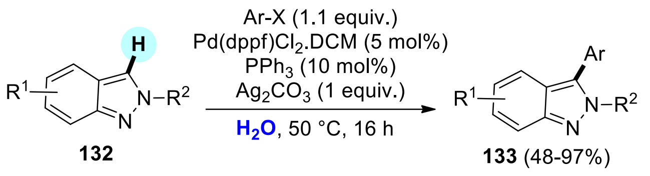
A H_2O/ethanol 5:1 (v/v) mixture was used in the same year by Cai and co-worker for the C2 direct arylation of NH-free indoles with aryl iodides catalysed by $Pd(Amphos)_2Cl_2$ (20 mol%), in the presence of tetrachlorophthalic anhydride (1.0 equiv.) and NaOH (1.0 equiv.), at 80 °C for 24 h.[168] Although the use of a sustainable solvent mixture as the reaction medium is highly desirable, here the use of a high loading of the palladium catalyst (that is, 20 mol%) is a major drawback to the real sustainability of the process. More interestingly was instead the α-arylation of 3-methylindole with a chlorinated nucleobase in DMSO/H_2O mixture: the protocol, described in 2017 by König and co-workers, was performed in the presence of rhodamine 6G as a photoredox catalyst (see also section 4.1.1).[143] The use of organocatalytic system is definitely highly appealing in the context of *Green Chemistry* protocols, mainly for their easier removal from coupling products compared to metal traces, therefore their use in combination with a environmental friendly solvent is highly favourable.

In 2020, an interesting study was reported by Vaccaro *et al.*: they described a C2 regioselective direct C-H bond arylation of indoles with diaryliodonium salts, using a Rhodiasolv® Polarclean/H_2O mixture 1:4 (v/v) as safe and recoverable reaction medium.[48] In fact, Polarclean is a promising solvent that can reduce carbon footprint; it is produced on ton scale by Solvay in a circular economy approach, it is not toxic and highly biodegradable. Despite iodonium salts are arylating agents typically characterized by a low atom economy, such protocol exhibited a great attention to sustainability, strengthened by the use of Pd/C as a recyclable supported catalyst (see section 2.1.2).

For the sake of completeness, papers using less sustainable solvent mixtures have to be mentioned. In 2017, Jiang and co-workers reported the use of DMA/water mixtures in the context of Pd-catalyzed direct C-H bond arylation of NH-free indoles with aryl iodides.[169] A THF/water mixture was instead applied by Loh *et al.* for Rh(III)-promoted oxidative direct arylation of *N*-(2-pyrimidyl)indoles with aryltrimethoxysilanes as convenient arylating agents.[170] In 2019, Volla, Maiti and co-workers described the C4 regioselective direct C-H bond arylation of indoles 3-carbaldehydes, performed in acetic acid/hexafluoroisopropanole/water (10:10:1 v/v) solvent mixture, in the presence of $Pd(OAc)_2$ as catalyst and glycine as an inexpensive transient directing group.[171] Despite their interest from a merely synthetic point of view, it is clear that these protocols are not of particular appealing from the point of view of the *Green Chemistry*.

The studies of direct C-H bond arylation under aqueous conditions on other bicyclic *N*-heteroarenes are quite limited. In 2010, Greaney *et al.* described an interesting "on water" strategy for the direct C-H arylation of 2*H*-indazoles **132** with (hetero)aryl iodides and bromides: reactions were performed with $PdCl_2(dppf)\cdot CH_2Cl_2$ (5 mol%) as catalytic precursor, PPh_3 (10 mol%) as the ligand, Ag_2CO_3 (1.0 equiv.) as the base, at 50 °C for 16 h, affording 3-(hetero)arylated 2*H*-indazoles **133** in 48-97% yields (**Scheme 53**).[172] Surprisingly, the same experimental conditions did not work on parent 1*H*-indazoles. However, very recently El Kazzouli demonstrated that working "on water" with the less expensive $Pd(OAc)_2$ instead of $PdCl_2(dppf)\cdot CH_2Cl_2$ and at 100 °C instead of 50 °C, direct C3 arylation of 1*H*-indazoles with (hetero)aryl iodides occurred in high yields.[173]

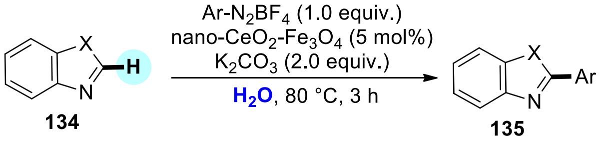
The only report on the direct arylation of benzimidazoles in aqueous conditions was described in 2020 by Peddiahgari and co-workers: a family of Pd-PEPPSI complexes was tested in the direct C2 arylation of *N*-substituted benzimidazoles in a water/ethanol 1:1 (v/v) mixture.[174] However, this work was actually mainly focused on the synthesis and catalytic performance of such complexes, rather to the development of an highly sustainable direct C-H arylation protocol of benzimidazoles.



X = Br, I R^1 = H, 5-Cl, 7-OMe
R^2 = Ph, *o*-MeC$_6$H$_4$, *p*-MeC$_6$H$_4$, CH$_3$, SEM, CH$_2$(*o*-IC$_6$H$_4$)
Ar = H, *p*-ClC$_6$H$_4$, *p*-BrC$_6$H$_4$, *p*-MeC$_6$H$_4$, *p*-CNC$_6$H$_4$, *p*-COOEtC$_6$H$_4$, *p*-NO$_2$C$_6$H$_4$, *p*-OMeC$_6$H$_4$, *p*-COMeC$_6$H$_4$, *o*-MeC$_6$H$_4$, *m*-ClC$_6$H$_4$, 2-Cl-pyridin-4-yl-

Scheme 53. Direct C-H bond arylation of 2*H*-indazoles **132** with (hetero)aryl iodides and bromides through "on water" strategy.

Nagarkar *et al.* reported the use of nano-CeO$_2$ supported on Fe$_3$O$_4$ for the C2 regioselective direct arylation of benzoxazoles or benzothiazoles **134** with aryldiazonium salts in H$_2$O at 80 °C for 3 h, affording the corresponding 2-aryl benzoxazoles/benzothiazoles **135** in good yields (**Scheme 54**).[105] Despite the substrate scope of this study was quite limited, the protocol actually appears in our opinion of very high interest in the context of the *Green Chemistry*: it combined the use of a supported metal catalyst (see section 2.2.2) which could be easily recovered and recycled, the use of diazonium salts as convenient arylating agents (due to their high waste prevention, associated to the production of N$_2$ as by-product), the use of water as a green reaction medium, and finally the need of quite mild reaction conditions (that is, 80 °C for only 3 h).



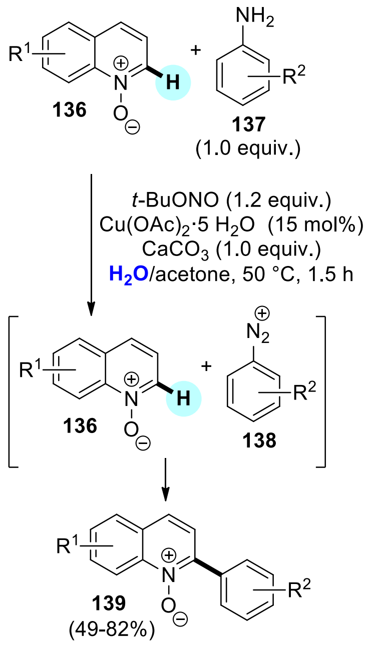
X = O, S
Ar = Ph, *p*-NO$_2$C$_6$H$_4$, *p*-OMeC$_6$H$_4$, *p*-MeC$_6$H$_4$,3,4-Me$_2$C$_6$H$_3$

Scheme 54. C2 regioselective direct arylation of benzoxazoles or benzothiazoles **134** with aryldiazonium salts in H$_2$O reported in 2015 by Nagarkar *et al.*[105]

In 2013, Maiti and co-workers proposed a trifluorotoluene (TFT)/water 1:1 (v/v) mixture for the iron-catalyzed oxidative direct arylation of benzothiazoles, quinolines and quinoxalines with aryl boronic acids.[175] It is clear that this work was mainly focused on the development of the synthetic protocol, rather than on a concrete interest in sustainable experimental conditions: in fact, the use of highly harmful TFT as co-solvent and the need of boronic acids as arylating agents (producing a stoichiometric amounts of boron salts as by-products) represent two severe issues to the sustainabily of the method.

Although aqueous conditions often enable the development of greener and more sustainable protocols, in some cases they make possible a reactivity that could hardly occur in organic solvents. This is the case of C2 regioselective direct C-H arylation of quinolines *N*-oxide **136** with aryl amines **137**: a Cu(OAc)$_2$·5 H$_2$O catalysed radical coupling to give the corresponding 2-arylquinolines *N*-oxide **139** was described by Qu *et al.*, performed in acetone/water 2:1 (v/v) mixture and in the presence of *tert*-butyl nitrite, which is able to generate aryldiazonium salts **138** (the effective arylating agents) *in situ* from aryl amines under aqueous conditions (**Scheme 55**).[176]

A biphasic H$_2$O/CH$_2$Cl$_2$ 1:1 (v/v) mixture was used as reaction medium for the oxidative direct C-H bond arylation of *N*-methoxyquinoline-1-ium tetrafluoroborate derivatives with aryl boronic acids: interestingly, working with AgNO$_3$ as the catalyst and Na$_2$S$_2$O$_8$ as a sacrificial oxidant at room temperature, the corresponding 2-arylquinolines were directly obtained in only 30 minutes.[177] A very similar protocol, only differing in the use of (NH$_4$)$_2$S$_2$O$_8$ as oxidant and H$_2$O/dichloroethane (instead of H$_2$O/CH$_2$Cl$_2$) as the reaction medium, was proposed by Du and co-workers for the C6 direct arylation of purines and purine nucleosides.[178] Despite the use of an organic solvent, the short reaction times and the absence of any heating make these two last protocols appealing from a sustainability perspective.

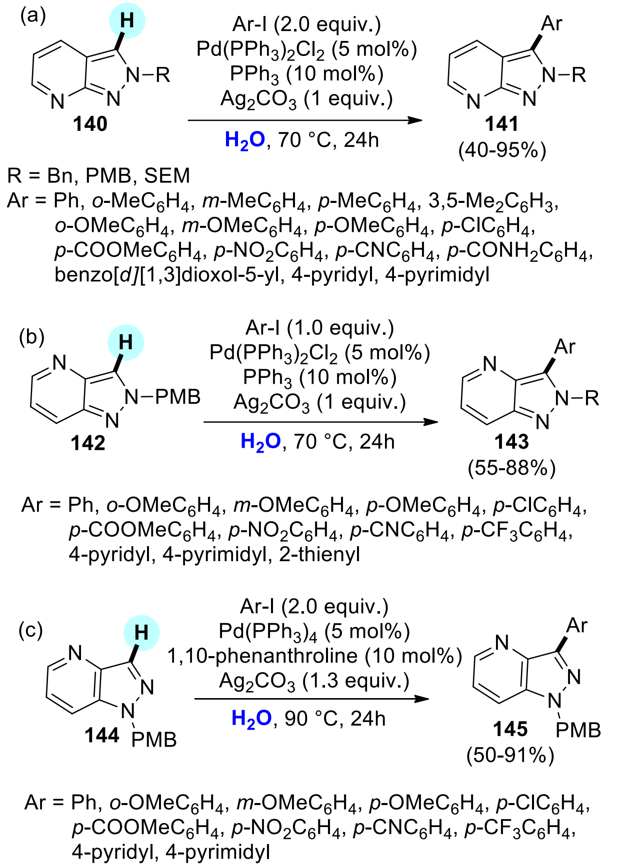


R^1 = H, 6-Me, 6-OMe, 8-Me, 6-Cl, 6-Br, 6-NO$_2$, 4-Me, 3-Br
R^2 = H, 4-Me, 4-Et, 4-OMe, 2-OMe, 4-F, 4-Cl, 4-Br, 4-I, 2-Cl, 3-Cl, 3,5-Cl$_2$, 4-COMe, 4-CN, 4-COOMe

Scheme 55. C2 regioselective direct C-H bond arylation of quinolines *N*-oxide **136** with aryl amines **137** performed in acetone/water.

The use of water as a solvent was also applied in the direct C-H bond arylation reactions of other bicyclic poly-nitrogen heteroarenes, such as caffeine, pyrazolopyridines, imidazopyridines and thiazolopyridines. Xue *et al.* described the use of aryldiazonium salts as arylating agents in the photochemical C2 arylation of caffeine, performed in water as reaction medium and in the presence of [Ru(bpy)$_3$]Cl$_2$ · 6 H$_2$O as photocatalyst under irradiation with a 45 W bulb lamp.[162] Although the use of H$_2$O as a reaction medium is very interesting, the most appealing feature in the field of the *Green Chemistry* here is represented by the application of a photochemical method as a non-conventional energy source (for more details, see section 4.1.1).

Guillaumet *et al.* worked on the Palladium-catalyzed direct arylation of pyrazolopyridines by "on water" protocols. In 2017, they reported a C3 arylation of 2*H*-pyrazolo[3,4-*b*]pyridines **140** with (hetero)aryl iodides: the reactions proceeded "on water" smoothly using low amounts of the Pd(PPh$_3$)$_2$Cl$_2$ catalyst (5 mol%) and PPh$_3$ ligand (10 mol%), 1.0 equiv. of Ag$_2$CO$_3$ as base, at moderate temperature (70 °C) for 24 h, affording the corresponding C3-(hetero)arylated products **141** in good to excellent isolated yields (**Scheme 56a**).[179] In a following paper, they applied two very similar “on water” procedures for the C3 arylation of 2*H*-pyrazolo[4,3-*b*]pyridines **142** (*i.e.*, $Pd(PPh_3)_2Cl_2$ 2.5 mol%, Ag_2CO_3 1.0 equiv., H_2O, 70 °C, 24 h) and of 1*H*-pyrazolo[4,3-*b*]pyridines **144** (*i.e.*, $Pd(PPh_3)_4$ 5 mol%, 1,10-phenanthroline 10 mol%, Ag_2CO_3 1.3 equiv., H_2O, 90 °C, 24 h) to obtain the corresponding coupling products **143** and **145**, respectively, in good yields (**Scheme 56b-c**).[180]



R = Bn, PMB, SEM
Ar = Ph, *o*-MeC_6H_4, *m*-MeC_6H_4, *p*-MeC_6H_4, 3,5-$Me_2C_6H_3$, *o*-$OMeC_6H_4$, *m*-$OMeC_6H_4$, *p*-$OMeC_6H_4$, *p*-ClC_6H_4, *p*-$COOMeC_6H_4$, *p*-$NO_2C_6H_4$, *p*-CNC_6H_4, *p*-$CONH_2C_6H_4$, benzo[*d*][1,3]dioxol-5-yl, 4-pyridyl, 4-pyrimidyl

Ar = Ph, *o*-$OMeC_6H_4$, *m*-$OMeC_6H_4$, *p*-$OMeC_6H_4$, *p*-ClC_6H_4, *p*-$COOMeC_6H_4$, *p*-$NO_2C_6H_4$, *p*-CNC_6H_4, *p*-$CF_3C_6H_4$, 4-pyridyl, 4-pyrimidyl, 2-thienyl

Ar = Ph, *o*-$OMeC_6H_4$, *m*-$OMeC_6H_4$, *p*-$OMeC_6H_4$, *p*-ClC_6H_4, *p*-$COOMeC_6H_4$, *p*-$NO_2C_6H_4$, *p*-CNC_6H_4, *p*-$CF_3C_6H_4$, 4-pyridyl, 4-pyrimidyl

Scheme 56. Pd-catalyzed direct arylation of pyrazolopyridines by “on water” protocols: (a) C3 arylation of 2H-pyrazolo[3,4-b]pyridines **140**; (b) C3 arylation of 2*H*-pyrazolo[4,3-*b*]pyridines **142**; (c) C3 arylation of 1*H*-pyrazolo[4,3-*b*]pyridines **144**.

Rode *et al.* focused their attention on the direct C-H bond arylation of imidazo[1,2-*a*]pyridines with (hetero)aryl iodides, carried out “on water” with the inexpensive $Pd(OAc)_2$ as catalyst (5 mol%), KOH (3.0 equiv.) as base, at 100 °C for 24 h;[181] similar experimental conditions were also described for the “on water” arylation of thiazolo[5,4-*d*]pyrimidines.[182] Once again, all these “on water” studies proved to be convenient in terms of environmental sustainability and economic impact, thus justifying their increasing interest in the field of *Green Chemistry*.

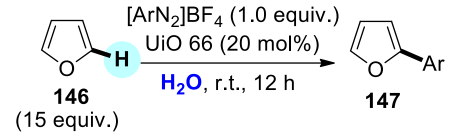
Finally, very recently Wu *et al.* have reported an efficient method for the palladium-catalyzed direct C-H arylation of imidazo[1,2-*a*]pyridines with aryl chlorides under aqueous conditions: working with 2.0 equiv. of the arylating agent, 5 mol% of $Pd(OAc)_2$, 10 mol% of $BuAd_2P$ as ligand, 3.0 equiv. of K_2CO_3 as base in a 1,4-dioxane/H_2O 2:1 (v/v) mixture at 110 °C, affording 3-arylimidazo[1,2-a]pyridines in good yields.[183]

3.1.3. Direct C-H bond arylation of *O*-heteroarenes in water. Studies on the direct C-H arylation of *O*-heteroarenes under aqueous conditions are quite limited, and performed only in combination with other *N*- and/or *S*-heteroarenes. In 2015, Zhang *et al.* used a H_2O/acetonitrile 1:1 v/v mixture in very few examples of direct C-H arylation of furan with 5-iodouracil or 5-iodouridine under irradiation with a Hg lamp.[142] Despite the substrate scope was quite limited, the strategy appeared quite interesting in terms of sustainability due to the absence of any catalyst, which is quite uncommon in the context of direct C-H bond arylation reactions.

Štefane and co-workers proposed a tandem Suzuki-Miyaura/direct C-H arylation of furan and benzofuran in 1,4-dioxane/water mixture for the synthesis of biologically active nitroxoline analogues.[141] Actually, in this case aqueous conditions were only used to allow the starting Suzuki-Miyaura step, but we decided to report it for the sake of completeness.

A more sustainable work was reported in 2020 by Zhang *et al.*: they proposed a C2 regioselective direct C-H bond arylation of furan **146** with variously functionalized aryl diazonium salts, performed in water as the only solvent at room temperature and in the presence of the zirconium-based UiO-66 metal organic framework as catalyst; the corresponding α-arylated furans **147** were obtained in satisfactory yields (**Scheme 57**).[103]

This protocol in our opinion is quite interesting from several point of view: in addition to the use of water as reaction medium, the presence of an heterogeneous (and easily removable) catalyst and the use of diazonium salts as arylating agents are highly desirable features in the context of the *Green Chemistry*.

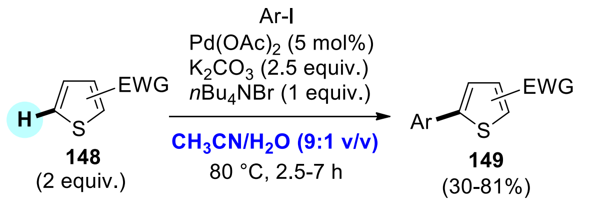


Ar = *p*-CN, *p*-CF_3, *p*-NO_2, *o*-NO_2, 2-NO_2-4-Cl, *p*-COMe, *m*-CN, *m*-NO_2, *o*-CN, *m*-COMe, *o*-CF_3, 1-naphthyl

Scheme 57. C2 regioselective direct C-H bond arylation of furan **146** with aryl diazonium salts performed in water as the solvent.

In 2018, Cai, Jiang and co-workers reported a very appealing strategy for the C2 regioselective direct C-H bond arylation of furan, where the micellar catalysis approach was combined with the advantages of the photoredox processes and organocatalysis.[184] Reactions were carried out in water, in the presence of Triton X-100 as commercially available and inexpensive surfactant in order to generate the micellar structures. The accumulation of organic compounds within the lipophilic pockets of micelles, in which is also located the organic photocatalyst (that is, eosin B), allowed for highly efficient direct C-H arylation. In particular, anilines were used as formal arylating agents, which can be then *in situ* converted into the corresponding diazonium salts in the presence of *tert*-butyl nitrite. It is clear that the combination of all these aspects makes this study of very high interest for all the organic chemists working in the development of sustainable and efficient synthetic protocols.

3.1.4. Direct C-H bond arylation of *S*-heteroarenes in water. To the best of our knowledge, the first work which described direct C-H bond arylation reactions of thiophene rings under aqueous conditions was reported in 1997 by Lemaire *et al.* A water/acetonitrile mixture was used as reaction medium for a C2 regioselective direct C-H arylation of activated thiophenes **148** (*i.e.*, thiophene rings bearing an electron withdrawing group) with aryl iodides, performed with $Pd(OAc)_2$ as the catalyst, K_2CO_3 as the base and tetra(*n*-butyl)ammonium bromide as a phase transfer catalyst; the corresponding coupling products **149** were obtained in moderate yields (**Scheme 58**).[185] A deeper investigation of the experimental conditions was performed in two following papers; interestingly, the synergistic effect of water and acetonitrile towards high yields and low reaction times was demonstrated.[186-187] These three works are of relevance only from an historical point of view, since at that time the development of the Twelve Principles of *Green Chemistry* was still in its infancy.

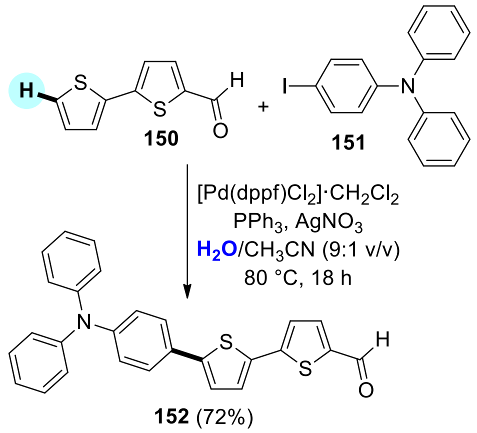


EWG = 2-CHO, 3-CHO, 2-NO$_2$, 2-CN, 3-CN
Ar = Ph, *p*-OMeC$_6$H$_4$, *o*-CF$_3$C$_6$H$_4$, *p*-CF$_3$C$_6$H$_4$, 1-naphthyl

Scheme 58. First study of direct C-H bond arylation reactions of thiophene rings **148** under aqueous conditions, reported in 1997 by Lemaire *et al.*[185]

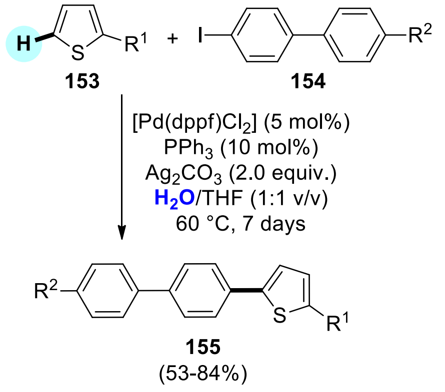
After the pioneering works of Lemaire and co-workers, no other studies of direct C-H bond arylation of thiophenes in aqueous conditions were reported for several years. Only in the last six-seven years, with the growing interest in *Green Chemistry* principles, an increasing number of investigation on this topic has been described, for the synthesis of both small molecules and polymers. Once again, most of them used biphasic aqueous/organic mixtures as a solvent.

Concerning small molecules, in 2015 Fuse and co-workers reported the synthesis of thiophene-based organic dyes for dye-sensitized solar cells by a tandem Suzuki-Miyaura coupling/direct C-H arylation/Knoevenagel condensation.[188] Despite the work was mainly focused on the detailed spectroscopic study of these dyes, an optimization of the experimental conditions was also performed: in this field, according to the previous studies of Lemaire *et al.*, the direct arylation step of 2,2'-bithiophene derivative **150** with *N*,*N*-diphenyl-4-iodoaniline **151** was carried out in a H_2O/CH_3CN mixture, affording the corresponding coupling product **152** in 72% yield (**Scheme 59**).



Scheme 59. Direct C-H bond arylation of 2,2'-bithiophene **150** with *N*,*N*-diphenyl-4-iodoaniline **151** in a H_2O/CH_3CN mixture, reported in 2015 Fuse and co-workers.[188]

In the same year, Lützen *et al.* proposed the use of H_2O/THF mixture for the direct C-H bond arylations of α-substituted thiophenes **153** with functionalized iodobiphenyls **154**: the reactions were performed with $Pd(dppf)Cl_2$, PPh_3 and Ag_2CO_3, affording the thiophene/phenylene systems **155** in 53-84% yields (**Scheme 60**).[189] Despite the use of an aqueous reaction medium, in our opinion this protocol does not show a very high sustainability: reactions were typically carried out for 7 days at 60 °C, thus needing for high energy requirements.



R^1 = CN, Br, NO$_2$, OMe R^2 = H, Cl, OMe, CN

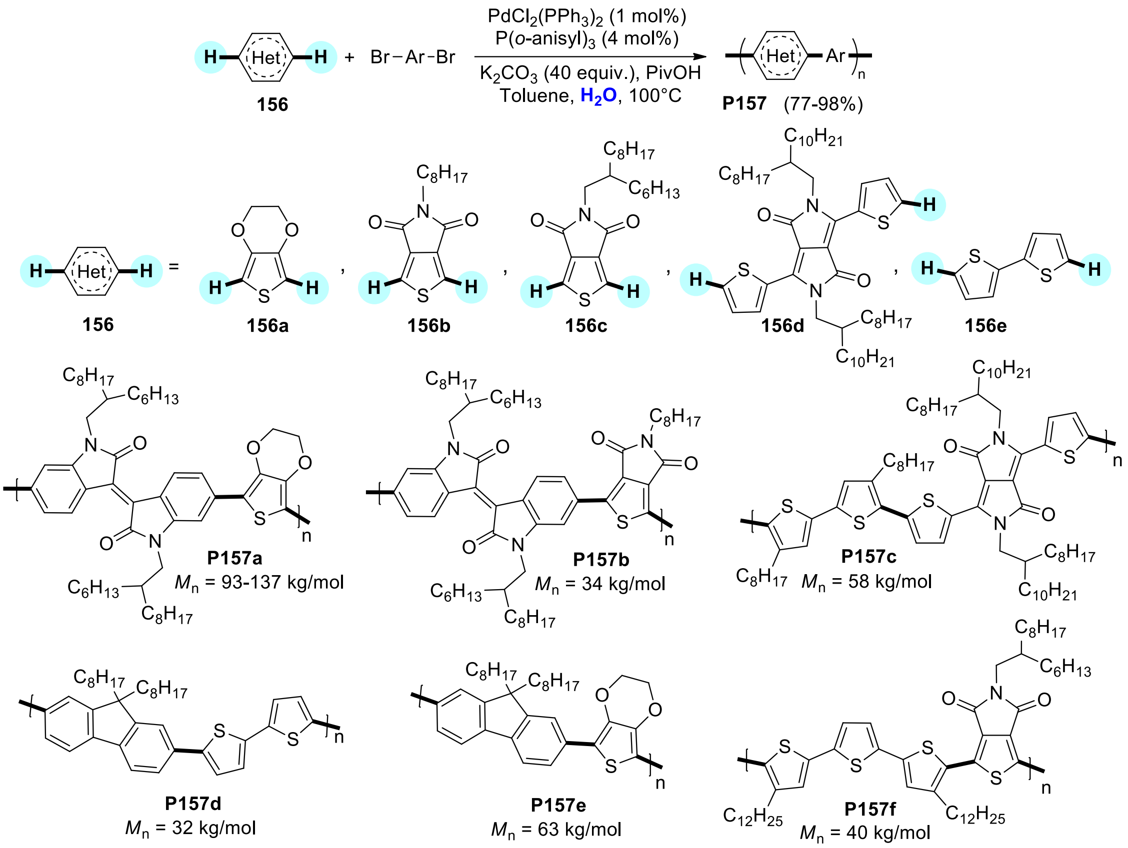
Scheme 60. Direct C-H bond arylations of α-substituted thiophenes **153** with functionalized iodobiphenyls **154** in H_2O/THF mixture, reported in 2015 by Lützen *et al.*[189]

In 2016, Štefane *et al.* proposed the preparation of biologically active nitroxoline analogues using a tandem Suzuki-Miyaura/direct C-H arylation protocols of thiophene in a 1,4-dioxane/water mixture.[141] Actually, in this case aqueous conditions were only used to allow the starting Suzuki-Miyaura step, but we decided to report this study in our ovierview for the sake of completeness

More sustainable protocols were developed only very recently. In 2019, Yildiz *et al.* proposed a transition metal-free approach for the oxidative direct arylation of thiophenes in H_2O: potassium peroxymonosulfate was used as mild and inexpensive catalyst for the oxidative direct homo-coupling of 3-(4-methyl-3'-thienyloxy)propyltriethylammonium bromide; consumption of the starting thiophene reagent was observed in 15 minutes, giving the corresponding dimer, trimer and tetramer.[190] In this specific case, the use of H_2O as the only solvent was mainly due to the better solubility of the cationic thiophene monomer.

In 2020, Zhang *et al.* reported some examples of C2 regioselective direct C-H bond arylation of thiophene with aryl diazonium salts, performed in water as the only solvent at room temperature and in the presence of the zirconium-based UiO-66 metal organic framework as catalyst.[103] As we already described in the previous section 3.1.3 for the ame reaction on furan, we believe that this protocol is interesting in the context of the *Green Chemistry* for several aspect: in addition to the use of water as reaction medium, the presence of a removable catalyst and the use of diazonium salts as very favourable arylating agents in waste prevention.

Beverina and co-workers reported an extensive investigation of sustainable direct C-H bond arylation reactions of 2-(*n*-hexyl)thiophene, 2,2'-bithiophene, 3,4-ethylenedioxythiophene and thieno[3,4-*c*]pyrrole-4,6-dione with aryl bromides, performed in Kollifor 2% in H_2O/toluene (9:1 v/v) mixture.[131] The use of Kolliphor allowed for the application of a micellar catalysis approach: direct C-H arylation reactions occurred within the lipophilic pockets of micelles, where thanks to the high concentration and local polarity effects, reactions are very efficient. In



Scheme 61. Leclerc's first report of direct C-H bond arylation-based polymerization of thiophene-based systems under aqueous conditions.

addition to the use of a micellar catalysis, the overall sustainability of the process was further confirmed by E-factors (*i.e.*, the mass ratio between organic wastes and product) in all cases in the order of 10^{-2} (between 179 and 556), which are low values, considering that they also include purification.

The first report of direct C-H bond arylation polymerization of thiophene systems under aqueous conditions was published in 2017 by Leclerc *et al.*[191] Thiophene-based monomers **156** (3,4-ethylenedioxythiophene **156a**, thieno[3,4-*c*]pyrrole-4,6-diones **156b-c**, *bis*-thienyldiketopyrrolo [3,4-*c*]pyrrole **156d**, 2,2'-bithiophene **156e**) were co-polymerized with suitable (hetero)aryl dibromides in a biphasic water/toluene mixture, using $PdCl_2(PPh_3)_2$ (1 mol%), P(*o*-anisyl)$_3$ (4 mol%), K_2CO_3 (40 equiv.) and pivalic acid at 100 °C: the corresponding π-conjugated polymers **P157** were always obtained in good yields (77-98%) and high molecular weights (**Scheme 61**). Their optical and thermal properties for potential optoelectronic applications were studied.

In the same year, Thompson and co-workers reported few example of Palladium-catalyzed direct C-H bond arylation polymerization of 4,7-di(thiophen-2-yl)benzo[*c*][1,2,5]thiadiazole with a *N*-alkylated 2,7-dibromocarbazole, performed in water/toluene or water/THF solvent mixture.[192] More recently, the 4,7-di(thiophen-2-yl)benzo[*c*][1,2,5] thiadiazole monomer was polymerized with 1,4-dibromo2,5-bis[(2-hexyldecyl)oxy]benzene in a toluene/water biphasic medium by Leclerc *et al.*[193]

In 2018, Yu and co-workers described the synthesis of anionic water-soluble poly(3,4-ethylenedioxythiophene)s in high yields and molecular weights by direct arylation polymerization: although most of the studies were performed in DMF as the solvent, looking for a greener synthetic route the polymerization water was also investigated as the solvent, in the presence of TBAB (1 equiv.) and $Pd(OAc)_2$ (5 mol%) at 70 °C.[194] These conditions afforded the corresponding polymer with higher yield (80%) and molecular weight (M_n = 6.4 kg/mol, M_w = 10.8 kg/mol, PDI = 1.69) with respect to those obtained in DMF, probably due to its better solubility in H_2O.

Lai *et al.* reported the use of deionized water as the only solvent for the homo-polymerization via direct arylation of 2-bromo-3-alkylthiophenes functionalized with ionic groups; also in this case, the choice of aqueous conditions is to be attributed to the greater solubility of monomers and polymers, rather than to the need of more sustainable conditions.[123]

The use of aqueous conditions has been less investigated in the direct C-H arylation reactions of bicyclic *S*-heteroarenes. A tandem Suzuki-Miyaura/direct arylation of benzo[*b*]thiophene in a 1,4-dioxane/water mixture was used by Štefane *et al.* for the synthesis of biologically active nitroxoline analogues.[141] More appealing from a sustainability point of view was instead the study of Beverina *et al.*, who described a protocol for the direct C-H bond arylation of thieno[3,2-*b*]thiophene with aryl bromides under the micellar catalysis approach, performed in Kollifor 2% in H_2O/toluene (9:1 v/v) mixture as a solvent.[131]

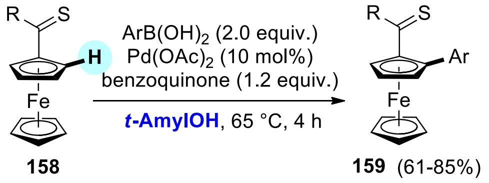
3.2. Direct C-H bond arylation of (hetero)arenes in alcohols

Alcohols have recently found extended application as solvents (or co-solvents) in direct C-H arylation reactions of (hetero)arenes. However, their features in terms of sustainability and environmental impact depends on their structure. Methanol, for example, meets very few of these criteria, due to its toxicity and flammability. Ethanol is instead a better choice for *Green Chemistry*, as it is a relatively low-cost solvent and it can be produced by fermenting renewable sources such as sugars, starches and lignocellulosics.[195] Pentan-1-ol and 3-methylbutan-1-ol are biodegradable and they can easily be prepared by fermentation or reduction of 1-valeraldehyde and 3-methylbutyraldehyde.[196] Exposure to small amounts of most alcohols is unlikely to exhibit adverse health effects. Therefore, generally the use of alcohols can be considered as a more sustainable and greener choice of reaction media compared to DMA, NMP and other traditional solvents for direct C-H arylations of (hetero)arenes.

In this section we report a critical overview of the direct C-H arylation of (hetero)arenes protocols involving the use of alcohols as the reaction medium, describing advantages and limitations in terms of sustainability associated with their use.

3.2.1. Direct C-H bond arylation of arenes in alcohols. In 2010, Guchhait *et al.* reported an highly sustainable protocol for the oxidative direct C-H arylation of several (hetero)arenes, including benzene, with several (hetero)aryl boronic acids as arylating agents: reactions were performed with $Mn(OAc)_3$ as a single-electron-transfer oxidant, under microwave irradiation and in the presence of ethanol as the solvent.[197] The choice of ethanol is the result of a quite extensive solvent screening: in addition to benefiting the sustainability of the method, its use perfectly fits with the oxidant reactivity.

More recently, You and co-workers described the application of *t*-amyl alcohol as an effective reaction medium for the thioketone chelation-assisted oxidative direct C-H arylation of ferrocene **158** with aryl boronic acids, using $Pd(OAc)_2$ as catalyst and benzoquinone as sacrificial oxidant, affording aryl-substituted thiocarbonylferrocenes **159** in high yields.[198] The use of *t*-amyl alcohol, in combination with mild and base-free conditions, enabled the development of an environmental friendly synthetic protocol, which is of significant interest in the context of the Green Chemistry (**Scheme 62**).



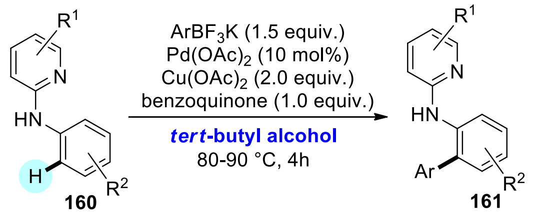
R = *t*-Bu, 1,1-dimethylpropyl, adamantyl
Ar = Ph, *p*-MeC_6H_4, *p*-$OMeC_6H_4$, *p*-FC_6H_4, *p*-ClC_6H_4, *p*-BrC_6H_4, *p*-CNC_6H_4, *p*-$COOEtC_6H_4$, *p*-$NO_2C_6H_4$, *m*-MeC_6H_4, *m*-ClC_6H_4, *o*-MeC_6H_4, 1-naphthyl, 2-naphthyl

Scheme 62. Oxidative direct C-H arylation of thiocarbonylferrocenes **158** with aryl boronic acids in *t*-amyl alcohol as the solvent, developed in 2018 by You and co-workers.[198]

The direct C-H *ortho*-arylation of substituted benzenes performed in alcohols as a solvent has been more extensively investigated in organic synthesis. To the best of our knowledge, the first example was reported in 1984 by Opalko *et al.*: in fact, 1-butanol was used in several tests of intramolecular direct C-H arylation of 2-iodobenzophenone, performed with $Pd(OAc)_2$ as catalyst, to give fluorenone as the main product.[199] However, in the same study most intramolecular reactions on other substrates were instead performed in DMA. This work was reported here only for the sake of completeness, since it is important only from an historical point of view.In fact, a real interest in the use of alcohols as sustainable solvents, and in particular for the direct C-H bond arylation of arenes, has gained a significant relevance only in the past decade.

The use of alcohols as a reaction medium for direct C-H bond arylation is often associated to the development of photocatalytic processes. In this frame, in 2011 Sanford and co-workers reported the use of MeOH as reaction medium for Palladium-catalyzed direct *ortho*-arylation of 2-phenylpyridine, 1-phenylpyrrolidin-2-one and other related arenes with aryldiazonium salts, performed at room temperature and under irradiation with visible light (26 W lightbulb), in the presence of a Ru species as photo-co-catalyst.[200] A very similar photocatalytic protocol, based on the same experimental conditions (including the use of MeOH as solvent), was extended more recently by Guo *et al.* to 6-arylpurine nucleosides: the direct C-H arylation occurred selectively on the *ortho*-position of the arene ring, affording mono-arylated products in good yields.[201] Methanol was also the solvent of choice for a photochemical direct *ortho*-arylation of anilides, performed under 3W green LED irradiation in the presence of eosin-Y as photocatalytic species; this last protocol was even more appealing since it used an organocatalyst (*i.e.*, eosin Y), whose interest in the context of *Green Chemistry* is mainly related to their easier removal from the crude product compared to metal traces (arising from more common transition metal catalysts).[202] However, it is worth to emphasize that the most important feature in these three works was the development of a photochemical process involving a non conventional energy source, rather than the use of an alcohol as the solvent (for more details, see section 4.1.1).

Although only in one case, methanol was also used as the solvent for a non-photocatalytic processes: a tandem oxidative direct C-H bond arylation/direct N-H arylation of *N*-methyl arylamides with arylboronic acids catalysed by a dinuclear Pd(II) benzhydrazone complex for the synthesis of phenanthridinone scaffolds.[203] Actually, in our opinion this protocol does not seem of particular convenience: the homogeneous Pd catalyst, used with 1 mol% of loading, needs to be *ad hoc* synthesized (it is not commercially available) and cannot be recycled; moreover, the use of boronic acids as arylating agents is not a particularly convenient choice from a *Green Chemistry* perspective.

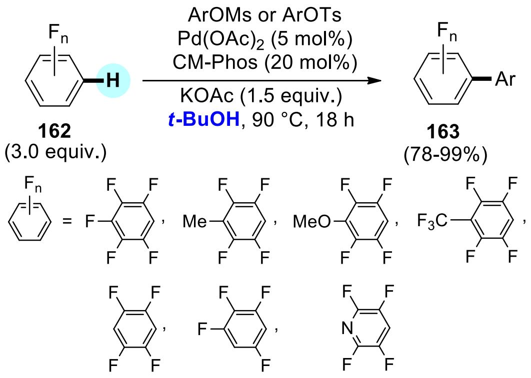


R^1 = H, 3-OMe, 3-Me, 3-NO_2, 4-OMe, 4-Me, 4-NO_2, 5-OMe, 5-Me, 6-OMe, 6-Me
R^2 = H, 4-F, 4-Cl, 4-Br, 4-NO_2, 2-OMe, 3-OMe, 4-OMe, 4-Me
Ar = Ph, *p*-FC_6H_4, *p*-ClC_6H_4, *p*-BrC_6H_4, *p*-IC_6H_4, *p*-MeC_6H_4, *p*-$OMeC_6H_4$, *p*-t-BuC_6H_4, *p*-$CHOC_6H_4$, *m*-$OMeC_6H_4$, *m*-$NO_2C_6H_4$

Scheme 63. Direct C-H *ortho*-arylation of 4-methyl-*N*-phenylpyridin-2-amine derivatives **160** with potassium aryltrifluoroborate as arylating agents in *t*-butyl alcohol as the solvent.

An interesting study of direct C-H *ortho*-arylations of arenes involving the use of alcohols as solvents was performed in 2014 by Wu and co-workers: 4-methyl-*N*-phenylpyridin-2-amines **160** were treated with potassium aryltrifluoroborate as arylating agents, in the presence of $Pd(OAc)_2$ (10 mol%) as the catalyst, $Cu(OAc)_2$ (2.0 equiv.) and *para*-benzoquinone (1.0 equiv.) as the oxidant in *t*-butyl alcohol as the solvent, affording the corresponding *ortho*-arylated products **161** from low to excellent yields (**Scheme 63**).[204] Although other less sustainable solvents were also tested in a preliminary screening, *t*-BuOH offered the best performance in terms of yields. The role of *t*-BuOH does not offer simply the possibility of more environmentally friendly experimental conditions, but its involvement in the reaction mechanism is likely.

Interestingly, *t*-butyl alcohol was used also in the Palladium-catalyzed direct C-H *ortho*-arylation reactions of polyfluoroarenes **162**, performed with aryl tosylates and mesylates as alternative arylating agents.[205] These reactions were carried out under relatively mild conditions, that is, $Pd(OAc)_2$ 5 mol%, CM-phos 20 mol%, potassium acetate as base, at 90 °C for 18 h; the corresponding products **163** were obtained in most cases in good yields (**Scheme 64**). It is worth to emphasize that tosylates and mesylates, if from a merely synthetic point of view are attractive because of their higher reactivity compared to the corresponding aryl halides, in the context of the *Green Chemistry* actually showed serious limits, due to their modest atom economy and subsequent production of organic waste as co-products.



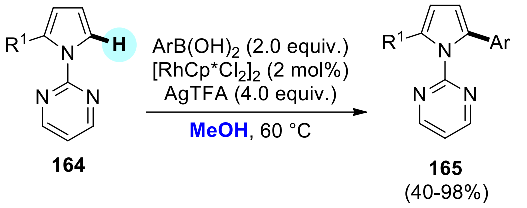
Ar = Ph, p-t-BuC_6H_4, p-$CHOC_6H_4$, p-CNC_6H_4, m-$COMeC_6H_4$, m-$OMeC_6H_4$, m-$NH_2C_6H_4$, p-$COOEtC_6H_4$, p-$COOPhC_6H_4$, 3,5-$Me_2C_6H_3$, 2-naphthyl, 6-quinolinyl

Scheme 64. Pd-catalyzed direct C-H *ortho*-arylation of polyfluoroarenes **162**, performed in *t*-butanol as solvent with aryl tosylates and mesylates as alternative arylating agents.

T-amyl alcohol has also found some applications in the direct C-H *ortho*-arylation of arenes. In 2013, Daugulis *et al.* reported a sustainable *ortho*-diarylation of benzylpicolinamides with aryl iodides, under ligand-free conditions and in the presence of *t*-amyl alcohol as the reaction medium, using $Pd(OAc)_2$ as the catalyst and cesium or silver acetate as the base.[206] In 2021, Hartwig and co-workers described an systematic study of direct C-H *ortho*-arylation of arenes (using $-OCH_3$, $-CF_3$, -Cl and -F as the *ortho*-directing groups) with aryl bromides, performed in *t*-amyl alcohol as reaction medium thanks to the synergistic effect of silver and palladium catalysis (arising from Ag_2O and $Pd(OAc)_2$, respectively).[207] In both cases, the use of *t*-amyl alcohol as a solvent was actually dictated by the need to develop highly efficient and versatile protocols, rather than highly sustainable and environmental friendly ones. This is partially confirmed by the use, in most cases, of a stoichometric amount of silver salts, that generally represent a severe source of metal contamination of the coupling products.

3.2.2. Direct C-H bond arylation of *N*-heteroarenes in alcohols. Once again, *N*-heteroarenes are the most investigated class of substrates for direct C-H bond arylation reactions in alcohols. Among five-membered *N*-heteroarenes, pyrroles were studied in depth. The first preliminary investigation was reported by in 2010 by Guchhait *et al.*, who described a quite sustainable protocol based on the use of EtOH in combination with microwave irradiation for the Palladium-catalyzed oxidative direct arylation of (hetero)arenes, including *N*-methyl pyrrole, with boronic acids as arylating agents.[197]

Peng *et al.* proposed the use of methanol as the reaction medium for Rh-catalyzed oxidative direct C-H arylation coupling of *N*-aryl pyrroles **164** with aryl boronic acids, affording selectively the corresponding α-arylated products **165** (**Scheme 65**).[208] From the synthetic point of view the procedure appears quite interesting, although the need of a very large excess (4.0 equivalents) of silver trifluoroacetate as oxidant represented a major drawback to its real sustainable impact.



R^1 = H, COOEt, COOBn, Ph

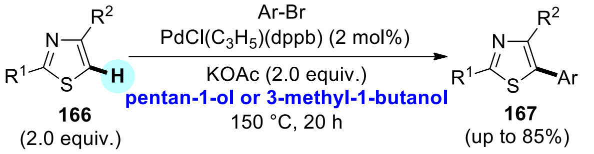
Ar = Ph, p-MeC_6H_4 p-t-BuC_6H_4, p-$OCF_3C_6H_4$, p-PhC_6H_4, p-FC_6H_4, 3,4-$F_2C_6H_3$, 3,5-$(CF_3)_2C_6H_3$, p-$CF_3C_6H_4$, p-ClC_6H_4, p-$NO_2C_6H_4$, p-$COOMeC_6H_4$, p-CNC_6H_4, m-$COMeC_6H_4$,2-naphthyl

Scheme 65. Rh-catalyzed oxidative direct C-H arylation coupling of *N*-aryl pyrroles **164** with aryl boronic acids in MeOH as the solvent, proposed in 2015 by Peng *et al.*[208]

However, more attention to the development of synthetic protocols in line with the principles of *Green Chemistry* was given by the Doucet's research group. In 2014, they reported a systematic study of the impact of reaction medium in the Pd-catalyzed direct C-H arylation reaction of five-membered monocyclic heteroarenes, including *N*-methyl pyrrole, with 4-bromoacetophenone: although toxic DMF and DMA gave the best results, among sustainable solvents 1-pentanol afforded the corresponding α-arylated product with the best conversion by using $Pd(OAc)_2$ as the catalyst and KOAc as the base.[209]

In a following publication, the use of 1-pentanol and 3-methyl-1-butanol as solvents was investigated in combination with recoverable Pd/C catalyst for direct C-H arylations of *N*-methyl pyrrole with several bromoarenes: only slightly lower yields were observed compared to the corresponding reactions in DMA, especially in the case of 3-methyl-1-butanol (see also section 2.1.2).[33] It is clear that the possibility of merging the use of a sustainable reaction medium with a recoverable and cheap catalyst in the same procedure is highly desirable in the context of the *Green Chemistry*, although it is far from trivial.

Moving our attention to other five-membered *N*-heteroarenes, Doucet *et al.* have performed several investigations in the last years. On one hand, not satisfactory results were obtained by using sustainable alcohols as reaction medium in direct C-H arylations of aryl bromides with 1-methylimidazole (< 5% in 3-methyl-1-butanol *vs.* 73-84% in DMA) or 3,5-dimethylisoxazole (10-34% in 3-methyl-1-butanol *vs.* 75-93% in DMA).[33] On the other hand, thiazoles worked very well in both 1-pentanol and 3-methyl-1-butanol: in 2011, they reported a C5-regioselective direct arylation of 2-substituted and 2,4-disubstituted thiazoles **166** with aryl bromides in 1-pentanol or 3-methyl-1-butanol, using $PdCl(C_3H_5)(dppb)$ (2 mol%) as the catalyst and KOAc (2.0 equiv.) as the base at 150 °C, affording the corresponding 5-arylthiazoles **167** in most cases with good yields (**Scheme 66**);[196] more recently, they have developed a more sustainable protocol for the same transformation, by changing $PdCl(C_3H_5)(dppb)$ with recoverable Pd/C, affording the desired C5-arylated coupling products in most cases with high yields (> 85%).[33]



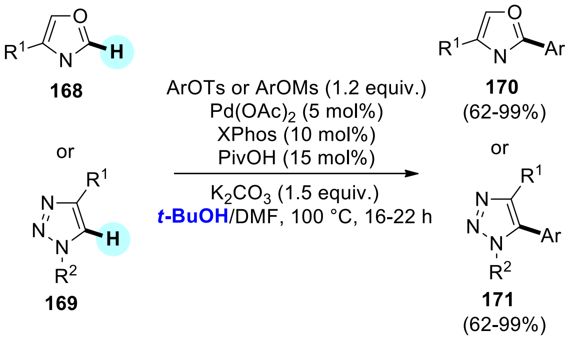
R^1 = n-Pr, Et R^2 = H, Me

Ar = Ph, p-MeC_6H_4, p-$OMeC_6H_4$, p-t-BuC_6H_4, p-FC_6H_4, p-$CF_3C_6H_4$, p-$NO_2C_6H_4$, p-$CHOC_6H_4$, p-$COMeC_6H_4$, p-$COEtC_6H_4$, p-CNC_6H_4, m-$NO_2C_6H_4$, m-$COMeC_6H_4$, m-CNC_6H_4, o-CNC_6H_4, o-$CHOC_6H_4$, o-FC_6H_4, 3,5-$(CF_3)_2C_6H_3$, 2-naphthyl, 3-pyridinyl, 3-quinolinyl, 4-isoquinolinyl, 5-pirimidinyl

Scheme 66. C5-regioselective direct C-H bond arylation of 2-substituted and 2,4-disubstituted thiazoles **166** with aryl bromides in 1-pentanol or 3-methyl-1-butanol as solvent.

Few selected examples of oxidative direct C-H arylation of thiazole with aryl boronic acids in ethanol were also reported by Guchhait *et al.*[197] Despite boronic acids as arylating agents did not represent the best choice in terms of the *Green Chemistry*, the use of ethanol, which is the the result of a quite extensive solvent screening, in combination with the use of microwave irradiation, confirmed a general sustainability for this method.

The only study on direct C-H arylation of pyrazoles involving the use of alcohols as the reaction medium was reported in 2012 by Zhong and co-workers: they proposed a Pd-catalyzed oxidative direct C-H arylation of 1,3,5-trisubstituted pyrazoles with aryl boronic acids, in the presence of $PdCl_2(PPh_3)_2$ (10 mol%) as the catalyst, $NaHCO_3$ (2.0 equiv.) as the base and *N*-iodosuccinimide (1.0 equiv.) as a sacrificial oxidant, in an ethanol/water 3:1 (v/v) mixture, affording good yields (≤ 88%) of the corresponding 4-arylated products, which are fipronil derivatives with a potential biological activity (see section 3.1.2).[145]



R^1 = H, Ph, n-Bu, n-Hex R^2 = Ph, p-$OMeC_6H_4$, m-MeC_6H_4

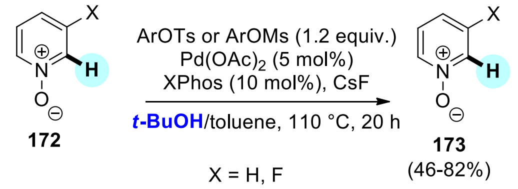
Ar = Ph, p-MeC_6H_4, p-FC_6H_4, 3,5-$(MeO)_2C_6H_3$, 3,4,5-$(MeO)_3C_6H_2$, m-$NMe_2C_6H_4$, p-$COOMeC_6H_4$, 2-naphthyl

Scheme 67. Palladium-catalyzed direct C-H bond arylation of oxazoles **168** and 1,2,3-triazoles **169** in a DMF/*t*-BuOH mixture.

Ackermann *et al.* proposed the use of tosylates and mesylates as arylating agents in Palladium-catalyzed direct C-H arylation of oxazoles **168** and 1,2,3-triazoles **169** in DMF/*t*-BuOH mixture as the solvent.[210] In particular, reactions were carried out with 1.2 equiv. of the arylating agent, $Pd(OAc)_2$ (5 mol%) as the catalyst, XPhos (10 mol%) as the ligand, pivalic acid (15 mol%) as an additive, K_2CO_3 (1.5 equiv.) as base, at 100 °C for 16-22 h, affording the corresponding 2-aryl oxazoles **170** and 4-aryl triazoles **171** in good yields (**Scheme 67**). In this work the use of *t*-BuOH as co-solvent is attributable to the observed good performances with tosylates, rather than to the need of sustainable conditions. Moreover, it is worth to emphasize that tosylates and mesylates, if from the synthetic point of view are attractive due to their higher reactivity compared to aryl halides, in the context of *Green Chemistry* actually showed serious limits, due to their modest atom economy and subsequent production of organic waste as co-products.

Few studies were instead reported relevant to direct arylation of other six-membered *N*-heteroarenes. In 2005, Sames *et al.* have reported the C2 regioselective phenylation of pyridine with iodobenzene catalyzed by a phosphido-bridged ruthenium dimer complex using *t*-butanol as the solvent.[211] The protocol appears in our opinion highly interesting from a synthetic point of view, but its real impact in the frame of sustainable chemistry actually seems to be quite low: in fact, the ruthenium catalyst is not commercially available (and therefore need to be synthesized by a quite expensive preparation), and reactions were carried out under quite harsh experimental conditions (150 °C of thermal heating for 17 h).

A mixture toluene/*t*-BuOH was chosen by Ackermann and co-worker for the direct C-H arylation of pyridine *N*-oxides **172** with aryl tosylates and mesylates.[212] In particular, the reaction conditions involved the use of $Pd(OAc)_2$ (5 mol%) as the catalyst, XPhos (10 mol%) as the ligand, CsF as the base, at 110 °C for 20 h, affording with high C2 regioselectivity the corresponding arylpyridine *N*-oxides **173** in 46-82% yields (**Scheme 68**).



Ar = Ph, p-MeC_6H_4, p-FC_6H_4, p-$MeOC_6H_4$, p-n-$PentC_6H_4$, p-t-BuC_6H_4, m-MeC_6H_4, m-$OMeC_6H_4$, m-$CF_3C_6H_4$, m-$NMe_2C_6H_4$, 3,5-$Me_2C_6H_3$, 3,5-$(MeO)_2C_6H_3$, 3,4,5-$(MeO)_3C_6H_2$, p-$COOMeC_6H_4$, p-$COOEtC_6H_4$, 3,5-$(COOMe)_2C_6H_3$,1-naphthyl, 2-naphthyl, 3-pyridyl

Scheme 68. Palladium-catalyzed direct C-H bond arylation of pyridine *N*-oxides **172** with aryl tosylates and mesylates in a toluene/*t*-BuOH mixture.

More recently, Rueping *et al*. proposed the use of ethanol for the C2 regioselective photocatalytic direct arylation of pyridine with diazonium salts as arylating agents, catalysed by recyclable TiO_2 as the catalyst.[106] In our opinion, the combination of a sustainable solvent with the use of a heterogeneous (and also recoverable) catalyst under a photocatalytic approach is highly desirable in the frame of the *Green Chemistry*.

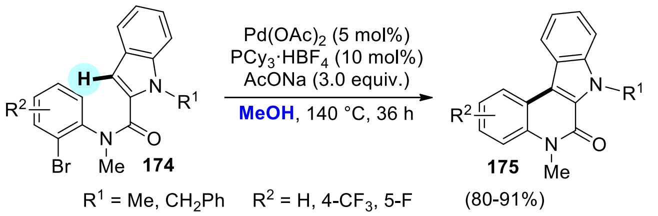
Indoles are definitely the most investigated byciclic *N*-heteroarenes for direct C-H bond arylation reactions in alcohols as reaction medium. The first study was published in 2012 by Correia *et al.*, describing the C2 arylation of *N*-methyl and *N*-Boc indoles with aryldiazonium salts, in the presence of unexpensive $Pd(OAc)_2$ under ligand-free conditions: quite interestingly, if reactions with *N*-methyl indole were performed with a water/diisopropylether mixture, *N*-Boc indole gave the best results in *t*-butanol.[167] Overall, the protocol appeared quite convenient in terms of sustainability, although its main disadvantage is the need of a 15 mol% loading of an homogeneous palladium catalytic species, which could contaminate the final coupling products, requiring tedious purification procedures.

In the same year, Cai and co-worker described the use of a H_2O/ethanol solvent mixture for the C2 regioselective direct C-H arylation of NH-free indoles with aryl iodides.[168] Although the use of a sustainable solvent mixture as the reaction medium is highly desirable, here the use of a high loading of the palladium catalyst (that is, 20 mol%) is a major drawback to the real sustainability of the process.

Methanol was the solvent of choice for both palladium- and rhodium-catalyzed oxidative direct α-arylation of NH-free and *N*-substituted indoles with boronic acids as arylating agents, performed in the presence of, respectively, $K_2S_2O_8$[51] and silver trifluoroacetate[213] as the sacrificial oxidant.

The use of aryliodonium salts as arylating agents typically required the need of ethanol as the reaction medium. McGlacken *et al.* studied the direct C-H arylation reaction of several heterocycles, including NH-free indoles, with aryliodonium salts in the presence of Pd impregnated on magnetite (PdO-Fe_3O_4): as already mentioned in the previous section 2.1.2, if such protocol could appear particularly convenient in terms of environmental sustainability since it was based on the use of an easily removable catalyst, *i.e.* by simply employing a magnet, in combination with ethanol as a solvent, on the other hand the complete deactivation of PdO-Fe_3O_4 after the first run, together with the low atom economy of aryliodonium salts, is actually quite detrimental and limited its real interest in the contex of the *Green Chemistry*.

In 2016, Fairlamb and co-workers reported a comparative investigation of four different Pd catalysts (homogeneous $Pd_2(dba)_3$ and $Pd(OAc)_2$ and supported Pd/C and PVP-Pd) in the model reaction of *N*-methylindole with diphenyliodonium tetrafluoroborate, performed in ethanol as the solvent.[46] A very interesting work was reported more recently by Jia *et al.*: a Pd-catalyzed intramolecular direct C3 arylation of 2-substituted indoles **174** was found, working in methanol as the solvent and in the presence of $Pd(OAc)_2$ as the catalyst (5 mol%), $PCy_3 \cdot HBF_4$ as the ligand (10 mol%) and sodium acetate as the base (3.0 equiv.), affording the corresponding [2,3-*b*]quinolinones products **175** in good yields (**Scheme 69**).[214] The procedure is quite appealing, since it allowed the synthesis of highly functionalized tetracyclicj scaffolds, but the need of high temperature (140 °C) for prolonged reaction times is a clear limit to its sustainability.



Scheme 69. Pd-catalyzed intramolecular direct C3 arylation of 2-substituted indoles **174** developed in 2017 by Jia *et al.*,[214] working in methanol as the solvent.

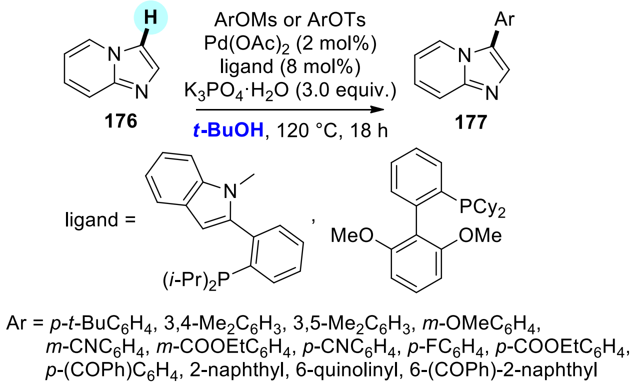
A couple of papers describing the direct C-H arylation of benzoxazoles in alcohols have been reported. In 2009, Ackermann *et al.* proposed the use of tosylates and mesylates as arylating agents in Pd-catalyzed direct C-H arylation of benzoxazoles in DMF/*t*-BuOH mixture.[210] More in detail, they used $Pd(OAc)_2$ (5 mol%) as the catalyst, XPhos (10 mol%) as the ligand, pivalic acid (15 mol%) as additive, K_2CO_3 (1.5 equiv.) as base, working at 100 °C for 16-22 h.Actually, the use of *t*-BuOH as co-solvent was attributable to its good performance in the presence of tosylates and mesylates, rather than to a real need of sustainability. Moreover, we already pointed out in several part of this review that tosylates and mesylates, despite the higher reactivity with respect to aryl halides, showed a quite modest atom economy and a significant production of organic waste as co-products. In a similar way, Kwong *et al.* used the same solvent mixture for the C2 regioselective arylation of benzoxazoles with aryl mesylates.[215] In this work, authors were actually interested in achieving high yields, rather than obtaining a fully sustainable protocol: the use of *t*-butanol as the co-solvent is mainly attributable to its good performance with these non-conventional arylating agents.

In the context of a more extended study of oxidative direct C-H bond arylations of heteroarenes with aryl boronic acids in ethanol as a solvent, Guchhait *et al.* reported few examples of coupling between benzothiazole and phenylboronic acid: despite boronic acids did not represent the best choice as arylating agents, their protocol is very effective in terms of *Green Chemistry*, also due to the use of microwave irradiation as a non-conventional energy source.[197]

Other bicyclic and polycyclic *N*-heteroarenes were investigated as starting reagents in the context of direct C-H arylation reactions in alcoholic reaction medium. In 2011, Ackermann *et al.* reported the application of a direct C-H bond arylation protocol to quinoline and quinoxaline *N*-oxides with aryl tosylates, performed with the help of *t*-butanol as co-solvent.[212] In particular, reaction conditions involved the use of $Pd(OAc)_2$ (5 mol%) as the catalyst, XPhos (10 mol%) as the ligand, CsF as the base, although a prolonged thermal heating (110 °C for 20 h) was required for achieving high yields.

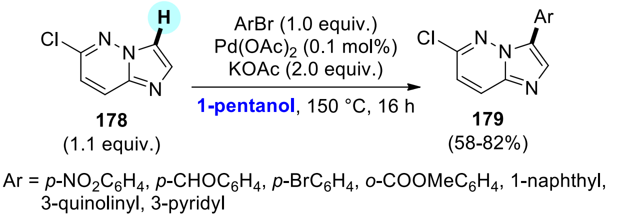
More recently, in the context of the synthesis of the biologically active isoquinoline alkaloids menisporphine and daurioxoisoporphine C, Lei and co-workers reported the photoredox direct C-H bond arylation of isoquinoline with aryldiazonium salts, performed in MeOH at room temperature under 40 W lightbulb, with $[Ru(bpy)_3]Cl_2 \cdot 6H_2O$ as a photocatalyst and CF_3COOH (able to protonate the heterocycle and increase its reactivity).[216] As already mentioned above for other similar protocols, the combination of a sustainable solvent with the use of arylating agents able of preventing organic waste and of a photocatalytic process is highly desirable in the field of the *Green Chemistry*.

The Kwong's research group have reported the C3-regioselective direct C-H arylation of imidazo[1,2-*a*]pyridine **176** with aryl tosylates and mesylates; in this case the reactions were performed in *t*-butanol as the only solvent: working with $Pd(OAc)_2$ as the catalyst, SPhos or 2-(2-(diisopropylphosphino)phenyl)-1-methyl-1*H*-indole as the ligand and $K_3PO_4 \cdot H_2O$ as the base, the monoarylated products **177** were obtained in yields up to 88% (**Scheme 70**).[217]



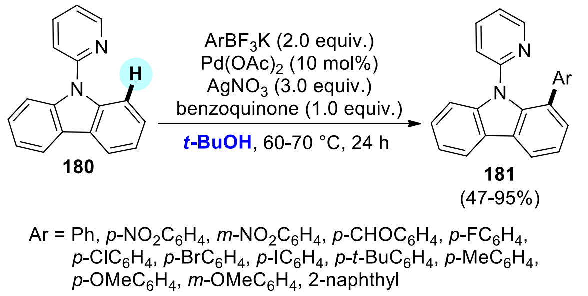
Scheme 70. C3-regioselective direct C-H bond arylation of imidazo[1,2-*a*]pyridine **176** with aryl tosylates and mesylates performed in *t*-butanol as the solvent, reported by Kwong *et al.*[217]

Doucet and co-workers have studied more sustainable experimental conditions for the direct C-H arylation of imidazo[1,2-*a*]pyridines and imidazo[1,2-*a*]pyridazines. In 2016, they studied the use of 1-pentanol as the medium for the reaction of 6-chloroimidazo[1,2-*a*]pyridazine **178** with aryl bromides, carried out with $Pd(OAc)_2$ (0.1 mol%) as the catalyst and potassium acetate (2.0 equiv.) as the base, under ligandless conditions, at 150 °C for 16 h; interestingly, using these conditions the C-Cl bond of imidazo[1,2-*a*]pyridazine does not react, making possible the arylation at C3 position with high regioselectivity to give products **179** in high yields (**Scheme 71**).[218] In a following study, they used 3-methyl-1-butanol as sustainable solvent, in combination with Pd/C as recoverable catalyst, for the direct C-H bond arylation reactions of the same imidazo[1,2-*a*]pyridazine scaffold.[33]



Scheme 71. C3 regioselective direct C-H bond arylation of 6-chloroimidazo[1,2-*a*]pyridazine **178** with aryl bromides in 1-pentanol, reported in 2016 by Doucet and co-workers.[218]

Finally, Wu *et al.* have described the use of *t*-butanol as a solvent in the synthesis of *ortho*-arylated 9-(pyridin-2-yl)-9*H*-carbazoles **181** by direct arylation of 9-(pyridin-2-yl)-9*H*-carbazoles **180** with aryltrifluoroborates (2.0 equiv.) as arylating agents, carried out with $Pd(OAc)_2$ (10 mol%), $AgNO_3$ (3.0 equiv.) and benzoquinone (1.0 equiv.), at 60-70 °C for 24 h (**Scheme 72**).[219] This *ortho*-arylation strategy, based on the presence of a pyridine moiety as directing group at the position 9 of the carbazole scaffold, is highly interesting from a synthetic point of view, but on the other hand it is actually associated to several limitation in the frame of *Green Chemistry*, in particular the need of a high palladium loading and a large amounts of a silver salts, which could contaminate the coupling products.



Scheme 72. Direct *ortho*-arylation of 9-(pyridin-2-yl)-9*H*-carbazoles **180** in *t*-butanol, reported in 2013 by Wu *et al.*[219]

3.2.3. Direct C-H bond arylation of *O*-heteroarenes in alcohols. The first report of direct C-H bond arylation of *O*-heteroarenes in alcohols was described in 2010 by Guchhait and co-workers: in their extensive work on oxidative direct C-H arylation of heteroarenes with aryl boronic acids, performed in ethanol as a solvent under microwave irradiation, a few examples of reactions of furan and benzofuran with phenylboronic acid were also reported.[197] Although their protocol was not developed in the frame of the *Green Chemistry*, the use of EtOH in combination with microwave was definitely an element of high sustainability in this method.

In 2012, Correia *et al.* used MeOH as solvent for the C2-regioselective direct arylation of benzofuran with aryldiazonium salts: interestingly, in most cases reactions were carried out under very mild and convenient experimental conditions, *i.e.*, at room temperature up to 120 minutes, giving 2-arylbenzofurans from modest to good yields (33-67%).[167] The development of direct C-H arylation protocols at room temperarure is far from trivial, as there reactions are typically characterized by high energy requirements; therefore, in our opinion this approach is quite appealing in the general context of sustainable synthetic protocols.

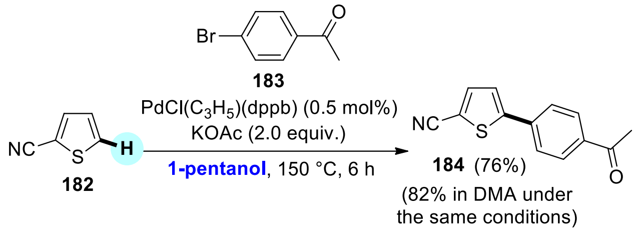
Recently, more sustainable conditions were investigated. Rueping *et al.* proposed the use of EtOH for the C2 regioselective direct arylation of furan with aryldiazonium salts under photocatalytic conditions, in the presence of recyclable TiO_2 as catalyst under irradiation with an 11 W lamp.[106] In 2016, McGlacken *et al.* described the C2 regioselective direct arylation of benzofurans with diaryliodonium salts, performed in EtOH using Pd impregnated on magnetite as easily removable catalyst.[24] In the same year, ethanol was also chosen by Fairlamb *et al.* as a solvent in a comparative kinetic study of different Palladium catalysts (including recoverable Pd/C and PVP-Pd) in the model direct C-H arylations of 2-*n*-butylfuran and benzofuran with diphenyliodonium tetrafluoroborate.[46] In all the above mentioned studies, the possibility of combining the use of ethanol as a solvent with a supported metal catalyst or with a non-conventional energy source makes them very attractive in view of the *Green Chemistry*.

It is worth to emphasize that the Doucet's research group studied in detail the possibility of using other greener alcohols (*i.e.*, 1-pentanol and 3-methyl-1-butanol) as solvents in the direct C-H arylation reactions of furans and benzofurans with aryl bromides, although they always showed modest results compared to DMA, NMP and DMF.[33,209]

3.2.4. Direct C-H bond arylation of *S*-heteroarenes in alcohols. Although thiophene substrates are highly investigated in the context of direct C-H bond arylation reactions, only a few studies involving the use of alcohols as solvents were reported, treated as a part of more extended studies including several heteroarenes as substrates.

The use of EtOH was reported: i) for the microwave irradiation-assisted oxidative direct C-H bond arylation with phenylboronic acid as arylating agent, which afforded 2-phenylthiophenes with high regioselectivity;[197] ii) for the C3 regioselective direct C-H arylation with diphenyliodonium tetrafluoroborate, performed in combination with Pd impregnated on magnetite as recoverable and reusable catalyst,[24] or alternatively by comparing performances of various homogeneous and heterogeneous Pd catalysts;[46] iii) for a TiO_2-catalyzed photocatalytic C2-regioselective direct C-H bond arylation with aryldiazonium salts as arylating agents, under irradiation with an 11 W lamp.[106] In these three works, the use of ethanol was coupled with the application of a non-conventional energy source (microwave irradiation or photochemical processes) or the use of a supported metal catalyst, thus improving their general interest as a sustainable synthetic method for the synthesis of (hetero)arylated thiophene scaffolds.

1-Pentanol was used by the Doucet's group in the reaction of thiophene 2-carbonitrile **182** with 4-bromoacetophenone **183** under different experimental conditions: the best performances were obtained with $PdCl(C_3H_5)(dppb)$ (0.5 mol%) as the catalyst and KOAc (2.0 equiv.) as the base at 150 °C, affording the corresponding product **184** with a yield (76%) similar to that obtained by using traditional DMA (**Scheme 73**).[209]



Scheme 73. Direct C-H arylation of thiophene 2-carbonitrile **182** with 4-bromoacetophenone **183** performed in 1-pentanol by by the Doucet's group.[209]

In 2018, they also showed that 3-methyl-1-butanol was in general less effective than other more traditional solvents in the reaction of 2-substituted thiophenes (bearing both electron-poor and electron-rich functionalities) with *para*- and *ortho*-functionalized aryl bromides.[33]

Aryldiazonium tetrafluoroborates were successfully used as arylating agents in the C3-regioselective direct arylation of benzo[*b*]thiophenes, performed in methanol in the presence of $Pd(OAc)_2$ only (*i.e.*, under ligand-free and base-free conditions),[167] or in ethanol by using PdO-Fe_3O_4 as an easily removable catalyst.[24] As already pointed out in other part of this section, ethanol is typically compatible with diazonium salts as arylating agents: this is very favourable from a sustainability point of view, since these compounds fit very well with several principles of the *Green Chemistry*, in particular in terms of atom economy and waste prevention. In particular, the study involving PdO-Fe_3O_4 is even more interesting since all these features were further combined with the use of a easily recoverable catalyst (although hardly recyclable due to a substantial changes of both Pd particle distribution and size, as above described in the section 2.1.4).

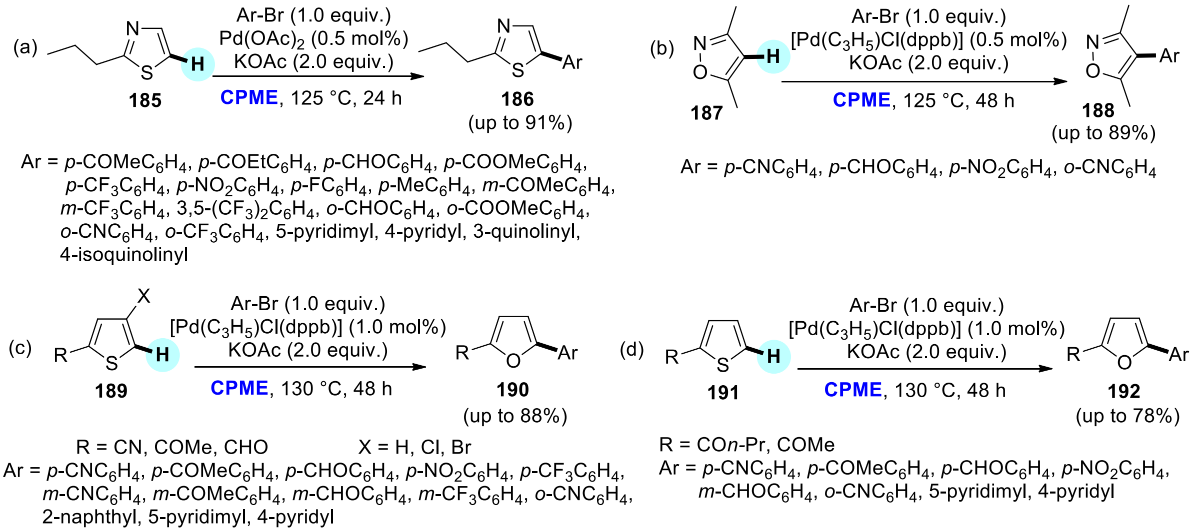
3.3. Direct C-H bond arylation of (hetero)arenes in biomass-derived solvents

Biomass-derived solvents represent a more recent and very appealing alternative as sustainable and environmental friendly reaction media: these materials are easily available (typically on a large scale) from renewable feedstocks, including agricultural and urban wastes and aquatic biomasses, and in most cases are characterized by low toxicity and high biodegradability. These solvents perfectly fits with the Twelve Principles of *Green Chemistry*.

In the context of direct C-H arylation of (hetero)arenes, their use is still quite limited, especially if compared to other sustainable reaction media such as water and alcohols, but it has been growing in recent years. In this section, we give an overview on the use of cyclopentyl methyl ether (CPME), diethyl carbonate (DEC) and other similar organic carbonates, 2-methyltetrahydrofuran (2-MeTHF), γ-valerolactone (GVL) and polyethylene glycol (PEG) in these transformations, highlighting advantages and limitations in terms of sustainability associated with their use.

3.3.1. Direct C-H bond arylation of (hetero)arenes in cyclopentyl methyl ether. The use of CPME as eco-friendly solvent in organic synthesis has grown in the last decade. In fact, CPME shows several advantages, including high boiling point (106 °C), low miscibility in water, modest peroxide formation rate (especially if compared with other ethers such as diisopropyl ether or THF), high chemical stability under both acid and basic conditions, and in particular low toxicity and narrow explosion range.[220] Although in most cases CPME is still produced by petrochemical industry, several biomass-based routes have been recently developed from cyclopentanone or cyclopentanol, which can be easily synthetized from furfural, a typical derivative of pentose saccharides.[221] For all these reasons, CPME is highly desirable as solvent for organic transformations, including direct C-H bond arylation reactions of (hetero)arenes.

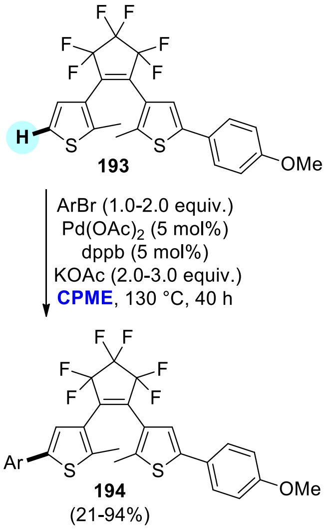
The Doucet's research group has investigated in depth the application of CPME as solvent in direct C-H bond arylation. Their first investigation was reported in 2011, describing an extended study of direct arylation of several heteroarenes with aryl bromides, focusing in particular on 2-*n*-propylthiazole **185**, 3,5-dimethylisoxazole **187**, 2-substituted thiophenes **189** and 2-substituted furans **191**.[222] For each heteroarene, the working conditions were finely optimized: a) reactions of 2-*n*-propylthiazole **185** were performed in most cases with $Pd(OAc)_2$ (0.5 mol%) and KOAc (2.0 equiv.), in CPME at 125 °C for 24 h, affording the corresponding 5-arylation products **186** (**Scheme 74a**); b) with 3,5-dimethylisoxazole **187**, reactions were typically performed with $[Pd(C_3H_5)Cl(dppb)]$ (0.5 mol%) and KOAc (2.0 equiv.), in CPME at 125 °C for 48 h, giving the 4-arylated



Scheme 74. Studies of Doucet *et al.* on the application of CPME as sustainable solvent in direct C-H bond arylation of different classes of heteroarenes: (a) 2-*n*-propylthiazole **185**; (b) 3,5-dimethylisoxazole **187**; (c) 2-substituted thiophenes **189**; (d) 2-substituted furans **191**.

products **188** (**Scheme 74b**); c) finally, direct C-H bond arylation reactions of 2-substituted thiophenes **189** and furans **191** were carried out using [Pd(C_3H_5)Cl(dppb)] (1.0 mol%) and KOAc (2.0 equiv.), in CPME at 130 °C for 48 h, affording the corresponding α-arylated products **190** and **192**, respectively (**Scheme 74c-d**). In this study, the use of CPME was found advantageous with respect to traditional DMA and DMF solvents: in all cases the reactions were performed with low amounts of the Pd catalyst, proceeding in moderate to high yields.

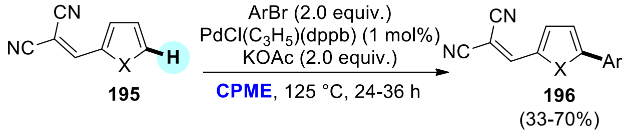
In two following papers published in 2012, Doucet *et al.* extended the use of CPME as sustainable solvent for the Pd-catalyzed direct arylation of other substrates. On one hand, dithienylperfluorocyclopentene (DTE) derivatives **193** were treated with several aryl bromides in the presence of Pd(OAc)$_2$ as the catalyst, dppb as the ligand and KOAc as the base, affording the corresponding arylated products **194** (**Scheme 75**).[223] On the other, the direct arylation reactions of *N*-methyl pyrrole, furan and thiophene bearing dicyanovinyl units at C2 position **195** were carried out with aryl bromides using [Pd(C_3H_5)Cl(dppb)] and potassium acetate, to give the corresponding 5-arylated products **196** (**Scheme 76**).[224] In both these studies, the nature of the solvent was crucial: by attempting such arylations in DMA, a complete decomposition of the starting substrates was observed, whereas they were found perfectly stable by using CPME. These results well highlithed that CPME was an appealing reaction medium in the context of direct C-H arylation not simply from a sustainability point of view, but more importantly also in assisting the reaction mechanism.



Ar = *p*-CNC$_6$H$_4$, *p*-NO$_2$C$_6$H$_4$, *p*-CHOC$_6$H$_4$, *p*-COMeC$_6$H$_4$, *p*-COOMeC$_6$H$_4$, *m*-NO$_2$C$_6$H$_4$, *o*-CNC$_6$H$_4$, 2-naphthyl, 3-pyridyl, 4-pyridyl hydrocloride, 3-quinolinyl, 5-pyrimidyl, 4-isoquinolinyl

Scheme 75. Direct C-H bond arylation of dithienylperfluorocyclopentene (DTE) derivatives **193** with aryl bromides, described in 2012 by Doucet *et al.*[223]

In 2014, in a comparative study of solvent and concentration effects in direct C-H bond arylation reactions, they described the direct coupling of 1-methylpyrrole, ethyl 2-methylfuran-3-carboxylate and thiophene 2-carbonitrile with 4-bromo acetophenone, using [Pd(C_3H_5)Cl(dppb)] as homogeneous catalyst and potassium acetate as the base.[209] Despite the use of a environmental friendly solvent, in this specific study Doucet and co-workers were mainly focused on the investigation of solvent and concentration effects, rather than to the concrete development of a sustainable synthetic protocol with broad applicability.



X = S, O, NMe

Ar = *p*-CNC$_6$H$_4$, *p*-CF$_3$C$_6$H$_4$, *p*-COMeC$_6$H$_4$, *p*-COOEtC$_6$H$_4$, *m*-CF$_3$C$_6$H$_4$, *m*-CNC$_6$H$_4$, *o*-CNC$_6$H$_4$, 3,5-(CF$_3$)$_2$C$_6$H$_3$, *o*-CF$_3$C$_6$H$_4$, 4-NO$_2$-CF$_3$C$_6$H$_3$

Scheme 76. Direct C-H bond arylation of *N*-methyl pyrrole, furan and thiophene derivatives **195** with aryl bromides performed in CPME as solvent.

In 2015, they reported the Pd-catalyzed reaction of pyrroles, indoles, furans, benzofurans and thiophenes with benzenesulfonyl chlorides as eco-friendly and very sustainable arylating agents, working through a desulfitative cross-coupling.[225] This study was definitely more appealing from the point of view of the *Green Chemistry*: in fact, the use of CPME as a sustainable solvent was here coupled with arylating agents highly convenient in terms of broad availability, easy handling and prevention of waste, thanks to the generation of SO$_2$ as by-product which moves away from the reaction mixture as a gas.

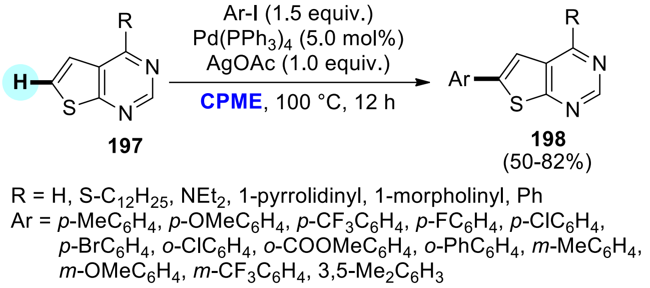
In 2016, Doucet *et al.* reported the use of CPME in comparative study with other sustainable solvents for the direct arylation of imidazo[1,2-*b*]pyridazine with 4-bromobenzonitrile, performed with Pd(OAc)$_2$ (0.05 mol%) as the catalyst and KOAc (2.0 equiv.) as the base; this kinetic study actually showed that the reaction in CPME was the slowest, albeit it was complete after only 2 h.[218]

More interesting was instead a following study reported in 2017: in this case, the Doucet's group reported a C3 regioselective direct C-H bond arylation of 2*H*-indazoles with aryl bromides, carried out under ligand-free conditions with a low loading (0.1-0.5 mol%) of Pd(OAc)$_2$ as the catalyst and KOAc as the base; although DMA was used in most of these reactions, some examples with CPE were also reported, demonstrating to be a suitable alternative to DMA.[226]

Finally, in 2018 an extended study of direct C-H bond arylation reaction of heteroarenes with aryl bromides, performed in many sustainable solvents (including CPME) in combination with the presence of Pd/C as recoverable and reusable catalyst, was reported by the same authors in order to develop highly eco-friendly protocols for direct C-H bond arylations (for more detail see section 2.1.2).[33]

In addition to the significant contribution provided by the Doucet's group, other interesting studies on the use of CPME as a sustainable solvent for direct C-H bond arylation of heteroarenes have been recently reported. In 2020, Itami *et al.* studied the regioselective arylation of thieno[2,3-*d*]pyrimidines **197** at two different positions: interestingly, if the reaction with aryl boronic acids as arylating agents occurred at the C5 position, using aryl iodides the coupling occurred instead at the C6 position.[227] In particular, in this last case the direct C-H bond arylation reactions were performed in CPME as the solvent, using Pd(PPh$_3$)$_4$ (5 mol%) as the catalyst and AgOAc (1.0 equiv.) as the base, at 100 °C for 12 h, to give the corresponding 6-arylated coupling products **198** in good yields and complete regioselectivity (**Scheme 77**).

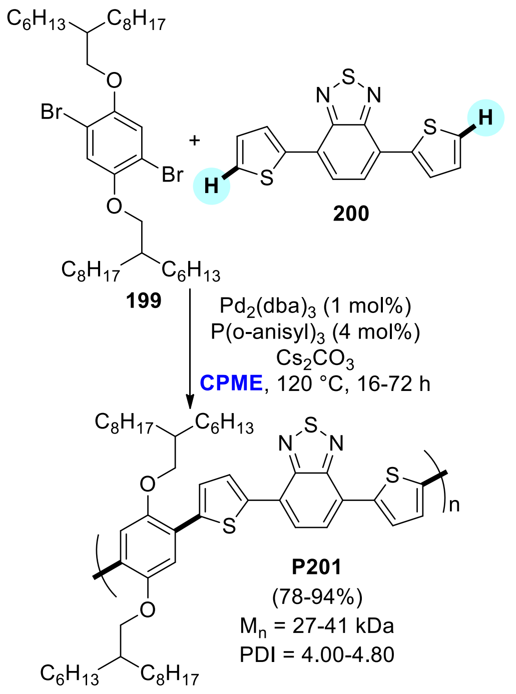
Walsh and co-workers reported the use of CPME as a solvent for the α-arylation and α,α-diarylation of 3-(methylsulfinyl)thiophenes with aryl bromides.[228] However, despite the use of this environmental friendly solvent, the protocol showed several drawbacks limiting the interest in the frame of the Green Chemistry: the need of a high loading of the palladium catalyst (10 mol%) and of quite expensive phosphine ligands, as well as the use of high temperatures for a prolonged time.



Scheme 77. C6 regioselective direct C-H bond arylation of thieno[2,3-d]pyrimidines **197** with aryl iodides in CPME as the solvent, reported in 2020 by Itami *et al.*[227]

Interestingly, CPME has also found some applications as a solvent in polymerization reactions based on direct arylation protocols. A first attempt was described in 2013 by Ozawa *et al.* in the reaction of 2,7-dibromo-9,9-dioctylfluorene with 1,2,4,5-tetrafluorobenzene: although the polymerization in CPME proceeded in high yield (96%), affording the co-polymer in high molecular weight (M_n = 91500) and quite good polydispersity (M_w/M_n = 1.93), authors chose to use THF.[229]

However, the Thompson's group studied in more detail the application of CPME as sustainable reaction medium for direct C-H bond arylation polymerization reactions. In 2018, they discussed about the possibility of using several sustainable solvents, including CPME, for the co-polymerization of 1,4-dibromo-2,5-bis[(2-hexyldecyl)oxy]-benzene **199** and 4,7-di(thiophen-2-yl)benzo[*c*][1,2,5]thiadiazole, **200** with Pd$_2$(dba)$_3$ as the catalytic precursor and P(*o*-anisyl)$_3$ as the ligand: among all the biomass-derived solvents used, CPME gave the best results for the polymer **P201** in terms of yields (78-94%), molecular weights (M_n = 27-41 kDa) and polydispersity (4.00-4.80) (**Scheme 78**).[230]



Scheme 78. Direct C-H arylation polymerization of 1,4-dibromo-2,5-bis[(2-hexyldecyl)oxy]-benzene **199** and 4,7-di(thiophen-2-yl)benzo[*c*][1,2,5]thiadiazole **200** in CPME as the solvent, reported in 2018 by Thompson *et al.*[230]

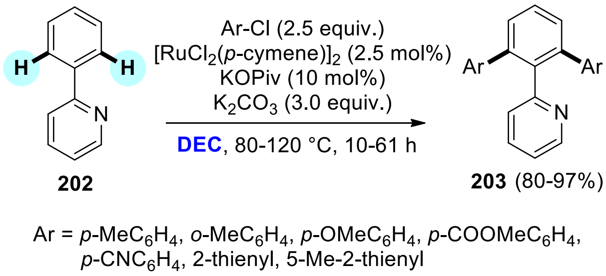
In a following study, CPME was selected as the solvent of choice for the co-polymerization of [2,2'-bithiophene]-4,4'-bis(2-butyloctyl)ester with dibromoheteroarenes, studying the influence of the ester directing groups on branching defect formation.[231] Very recently, Thompson *et al.* also reported the first synthesis of poly(3-alkylamide thiophenes) by direct arylation polymerization in CPME as a solvent, showing M_n up to 15.4 kDa and yields up to 90% ,[232] as well as of other polythiophene derivatives by direct C-H bond arylation polymerization in CPME of thiophene-based monomers bearing suitable ester directing groups, in order to study the inhibition of defect formation.[233]

In 2020, the homo-polymerization of 2-bromo-3-hexylthiophene, as well as the co-polymerization of a *bis*-thienylDPP derivative with dibromoarenes, by direct arylation reactions in CPME as sustainable reaction medium was described by Grisorio *et al.*[234]

3.3.2. Direct C-H bond arylation of (hetero)arenes in organic carbonates.

Organic (in particular dialkyl) carbonates represent one of the main green chemical raw materials of the 21st century, due to their high biodegradability and low toxicity.[235] Therefore, it is not surprising that they are recently used as highly sustainable and environmental friendly reaction media for organic transformation, including direct C-H bond arylation reactions of (hetero)arenes. The industrial synthesis of organic carbonates typically involves the use of carbon dioxide as a reagent, which received high attention in the last decades due to its role as pollutant, thus contributing to its reduction in the environment.[236] In particular, cyclic carbonates can be produced from the reaction of bioethene with carbon dioxide, and for this reason organic carbonates are typically considered bio-based solvents.[237] However, within this family diethyl carbonate (DEC) is the most investigated as a solvent: it is a colourless, transparent liquid with low toxicity; moreover, its bio-accumulation is also low, as it decomposes to CO$_2$ and ethanol when released into the environment.[238]

The first application of an organic carbonate (that is, DEC) in the direct C-H bond arylation reactions of (hetero)arenes was reported in 2009 by Dixneuf *et al.*: the *ortho*-arylation of benzene ring of 2-phenylpyridine **202** with (hetero)aryl chlorides was found, using [RuCl$_2$(*p*-cymene)]$_2$ (2.5 mol%), KOPiv (10 mol%), K$_2$CO$_3$ (3.0 equiv.), affording the corresponding diarylated products **203** in good to excellent yields (**Scheme 79**).[239] The use of aryl chlorides, in combination with DEC as the solvent, was here highly desirable in terms of the *Green Chemistry*:compared to other typical arylating agents, (hetero)aryl chlorides are less expensive and readily available. However, the use of a prolonged thermal heating (up to 61 h) represented an issue, since it demonstrated that such protocol needed of high energy requirements to be efficiently performed.

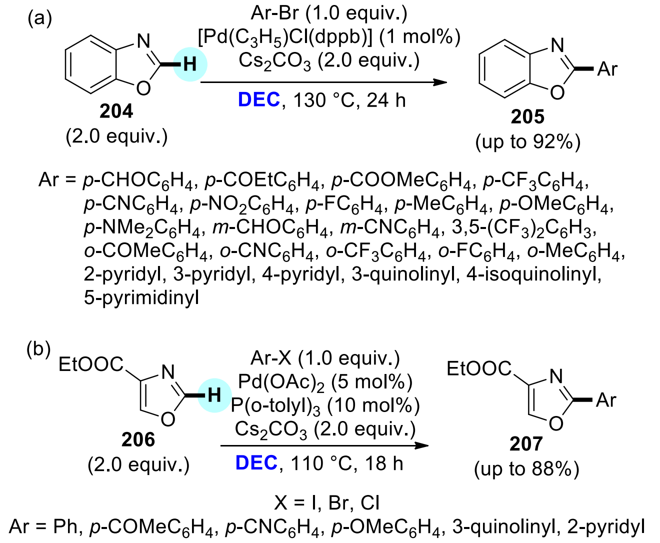


Scheme 79. First application of DEC as solvent in direct C-H arylation of (hetero)arenes: *ortho*-arylation of 2-phenylpyridine **202** with (hetero)aryl chlorides reported by Dixneuf *et al.*[239]

Further applications of carbonates as solvents in direct *ortho*-arylation of arenes were reported only in the last few years. In 2017, Balaraman *et al.* described the photocatalytic direct *ortho*-arylation of anilides with aryldiazonium salts as arylating agents, performed under visible light irradiation in dimethyl carbonate, in the presence of $Pd(OAc)_2$ as the main catalyst and $[Ru(bpy)_3]Cl_2$ as photocatalyst.[240] The use of a highly sustainable solvent, in combination with arylating agents characterized by high atom economy and waste prevention, as well as the application of a photocatalytic process, made this procedure of significant interest from a sustainability point of view.

In 2018, the *ortho*-diarylation of the benzene ring of 1-phenylpyrazoles with aryl triflates, catalyzed by $RuCl_2$(*p*-cymene)$]_2$ and in the presence of KOAc as base, was performed in DEC.[241] From a synthetic point of view this reaction is definitely interesting since it allowed to access to highly functionalized compounds. However, in our opinion its impact in the context of the *Green Chemistry* appeared quite modest: only a limited number of aryl triflates were actually used in DEC, and in these cases a large excess (3.0 equiv.) of them was required, despite their typically higher reactivity in comparison to aryl halides and other arylating agents.

The Doucet's group studied in detail the use of this class of sustainable solvents in the direct C-H bond arylation of (hetero)arenes. In their first work, published almost simultaneously with the above-mentioned work of Dixneuf *et al.*, they proposed the use of DEC as an effective and green alternative to the classic reaction media for direct C-H arylations of benzoxazole **204** and oxazole-4-carboxylate **206** with (hetero)aryl halides.[242] In the case of **204**, reactions were carried out in DEC at 130 °C for 24 h, using $[Pd(C_3H_5)Cl(dppb)]$ (1 mol%) as the catalyst and Cs_2CO_3 (2.0 equiv.) as the base, affording 2-arylated products **205** (**Scheme 80a**); in the case of **206**, direct arylations were instead performed with $Pd(OAc)_2$ (5 mol%), P(*o*-tolyl)$_3$ (10 mol%) and Cs_2CO_3 (2.0 equiv.), at 110 °C for 18 h, to give 2-arylated coupling products **207** (**Scheme 80b**).



Ar = *p*-CHOC$_6$H$_4$, *p*-COEtC$_6$H$_4$, *p*-COOMeC$_6$H$_4$, *p*-CF$_3$C$_6$H$_4$, *p*-CNC$_6$H$_4$, *p*-NO$_2$C$_6$H$_4$, *p*-FC$_6$H$_4$, *p*-MeC$_6$H$_4$, *p*-OMeC$_6$H$_4$, *p*-NMe$_2$C$_6$H$_4$, *m*-CHOC$_6$H$_4$, *m*-CNC$_6$H$_4$, 3,5-(CF$_3$)$_2$C$_6$H$_3$, *o*-COMeC$_6$H$_4$, *o*-CNC$_6$H$_4$, *o*-CF$_3$C$_6$H$_4$, *o*-FC$_6$H$_4$, *o*-MeC$_6$H$_4$, 2-pyridyl, 3-pyridyl, 4-pyridyl, 3-quinolinyl, 4-isoquinolinyl, 5-pyrimidinyl

X = I, Br, Cl

Ar = Ph, *p*-COMeC$_6$H$_4$, *p*-CNC$_6$H$_4$, *p*-OMeC$_6$H$_4$, 3-quinolinyl, 2-pyridyl

Scheme 80. Direct C-H arylations of benzoxazole **204** and oxazole-4-carboxylate **206** with (hetero)aryl halides in DEC as sustainable medium, reported in 2009 by Doucet *et al.*[242]

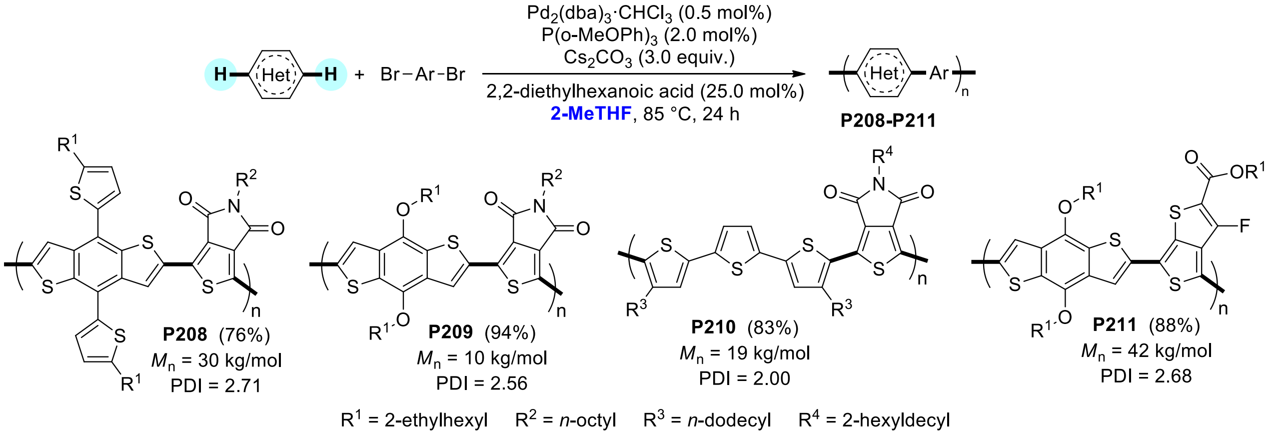
In 2010, they extended the use of DEC and propylene carbonate to other classes of heteroarenes: pyrroles, thiazoles, isoxazoles, furans and thiophenes; interestingly, reactions were performed again with $[Pd(C_3H_5)Cl(dppb)]$ as catalyst, but in the presence of KOAc as base.[243]

In 2015, carbonates were also found as the solvent of choice for desulfitative C-H bond arylation of *N*-substituted pyrroles, *N*-substituted indoles, furans, benzofurans and thiophenes, *i.e.*, based on the use of benzenesulfonyl chlorides as arylating agents.[225] This protocol was of high interest: indeed, sulfonyl chlorides are among the most sustainable arylating agents, due to their waster prevention (with the production of gaseous SO_2 as the only by-product), quite broad availability and easy handling. The use of DEC seems to be highly compatible with this class of arylating agents. Therefore, it should not be surprisingly that in a following study the same group reported the use of this sustainable solvent was also used for the Pd-catalyzed direct desulfitative mono-heteroarylation of benzene-1,3-disulfonyl dichloride: working with $PdCl_2(CH_3CN)_2$ (5 mol%) and Li_2CO_3 (3.0 equiv.), several heteroarenes such as pyrroles, furans, benzofurans, thiophenes and benzothiophenes were used.[244]

The Doucet's research group, in the frame of their extended studies on sustainable experimental conditions for direct C-H bond arylation of heteroarenes, often compared the performance of carbonates with that of other biomass-derived solvents. In 2014, they studied the impact of both solvent and concentration in the direct C-H arylation of *N*-methylpyrrole, 2-methylfuran-3-carboxylate and thiophene 2-carbonitrile with 4-bromoacetophenone: in DEC a complete reagent conversion was only observed with $[Pd(C_3H_5)Cl(dppb)]$ catalyst (0.5 mol%) at a concentration 15 M of heteroarene.[209] In a further study of 2016, the C3 arylation of imidazo[1,2-*b*]pyridazines with aryl bromides and chlorides, catalyzed by $Pd(OAc)_2$, was reported in different green, safe and renewable solvents – including DEC – with no loss of efficiency with respect to more traditional solvent such as DMA or DMF.[218] In order to develop highly sustainable direct C-H arylation protocols, the use of biomass-based solvents was also coupled with recoverable Pd/C; in the specific case of DEC, good performance were obtained in the C5 arylation of thiazole derivatives, whereas low yields were found with other heteroarenes.[33]

3.3.3. Direct C-H bond arylation of (hetero)arenes in 2-methyltetrahydrofuran. The use of 2-MeTHF as a solvent for organic reactions is a promising greener alternative to tetrahydrofuran (THF), since it can be easily produced at industrial scale from furfural and levulinic acid as biomass-derived reagents (more in particular, renewable lignocellulosic biomass).[245] Compared to THF, 2-MeTHF exhibits lower volatility and water miscibility but higher chemical stability (in both acidic and basic conditions), as well as a considerable biodegradability.[246] For all these reasons, 2-MeTHF has recently raised growing interest in the context of direct C-H bond arylation of (hetero)arenes: in particular, it was found to enable very efficiently C-H bond functionalization for rapid, high-conversion polymerizations.

The first example of direct C-H arylation polymerization in 2-MeTHF was reported in 2016 by Sommer *et al.*, who described co-polymerization of 2,2'-bithiophene with a dibromonaphthalene diimide derivative.[247] Under the optimized conditions, direct arylation polymerizations were carried out in 2-MeTHF, using Pd_2(dba-OMe)$_3$ as the catalyst, Na_2CO_3 as the base and pivalic acid as additive, at 90 °C for 20 h, which afforded the final co-polymer in 98% yield and high molecular weight (M_n =19.9 kDa; M_w = 45.3 kDa). The use of 2-MeTHF was here highly desirable in the context of the *Green Chemistry*, but it is worth to emphasize that authors were here interested in the synthesis and characterization of



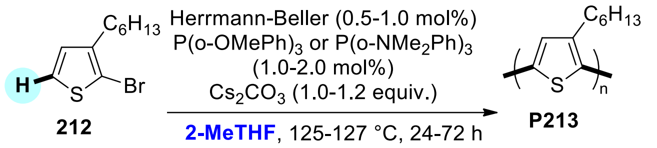
Scheme 81. Direct C-H bond arylation co-polymerization of S-heteroarene-based monomers with suitable dibromoheteroarenes, performed in 2-MeTHF as environmental friendly reaction medium.

the polymeric material, rather than to the real development of a highly sustainable polymerization protocol.

A more extended and general study was performed in the same year by Marks *et al.*: they described the direct arylation co-polymerization of suitable monomers, performed with $Pd_2(dba)_3·CHCl_3$ (0.5 mol%), P(*o*-MeOPh)$_3$ (2.0 mol%), Cs_2CO_3 (3.0 equiv.) and 2,2-diethylhexanoic acid (25.0 mol%), in 2-MeTHF as solvent at 85 °C for 24 h.[248] Interestingly, the resulting co-polymers **P208–P211** were obtained with general features (yield, M_n, polydispersity) always higher than those of the same polymers synthetized by the Stille coupling reaction (**Scheme 81**): in this way, authors demonstrated that the use of direct C-H arylation in 2-MeTHF not only allowed the achievement of more sustainable experimental conditions, but also the production of polymers with better performance, showing in particular high photovoltaic efficiency. In this context, a critical point is represented by structural defects: the presence of polymeric branching arising from the non-regioselective direct C-H arylation of starting monomers may have strong effects on the photovoltaic performance of the material. Therefore, in a recent work they studied in detail how it could be possible to suppress defect formation pathways in the direct C-H arylation polymerization using 2-MeTHF as a reaction medium.[249]

The use of 2-MeTHF as a green and sustainable reaction medium for direct arylation polymerization was also investigated by Thompson *et al.* In 2017, they compared the use of Pd-catalyzed Stille coupling and direct C-H arylation for the preparation of several class of polymers, ranging from simple poly(3-hexylthiophene)s to three-component co-polymers with diketopyrrolopyrrole, 3-hexylthiophene and thiophene units.[250] In this last case, the use of 2-MeTHF as solvent, in combination with neodecanoic acid as additive, was fundamental in order to obtain co-polymers with a very low degree of structural defects. In 2018, the same authors studied the impact of different biomass-derived solvents, including 2Me-THF, in the co-polymerization of 1,4-dibromo-2,5-bis[(2-hexyldecyl)oxy]benzene with 4,7-di(thiophen-2-yl)benzo[*c*][1,2,5] thiadiazole, in the presence of $Pd_2(dba)_3$ (1 mol%) as the catalyst and P(*o*-anisyl)$_3$ (4 mol%) as the ligand.[230]

There also few other recent examples of direct arylation polymerization involving the use of 2Me-THF as a solvent, although these studies were actually not focused on the sustainability of the method (as for the above mentioned investigations of Marks *et al.* and of Thompson *et al.*). In 2018, Pappenfus and co-workers studied the possibility to scale-up (from 0.5 to 10 g) for the direct C-H bond arylation polymerization of 2-bromo-3-hexylthiophene **212** to give poly(3-hexylthiophene) **P213**, performed with the use of Herrmann-Beller catalyst (0.5-1.0 mol%) in combination with a tertiary phosphine (1.0-2.0 mol%) using 2-MeTHF as solvent (**Scheme 82**).[251] In the same year, Ozawa *et al.* described the use of 2-MeTHF as a solvent in representative examples of direct C-H arylation polymerization of 1,2-dithienylethene with dibromoisoindigo derivatives.[252]



Scheme 82. Direct C-H bond arylation polymerization of 2-bromo-3-hexylthiophene **212** to give poly(3-hexylthiophene) **P213** using 2-MeTHF as solvent.

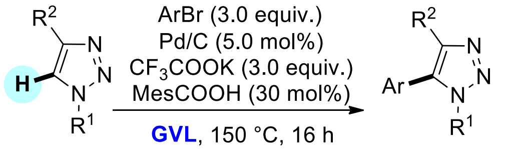
3.3.4. Direct C-H bond arylation of (hetero)arenes in γ-valerolactone.

GVL is generally prepared at the industrial level by hydrogenative cyclization of levulinic acid, which can be obtained from carbohydrates and lignocellulosic biomasses.[253] As for other biomass-derived solvents, GVL is characterized by low volatility and toxicity, high chemical stability at different pH with very low formation of peroxides, as well as good biodegradability.[254] In light of these very appealing features, in the last few years it was used as a sustainable reaction medium for several transition metal-catalyzed reactions,[255] including direct C-H bond arylation of (hetero)arenes.

The first use of GVL as a solvent in direct C-H arylation was described in 2016 by Ackermann and Vaccaro's groups for the Catellani reaction, *i.e.*, a direct C-H *ortho*-arylation of aryl iodides mediated by norbornene, allowing a tandem *ipso*-vinylation via a Mizoroki-Heck-type process; in particular, they developed an highly sustainable process, thanks to the combination of the green GVL solvent with the use of recoverable Pd EnCat™ 30 and Pd/Al_2O_3 catalyst (for more details, see section 2.1.1).[20]

Interestingly, GVL was used by Ackermann *et al.* also for the oxidative direct C-H *ortho*-arylation of benzamides with arylsiloxanes as user-friendly arylating agents: the reactions were carried out with $Co(OAc)_2$ (20 mol%) as the catalyst, CsF (3.0 equiv.) as a fluoride source and CuF_2 (2.0 equiv.) as the oxidant, affording the corresponding mono-arylated products in good yields.[256] Despite the present protocol could appear quite convenient from the point of view of the *Green Chemistry*, in our opinion there are actually some drawbacks: first, the need of very large amounts of both catalyst and oxidant, which definitely representa source of metal contamination of the corresponding coupling products; second, the modest atom economy of the arylsiloxanes, producing significant amounts of siloxane waste that need to be removed by tedious purification procedures.

Ackermann and Vaccaro successfully applied GVL as environmentally-benign solvent to the direct C-H bond arylation of 1,4-disubstituted-1*H*-1,2,3-triazoles **214** with aryl bromides: the reactions were performed with recyclable Pd/C catalyst (5.0 mol%), potassium trifluoroacetate (3.0 equiv.) as the base and 2,4,6-trimethylbenzoic acid (30 mol%) as additive, in GVL at 150 °C for 16 h, affording the corresponding 5-aryltriazoles **215** in good yields (**Scheme 83**).[30] In a following study, the protocol was performed in continuous flow conditions, demonstrating the compatibility of GVL with the facilities of flow chemistry.[31] The possibility of combining highly sustainable experimental conditions with the facilities of flow chemistry make in our opinion this study very appealing in the context of the *Green Chemistry*: in fact, it allowed for an optimal reuse and durability of the catalyst, which combined with the simple purification of the products and the recovery of the solvent made such protocol operationally simple and very efficient in terms of waste minimization and a low E-factor



214 **215** (50-82%)

R^1 = CH_2Ph, *n*-octyl, Ph, *o*-MeC_6H_4, *m*-MeC_6H_4, *p*-$OMeC_6H_4$, *o*-$OMeC_6H_4$, *p*-ClC_6H_4
R^2 = H, *n*-Bu, Ph
Ar = Ph, *o*-MeC_6H_4, *m*-MeC_6H_4, *p*-$OMeC_6H_4$, *p*-$COOMeC_6H_4$, *p*-ClC_6H_4, *p*-$COMeC_6H_4$

Scheme 83. Direct C-H bond arylation of 1,4-disubstituted-1*H*-1,2,3-triazoles **214** with aryl bromides in GVL, described by Ackermann and Vaccaro's groups.[30]

In 2020, Vaccaro *et al.* successfully applied GVL in the C2 regioselective direct C-H bond arylations of both NH-free and *N*-substituted indoles with diaryliodonium salts, performed with a palladium-containing metal-organic framework (*i.e.*, Pd@UiO66-BTeC) as recoverable and reusable catalyst, in order to develop an highly sustainable protocol.[257] This procedure combined the advantages of a green solvent with the features of a recoverable catalyst, which is highly desirable in the field of the *Green Chemistry*; however, on the other hand authors reported the use iodonium salts, that undermined the global sustainability of this synthetic methods due to their low atom economy and high organic waste production.

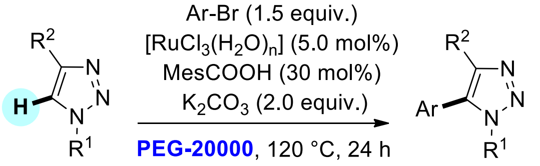
Finally, for the sake of completeness we also reported that Cravotto *et al.* described in 2017 a Palladium-catalyzed C2 regioselective direct C-H arylation of thiophenes with aryl bromides, performed using GVL as reaction medium in combination with the microwave irradiation as a non-conventional energy source (for more details see also section 4.2.4).[258]

3.3.5. Direct C-H bond arylation of (hetero)arenes in polyethylene glycol. Polyethylene glycol (PEG) is a low volatile liquid polymer typically synthesized by polymerization of ethylene glycol, which in turn is obtained as by-product of petrochemical industrial processes. However, several routes to bio-based ethylene glycol have been recently developed, starting from carbohydrate-based biomass feedstocks.[259]

PEG is commercially available over a very wide range of molecular weights, showing significantly different physico-chemical properties in terms of volatility and water miscibility. However, thanks to its non-flammable, non-corrosive and non-toxic nature, PEG can be counted in the class of sustainable solvents.[260]

The first investigation of direct C-H bond arylation in PEG was described in 2009 by Ackermann and co-worker: the *ortho*-arylation of benzene ring of 2-phenylpyridines, 1-phenylpyrazoles and 1-phenyltriazoles was carried out in PEG-2000 at 120 °C for 24 h, using $[RuCl_3(H_2O)_n]$ (5.0 mol%), 2,4,6-trimethylbenzoic acid (30 mol%) as additive and K_2CO_3 as the base.[261] Interestingly, the combination of PEG-400 as a green medium with relatively inexpensive $RuCl_3 \cdot x\ H_2O$ without any other additive or ligand was recently applied in an extended study of *ortho*-arylation of 2-phenylpyridines.[262]

However, PEG was used most often in the reactions of *N*-heteroarenes as substrates. Ackermann *et al.* studied the direct C-H bond arylation of 1,4-disubstituted 1,2,3-1*H*-triazoles **216** with aryl bromides, performed with $Pd(OAc)_2$ (5 mol%), 2,4,6-trimethylbenzoic acid (30 mol%) and K_2CO_3 (1.0 equiv.) in PEG-20000: after 24 h at 120 °C, the C5 arylated products **217** were obtained in 52-85% yields (**Scheme 84**).[261]



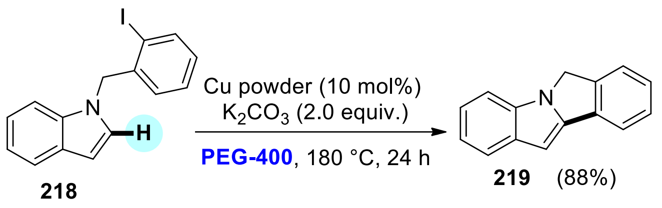
216 **217** (52-85%)

R^1 = CH_2Ph, Ph, *o*-MeC_6H_4, *m*-MeC_6H_4, *p*-$OMeC_6H_4$
R^2 = H, *n*-Bu, *n*-hexyl, Ph
Ar = *p*-$OMeC_6H_4$, *p*-$COOEtC_6H_4$, *p*-$COPhC_6H_4$, *p*-$COMeC_6H_4$, *m*-$COMeC_6H_4$

Scheme 84. Direct C5 arylation of 1,4-disubstituted-1*H*-1,2,3-triazoles **216** with aryl bromides in PEG-20000, reported by Ackermann *et al.*[261]

Vidavalur *et al.* proposed the use of low molecular weight PEG-400 as the solvent of the copper powder catalysed direct arylation of 1,2,4-triazoles and 1,3,4-oxadiazoles with aryl iodides.[88] As already pointed out in section 2.2.1**,** this procedure is experimentally simple and free from addition of external chelating ligands or co-catalysts, although we could not to rule out the occurrence of a possible solubilization of copper species during reactions.

Low molecular weight PEGs (in particular PEG-400) have found some applications in the direct arylation reactions of bicyclic *N*-heteroarenes. Domínguez *et al.* described the Cu-catalyzed intramolecular direct C-H arylation of *N*-(2-iodobenzyl)indole **218** to give isoindolo[2,1-*a*]indole **219** in 88% yield, performed under ligand-free conditions with copper powder (10 mol%) in the presence of 2.0 equiv. of K_2CO_3, at 180 °C for 24 h (**Scheme 85**) .[263] It is clear that such protocol actually showed only a limited sustainability, despite the use of PEG-400 as the solvent: the very high energy requirements of the process, together with the use of large amounts of metallic copper (which can easily be leached into the solution), made this protocol not of such interest in the frame of the *Green Chemistry*.



Scheme 85. Copper-powder-catalyzed intramolecular direct C-H bond arylation of *N*-(2-iodobenzyl)indole **218** to give isoindolo[2,1-*a*]indole **219** in PEG-400 as the solvent, described in 2009 byDomínguez *et al.*[263]

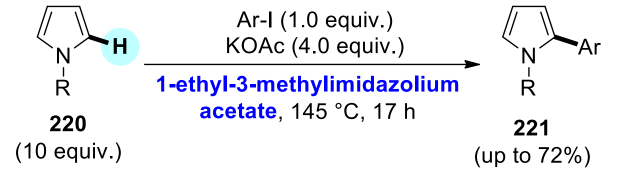
In 2014, Berteina-Raboin *et al.* have developed a one pot process for the synthesis of 2,3-diarylimidazo[1,2-*a*]pyridines in PEG-400: the formation of 2-arylimidazo[1,2-a]pyridine core by microwave-assisted condensation of 2-aminopyridines with α-bromo ketones, followed by a $Pd(OAc)_2$-catalyzed direct C-H arylation at C3 position with an aryl bromide.[264] The combination of a eco-friendly solvent with the use of microwave as non-conventional efficient energy source and with the typical advantages of tandem processes (*i.e.*, reduction of the isolation and/or purification operations) is very appealing and perfectly matches with most of the Twelve Principles of the Green Chemistry.

3.4. Direct C-H bond arylation of (hetero)arenes in ionic liquids and deep eutectic solvents

Ionic liquids (ILs) are organic salts, consisting of an organic cation and a polyatomic (in)organic anion, which are liquid under working conditions (typically at room temperature).[265] The physico-chemical features of ILs can be finely tuned by changing the chemical structure of both cation and anion. However, the most important property of ILs is their almost negligible vapour pressure: for this reason, in general ILs are considered as an environmental benign alternative to volatile organic solvents.[266] Unfortunately, there is often a lack of information on their real toxicity, which has limited (especially in the last few years) the increase of their use in organic synthesis.[267]

Examples of direct C-H arylation of (hetero)arenes involving the use of ILs as solvents are very limited. In 2011, Gryko *et al.* reported the C2 regioselective direct C-H arylation of *N*-substituted pyrroles **220** with aryl iodides: interestingly, reactions were performed under transition metal-free conditions, *i.e.*, only in the presence of potassium acetate as the base, using 1-ethyl-3-methylimidazolium acetate as the solvent, at 145 °C for 17 h, affording the corresponding 2-aryl pyrroles **221** in good yields, up to 72% (**Scheme 86**).[268] The present protocol is very interesting from the point of view of the *Green Chemistry*, since the use of a IL as the reaction medium was performed in combination with the absence of any transition metal catalyst. However, authors were not able to fully explain the mechanism, although they supposed the possibility of a radical-based path thanks to the combined effect of the base with the imidazolium salt, thus acting not only as a solvent but also as a real organocatalyst.

Few representative examples of direct C-H arylation in 1-butyl-3-methylimidazolium hexafluorophosphate were also reported in 2017 by Kouznetsov and co-workers in the context of the synthesis of 6*H*-benzo[*c*]chromenes by intramolecular *ortho*-arylation of chloro- and bromo-aryl benzyl ethers.[269] Interestingly, also in these case reactions were carried out under transition metal-free conditions, in the presence of potassium *t*-butoxide (3.0 equiv.)as base and phenanthroline (20 mol%) acting as an organocatalyst through s radicalic mechanism. As we already emphasized in other points of this review, organocatalytic system are very appealing in the context of *Green Chemistry* thanks to their easier removal from a reaction mixture compared to metal traces, therefore their use in combination with ILs could be favourable.



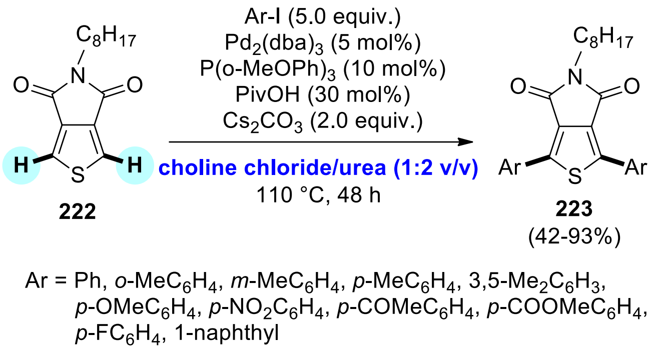
R = Me, Ph, CH_2Ph, NMe_2, SEM
Ar = Ph, p-$NO_2C_6H_4$, p-CNC_6H_4, m-$NO_2C_6H_4$, m-CNC_6H_4,
o-$NO_2C_6H_4$, o-CNC_6H_4, p-$OMeC_6H_4$

Scheme 86. C2 regioselective direct C-H bond arylation of *N*-substituted pyrroles **220** with aryl iodides in 1-ethyl-3-methylimidazolium acetate IL as the solvent, reported in 2011 by Gryko *et al.*[268]

Ryu *et al.* showed that imidazolinium- or thiazolium-based ILs are not inert during Pd-catalyzed reactions involving aryl halides, since a direct C-H arylation at the C2 position of the imidazolium or thiazolium ring of the ionic liquid may occur.[270] This study demonstrated that ILs are not among the best solvents for direct C-H bond arylation reactions of (hetero)arenes.

Deep eutectic solvents (DESs) represent a valid alternative to ILs. They are formed by a mixture of Lewis or Brønsted acids and bases, containing a variety of anionic and/or cationic species. In most cases, DESs are composed by quaternary ammonium salts complexed with an organic molecule, typically a hydrogen bond donor (urea, amides, acids, alcohols). By mixing these inexpensive and safe components, hydrogen-bonding interactions give rise to an eutectic mixture, whose melting point is lower than those of individual components.[271] Many physico-chemical properties of DESs are similar to conventional ILs, *e.g.*, low volatility and insensitivity to water, but they offer clear advantages in terms of large-scale synthetic applications since they are less expensive, more synthetically accessible and less toxic.[272] Overall, DESs fits better than ILs with the Twelve Principles of *Green Chemistry*.

In the last few years, DESs are finding large use as green and sustainable media for many chemical processes in organic synthesis. However, in the context of direct C-H arylation of (hetero)arenes, only one study has been reported to date: our research group explored the possibility of direct arylation of 5-octylthieno[3,4-*c*]pyrrole-4,6-dione **222** with aryl iodides in a DES made of choline chloride and urea.[273] In particular, reactions were performed with $Pd_2(dba)_3$ as a catalytic precursor, P(*o*-MeOPh)$_3$ as the ligand, cesium carbonate as the base, pivalic acid as an additive, at 110 °C for 48 h, affording the corresponding diarylated products **223** in good yields (**Scheme 87**). The present protocol was highly sustainable, due to the fact that the choline chloride/urea (1:2) mixture is a green, convenient and inexpensive reaction medium, and the reactions were performed in non-anhydrous conditions and under air.



Scheme 87. Application of DESs as green and sustainable solvents in direct C-H bond arylation of (hetero)arenes: direct arylation of 5-octylthieno[3,4-c]pyrrole-4,6-dione **222** in choline chloride/urea (1:2), recently developed by our research group.[273]

3.5. Solvent-free direct C-H bond arylation of (hetero)arenes

The last part of this section will be dedicated to solvent-free methods used in direct C-H bond arylation reactions of (hetero)arenes.

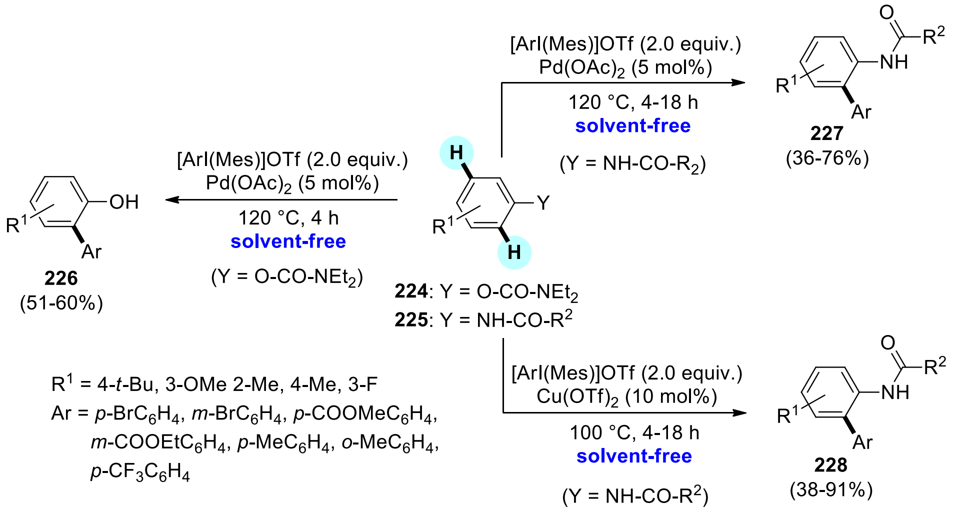
As recommended by the Principle 5 of *Green Chemistry*, avoiding the production of waste, including solvents, is highly preferable; therefore, it is not surprising that the development of synthetic protocols in the absence of any solvent represents one of the most appealing approaches towards green and sustainable organic processes.[274] However, the development of efficient solvent-free procedures is far from simple: first, the absence of a reaction medium could make quite difficult an appropriate mixing of reagents, particularly in the presence of solid reagents and products; second, the solvent-free approach is more difficult on a large scale, especially for exothermic reactions; third, the use of solvents is still often required for isolation and purification of the products.[275] Despite these issues, in the last decade solvent-free protocols have found a growing interest in the context of direct C-H arylation bond reactions of (hetero)arenes.

The first solvent-free study was reported in 2010 by Bedford *et al.*, which described the *ortho*- and *meta*-arylation of anilides **224** and aryl *N*,*N*-diethyl carbamates **225** with diaryliodonium salts as the arylating agents; more In detail, *ortho*-arylation of both substrates were carried out in the presence of $Pd(OAc)_2$ (5 mol%) at 120 °C for 4-18 h, affording the corresponding *ortho*-arylated products **226** and **227** in 51-60% and 36-76% yields, respectively, while *meta*-arylation of anilides were carried out with $Cu(OTf)_2$ (10 mol%) at 100 °C for 4-18 h, affording the *meta*-arylated anilides **228** in 38-91% yields (**Scheme 88**).[276] This protocol is highly appealing from a merely synthetic point of view, since it allowed for the preparation of highly functionalized compounds; on the other hand, despite the solvent-free conditions there are several drawbacks which limited its sustainability: first, the use of iodonium salts as arylating agents, due to ther well-known poor atom economy; second, the need of high loading of metal catalysts (in particular in the case of *meta*-arylation with copper catalysts); third, the use of an high temperature for a prolonged time.

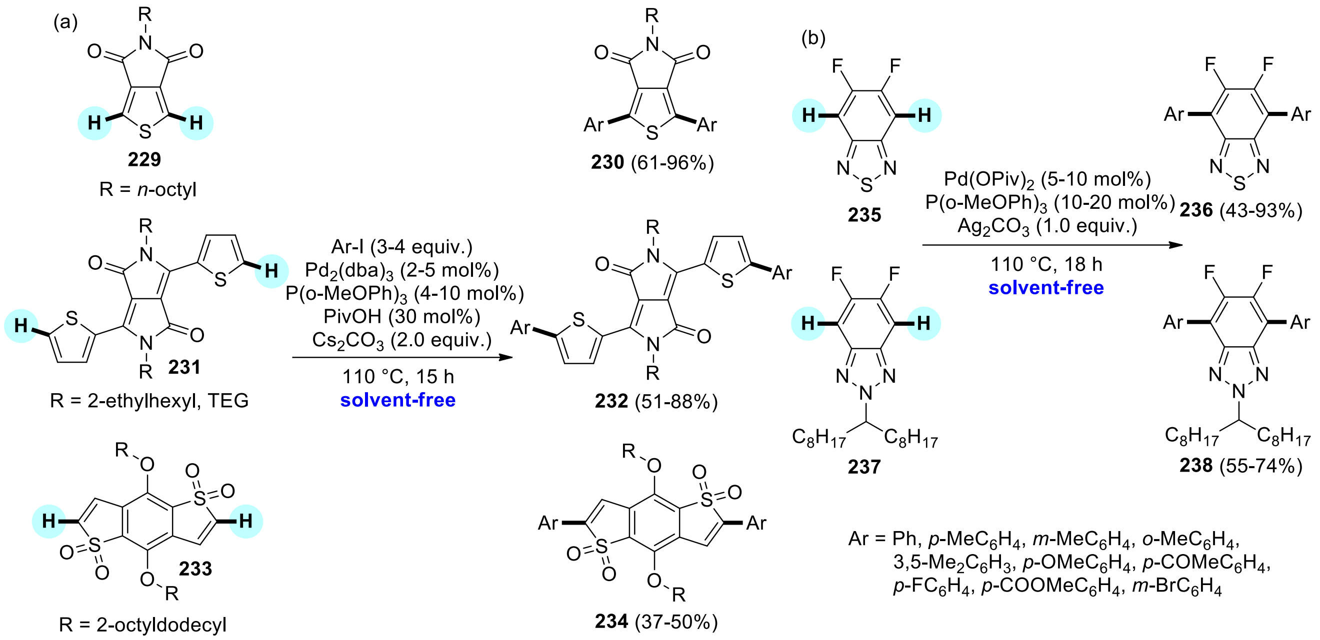
In 2014, Larrosa and co-workers described an extended study of direct *ortho*-arylation of benzoic acids, benzamides and polyfluoroarenes with aryl iodides in solvent-free conditions: reactions were performed with $Pd(OAc)_2$ (5 mol%) as the catalyst, KOAc (2.8-4.0 equiv.) as the base, AcOH (1.5 equiv.) and Me_4NCl (2.05-3.25 equiv.) as additive, at 80-140 °C, affording *ortho*-arylated coupling products in good yields.[277]

Rodríguez *et al.* reported in 2012 an appealing study for metal-free, base-free and solvent-free direct arylation of naphthalene and other unactivated arenes with diaryliodonium triflates, performed in the presence of microwave irradiation as energy source; in particular, in the case of naphthalene the reaction occurred with good regioselectivity on the α position.[278] In our opinion this study appeared quite interesting, since the solvent-free conditions were efficiently coupled with the use of microwave irradiation and, above all, the absence of any catalyst and additive, although the use of iodonium salts as arylating agents did not represent the best choice in terms of the *Green Chemistry*.

Doucet *et al.* developed in 2012 a quite general protocol for solvent-free Palladium-catalyzed direct C-H arylation of heteroarenes with aryl bromides: reactions were successfully performed on *N*-heteroarenes (*N*-methylpyrrole, 2-substituted thiazoles, 3,5-dimethylisoxazole), *O*-heteroarenes (2-substituted and 2,3-disubstituted furans) and above all *S*-heteroarenes (2-substituted and 2,4-disubstituted thiophenes) with $PdCl(C_3H_5)(dppb)$ (1 mol%) as the catalyst and KOAc (2.0 equiv.) as the base.[279] In a following study, the same research group reported some examples of solvent-free conditions in the Pd-catalyzed desulfitative direct arylation of 1-methylindole with benzenesulfonyl chlorides as user-friendly and highly sustainable arylating agents.[225]



Scheme 88. Solvent-free protocols for direct C-H *ortho*- and *meta*-arylation of anilides **224** and aryl *N*,*N*-diethyl carbamates **225** with diaryliodonium salts.



Scheme 89. Solvent-free protocols for Palladium-catalyzed direct C-H bond arylation of several (hetero)arenes with aryl iodides, recently developed by our research group.

A more extended investigation on solventless direct C-H bond arylation of indoles was reported in 2020 by Punji *et al.*: *N*-(2-pyridinyl)indoles were treated with aryl iodides in the presence of CuCl (5.0 mol%) and lithium bis(trimethylsilyl)amide (1.3 equiv.) without any ligand, under solvent-free conditions at 120 °C for 16 h, affording the corresponding 2-arylated indoles in good yields and high regioselectivity.[280]

In the last years, our research group has developed solvent-free strategies for direct C-H bond arylation of (hetero)arenes. In 2018, we reported an extended study involving several heteroarenes.[281] In particular, reactions of 5-octylthieno[3,4-*c*]pyrrole-4,6-dione **229**, *bis*-thienylDPP derivatives **231** and benzodithiophene-*S,S*-tetraoxide derivatives **233** were carried out with aryl iodides having different stereo-electronic properties, in the presence of $Pd_2(dba)_3$ as a catalytic precursor, P(*o*-MeOPh)$_3$ as the ligand, Cs_2CO_3 as the base and pivalic acid, affording the diarylated coupling products **230**, **232** and **234** in good yields. Direct C-H bond arylation reactions of 5,6-difluorobenzo[*c*][1,2,5]thiadiazole **235** and 5,6-difluoro-2-heptadecyl-2*H*-benzo[*d*][1,2,3]triazole **237** occurred by using Pd(OPiv)$_2$, P(*o*-MeOPh)$_3$ and Ag_2CO_3 to give diarylated products **236** and **238**, respectively (**Scheme 89**).

In 2020, we also explored the possibility of combining the advantages of solvent-free conditions with the use of a recoverable and recyclable catalysts, thus developing a solventless protocol for direct C-H arylation of 1,2,3-triazoles based on commercial Pd/C, performed at 110 °C for 24 h in the presence of Bu_4NOAc: the treatment of 1,4-disubstituted 1,2,3-triazoles with aryl iodides gave the corresponding C5 arylated products with yields in the range 45-81%.[32] Very recently we reported the development of a highly sustainable and environmentally friendly protocol for the direct C-H bond arylation of several (hetero)arenes (benzo[*b*]thiophene, thieno[3,4-*c*]pyrrole-4,6-dione, 1,2,3-1*H*-triazole, pentafluorobenzene) with aryl iodides, combining the solvent-free conditions with the use of infrared irradiation as non-conventional, eco-friendly and efficient source of energy, alternative to the thermal heating (for more details, see section 4.3.4).[282]

4. Non-conventional energy sources in direct C-H bond arylation of (hetero)arenes

Among all the Twelve Principles of *Green Chemistry*, one of the least investigated is definitely Principle 6 ("Design for energy efficiency"): in fact, energy requirements for an organic process should be recognized for their environmental impact and should be minimized. This is a very critical point in the context of direct C-H bond arylation reactions, as high temperatures are typically required to enable the activation of the (hetero)aryl C-H bonds. Although the use of traditional thermal heating (with the help of a pre-warmed sand or oil bath) is still the preferred choice to supply energy to the reaction environment, in laboratory scale processes the use of non-conventional energy sources has recently attracted significant attention in organic synthesis as a valid alternative to thermal heating, since they often lead to minimized reaction time, affording higher product yields and reduced undesired by-products.[283] Despite most of these techniques often require the access to specific equipments, their improved sustainability and very low environmental impact have made them an important class of fundamental *enabling technologies* in the context of synthetic organic chemistry.

In this section we will give a critical overview of all the applications of non-conventional energy sources in the direct C-H bond arylation of (hetero)arenes. In particular, we will main focus on the more common photochemical strategies (both in the presence and in the absence of photoredox catalysts) and microwave-assisted protocols, but also the few examples of electrochemical methods, as well as of ultrasound-, mechanical milling- and infrared irradiation-promoted reactions will be discussed.

4.1. Photochemical direct C-H bond arylation of (hetero)arenes

Organic chemists have been always interested in the use of light as an energy source to induce chemical transformations.[284] By absorbing the

UV-Vis light, molecules reach electronically excited states; in this way, their chemical properties – including reactivity – significantly change, thus making possible reactions which may hardly occur with traditional thermal heating.

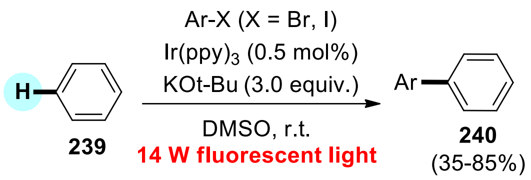
Currently, photochemical processes are among the most elegant and environmental friendly approach in organic synthesis:[285] the UV-Vis light is a clean, green and very convenient source of energy, which can be obtained from renewable sources, in particular sunlight. Actually, for long time the need for high-energy UV radiations for several chemical transformations has limited the environmental benefits of photochemical synthesis on industrially significant scale, as UV wavelengths generally required are not abundant in the solar spectrum.[286] However, recently the interest in photochemical processes has increased thanks to the use of light emitting diodes (LEDs) as energetically efficient sources of both UV and visible light.[287] Nevertheless, the cleanest and most sustainable photochemical methods remained those promoted by the visible light (whose wavelengths are quite abundant in the solar spectrum) or, even more desirable, directly by the solar light.

In photochemical processes, a critical point is to prevent unwanted side reactions, which can be promoted under the UV-Vis light irradiation. In this context, the choice of solvent is fundamental: many photochemical reactions were carried out in benzene or acetonitrile, since these solvents are less reactive towards free radical species generated during photo-excitation, although they are quite toxic; more sustainable alternatives are represented by methanol or DMSO.[288]

In the last decade, photochemical processes found large application also in the context of direct C-H arylation of (hetero)arenes. Typically, this approach uses photo-excitation with UV or visible light to initiate a single-electron-transfer (SET) process between a suitable metal or organic photocatalyst and an appropriate aromatic substrate. In some cases, the sustainability of the process can be improved by using a solid-supported photocatalyst, which can be recovered and reused. However, there are also some examples of photochemical direct C-H bond arylation of (hetero)arenes performed without the presence of photocatalyst.

In this section we will give an overview of the photochemical processes, first analyzing the photocatalyst-assisted protocols and then showing those which do not require the use of a photoredox catalyst. In the following we will not discuss the detailed mechanistic hypotheses of the photochemical processes, which is beyond the scope of this review, we will rather focus our attention on the advantages and limitations of these photochemical protocols from the sustainability point of view, framing them whenever possible in the context of *Green Chemistry*.

4.1.1. Photochemical direct C-H arylation of (hetero)arenes assisted by photoredox catalysts. The first photochemical direct C-H arylation of unactivated arenes with aryl halides was reported in 2013 by Li and co-workers: they proposed a photoredox process, where benzene **239** was treated with an aryl iodide or bromide (0.5 mmol) in the presence of potassium *tert*-butoxide (3.0 equiv.) as the base, $Ir(ppy)_3$ (0.5 mol%) as the photoredox catalyst and DMSO as a solvent, at room temperature for 24 h under irradiation with a 14 W compact fluorescent light lamp.[289] Reaction proceeded at room temperature for aryl iodides but at higher temperatures (70 °C) for the more accessible and less expensive bromides, affording the biaryl products **240** in good yields (**Scheme 90**). However, one of the main disadvantages of this protocol is that it required the use of a very large excess (about 100 equivalents) of the arene, which clearly limited the overall sustainability of the process.



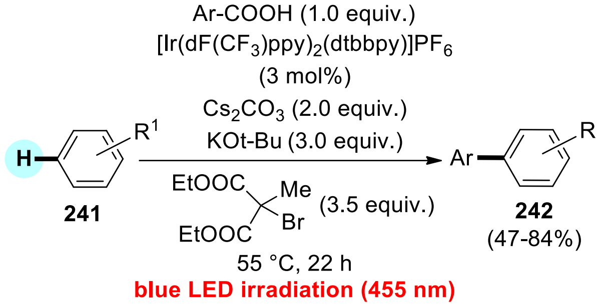
Ar = Ph, p-$OMeC_6H_4$, m-$OMeC_6H_4$, o-$OMeC_6H_4$, p-MeC_6H_4, m-MeC_6H_4, o-MeC_6H_4, 3,4-$Me_2C_6H_3$, 3,5-$Me_2C_6H_3$, p-$NMe_2C_6H_4$, p-$CF_3C_6H_4$, p-FC_6H_4, p-ClC_6H_4, p-BrC_6H_4, p-IC_6H_4, 1-naphthyl, 2-naphthyl

Scheme 90. Photochemical direct C-H bond arylation of benzene **239** catalyzed by $Ir(ppy)_3$ (0.5 mol%) as the photoredox catalyst under irradiation with a 14 W compact fluorescent light lamp, reported in 2013 by Li and co-workers.[289]

In 2015, Malacria *et al.* described the direct arylation of unactivated arenes (benzene, toluene, *p*-xylene, naphthalene) with aryldiazonium salts, performed at room temperature in acetonitrile, under irradiation of a blue LED and in the presence of $Ru(bpy)_3(SbF_6)_2$ (0.5 mol%) as the photocatalyst; reactions gave biaryl coupling products after 1-96 h in good yields.[290] Also in this case, the starting arenes were used in a large excess (40 equiv.), which is hardly compatible with the principles of the Green Chemistry; however, on the other hand the use of diazonium salts as arylating agents with high waste prevention, together with the need of low amounts of the ruthenium catalyst, was quite appealing. In our opinion, possible further improvements on this protocol should be focused on the reduction of the excess of arene.

A further appealing photocatalytic approach for the direct C-H arylation of unactivated arenes was reported in 2017 by Glorius and co-workers, who developed the photocatalytic version of Minisci-type reactions.[291] They found that the treatment of arenes **241** with electron deficient and electron rich aryl carboxylic acids as arylating agents, carried out with a iridium-centred photocatalyst $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (3 mol%), Cs_2CO_3 (2 equiv.) as base and a bromomalonate derivative (3.5 equiv.), under blue LED irradiation (455 nm) at 55 °C for 22 h, afforded the corresponding biaryl products **242** in 47-84% yields (**Scheme 91**). As for the conventional Minisci reaction, the coupling occurred here through the decarboxylation of aryl carboxylic acids to give the corresponding radicals, which are the real arylating species; however, in this case the formation of radicals was promoted by a visible light irradiation in the presence of a suitable photocatalyst, which allowed to work under quite mild experimental conditions. However, as for the other above mentioned photocatalytic protocols, one of the major issue is represented by the need of a large excess of arenes, used not only as substrate but also as solvent. It is clear that such conditions were hardly compatible with the principles of the *Green Chemistry*.

More common is the direct C-H bond arylation of unactivated arenes promoted by an organic photocatalyst. In general, in synthetic organic chemistry the development of organocatalyzed protocols is a topic of high interest: the possibility to carry our reactions in the absence of any metal catalysts is highly desirable, in order to reduce the overall cost of the process and also simplify the purification procedures. It is clear that the development of an organocatalyzed synthetic approach is very important in the field of the *Green Chemistry*, especially if combined with photochemical strategies as non-conventional energy source, even if there is always plenty of room for further improvement.



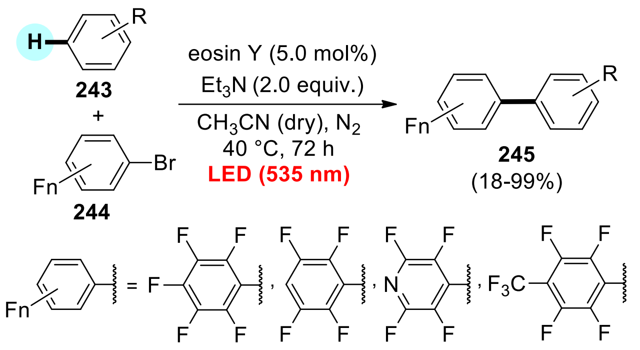
R^1= H, *t*-Bu, CF_3, Cl, F
Ar = *o*-FC_6H_4, *o*-ClC_6H_4, *o*-BrC_6H_4, *o*-IC_6H_4, 2,4-$Cl_2C_6H_3$, *m*-BrC_6H_4, *p*-BrC_6H_4, Ph, *p*-PhC_6H_4, *p*-*t*-BuC_6H_4, *p*-$OMeC_6H_4$, *p*-$OTBSC_6H_4$, *m*-$OMeC_6H_4$, *p*-CNC_6H_4, *o*-$COMeC_6H_4$, 2-Cl-3-pyridyl, 2-Br-3-pyridyl, 2-OMe-3-pyridyl, 2-Br-5-CF_3-C_6H_3

Scheme 91. Photochemical version of the Minisci-type reaction for the direct C-H bond arylation of arenes **241** with aryl carboxylic acids as arylating agents, performed under blue LED irradiation with $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ as the photocatalyst.

In 2014, Guo and co-workers developed an amine-catalyzed (*N,N,N′,N′*-tetramethyl-ethane-1,2-diamine, TMEDA, 20 mol%) direct arylation of benzene and other unactivated arenes with aryl iodides, performed under irradiation with UV lamps (254 nm).[292] The use of an amine as the photo-catalyst avoided resorting to toxic transition metal catalysts and/or strong bases, but the use of the same arene as the solvent limited the real sustainability of the protocol. Similar protocols, based on 1,10-phenanthroline[293] or 4,7-diphenyl-1,10-phenanthroline[294] in combination with potassium *t*-butoxide, were also developed, showing almost the same advantages and drawbacks in the frame of the *Green Chemistry*.

In 2016 König *et al.* proposed the use of eosin Y (5 mol%) as photoredox organocatalyst for the direct C-H bond arylation of simple arenes **243** with perfluoroaryl bromides **244**, performed in acetonitrile under irradiation at 535 nm and in the presence of Et_3N (2.0 equiv.); different perfluoroaryl bromides and arenes reacted and produced the expected products **245** in yields ranging between 18 and 99% (**Scheme 92**).[295] The use of a photochemical process, which allowed mild experimental conditions (40 °C), in combination with the typical advantages of the organocatalysis were appealing from the point of view of the *Green Chemistry*, but the need for very long reaction times (72 h) and of an strictly anydrous atmosphere reduced the overall interest in terms of sustainability.

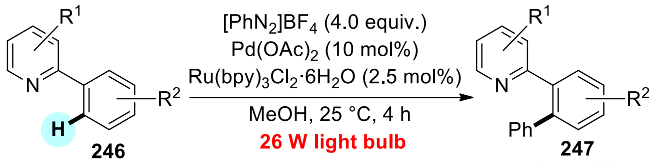
More recently, photocatalytic direct C-H arylation of unactivated arenes was also performed with the help of 9,10-dihydro-10-methylacridine, which is a NADH coenzyme model compound,[296] and by the naturally occurring perylenequinonoid pigments, due to their good properties of photosensitization.[297] Despite the highly desirable combination of the photochemical approach with the advantages of organocatalysis, in both these studies one of the main limitations to the sustainability was represented by the use of a very large excess of arene (in some cases, working as both the reagent and the solvent).



R = H, Me, *i*-Pr, OMe, F, Cl, NO_2

Scheme 92. Photochemical direct C-H arylation of simple arenes **243** with perfluoroaryl bromides **244**, performed with the photoredox organocatalyst eosin Y under irradiation at 535 nm, reported in 2016 by König *et al.*[295]

Photochemical processes promoted by photoredox catalysts are quite common also in the context of direct *ortho*-arylation of benzene rings. The first study was reported in 2011 by Sanford and co-workers, with the development of a direct C-H *ortho*-arylation of the benzene ring of 2-phenylpyridines **246** with phenyldiazonium salts as arylating agents, performed in methanol at room temperature under irradiation with a 26 W household fluorescent compact bulb as source of visible light, in the presence of $Pd(OAc)_2$ 10 mol% as the catalyst and $Ru(bpy)_3Cl_2{\cdot}6\ H_2O$ (2.5 mol%) as the photocatalyst, affording the corresponding *ortho*-arylated products **247** in good yields (**Scheme 93**).[200] The protocol, successfully extended to arenes bearing other *ortho*-directing groups including amides, pyrazoles, pyrimidines and oxime ethers, showed a fair sustainability thanks to the need of short reaction times and room temperature, as well as to the use of an alcohol as the solvent and of diazonium salts as arylating agents showing high atom economy and waste prevention.

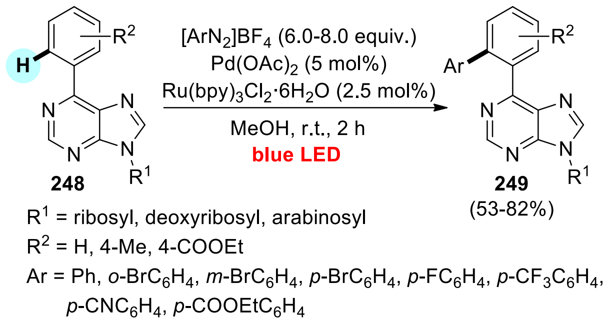


R^1 = H, 4-Cl, 4-F, 4-Br, 3-CF_3, 3-NO_2, 2-Me
R^2 = 2-Me, 2-OMe, 4-CF_3

Scheme 93. Photochemical direct C-H *ortho*-arylation of 2-phenylpyridines **246**, performed with a 26 W household fluorescent bulb light and $Ru(bpy)_3Cl_2{\cdot}6\ H_2O$ as photocatalyst.

In light of these results, more recently Guo and co-workers used the same conditions for the direct ortho C–H arylation of the benzene ring of 6-arylpurine nucleosides **248**: by using 6.0-8.0 equiv. of an aryldiazonium salt as arylating agent, in the presence of 5 mol% of $Pd(OAc)_2$ and 2.5 mol% of $Ru(bpy)_3Cl_2{\cdot}6\ H_2O$, in MeOH as the solvent under blue LED irradiation, for 2 h at room temperature, the direct C-H arylation occurred selectively on the *ortho*-position of the arene ring, affording mono-arylated products **249** in good yields (**Scheme 94**).[201]

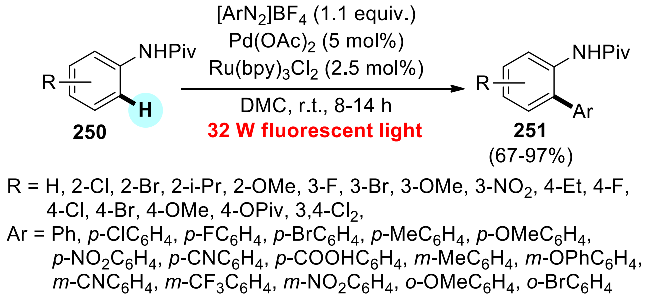
Su *et al.* proposed the use of $Ru(bpy)_3(PF_6)_2$ (5 mol%) as photocatalyst for the *ortho*-arylation of *p*-xylene, anysole and *p*-dimethoxybenzene with aryldiazonium salts.[298] The reactions were carried out with 5.0 equiv. of the arene, at room temperature under irradiation with a 45 W household fluorescent compact bulb lamp, using 10 equiv. of pivalic acid as additive and nitromethane as a solvent. The large excess of the arene and pivalic acid, as well as the use of $MeNO_2$ as reaction medium clearly limited its impact in the context of *Green Chemistry*.



R^1 = ribosyl, deoxyribosyl, arabinosyl
R^2 = H, 4-Me, 4-COOEt
Ar = Ph, *o*-BrC_6H_4, *m*-BrC_6H_4, *p*-BrC_6H_4, *p*-FC_6H_4, *p*-$CF_3C_6H_4$, *p*-CNC_6H_4, *p*-$COOEtC_6H_4$

Scheme 94. Photochemical direct *ortho* C–H arylation of the benzene ring of 6-arylpurine nucleosides **248** under blue LED irradiation with $Ru(bpy)_3Cl_2 \cdot 6\ H_2O$ as photocatalyst, carried out in 2017 by Guo and co-workers.[201]

In 2017, Balaraman and co-workers proposed the combination of $Pd(OAc)_2$ catalyst (5 mol%) with $Ru(bpy)_3Cl_2$ photocatalyst (2.5 mol%) for the direct *ortho*-arylation of anilides **250** with aryldiazonium salts, performed at room temperature in 8-14 h under visible light irradiation with a 32 W compact fluorescent light lamp, using dimethyl carbonate (DMC) as solvent, affording the corresponding *ortho*-arylated anilides **251** in 67-97% yields (**Scheme 95**).[240] The protocol is in our opinion appealing in the frame of the *Green Chemistry*: reactions proceeded under very mild experimental conditions, thanks to the combination of a photochemical approach as non-coventional energy source with the use of an environmentally benign medium and the choice of aryl diazonium as arylating agents, characterized by high atom economy and waste prevention.



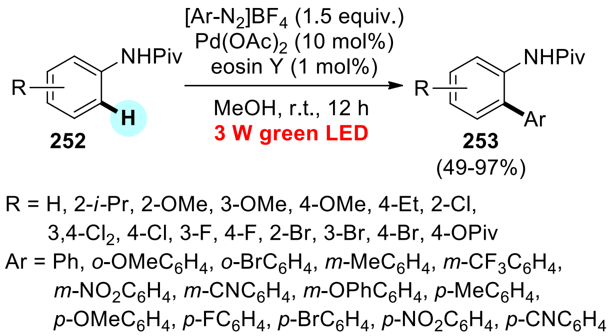
R = H, 2-Cl, 2-Br, 2-i-Pr, 2-OMe, 3-F, 3-Br, 3-OMe, 3-NO_2, 4-Et, 4-F, 4-Cl, 4-Br, 4-OMe, 4-OPiv, 3,4-Cl_2,
Ar = Ph, *p*-ClC_6H_4, *p*-FC_6H_4, *p*-BrC_6H_4, *p*-MeC_6H_4, *p*-$OMeC_6H_4$, *p*-$NO_2C_6H_4$, *p*-CNC_6H_4, *p*-$COOHC_6H_4$, *m*-MeC_6H_4, *m*-$OPhC_6H_4$, *m*-CNC_6H_4, *m*-$CF_3C_6H_4$, *m*-$NO_2C_6H_4$, *o*-$OMeC_6H_4$, *o*-BrC_6H_4

Scheme 95. Photochemical direct C-H *ortho*-arylation of anilides **250** under visible light irradiation with $Ru(bpy)_3Cl_2$ as photocatalyst, carried out in 2017 by Balaraman and co-workers.[240]

Although Ru-based photoredox catalysts are the most explored in the photochemical direct C-H *ortho*-arylation of arenes, the use of other metal species as photosensitizers has been described. An extended investigation of photocatalytic *ortho*-arylation of substituted arenes with bromoazoles was performed by Weaver *et al.*: the reaction proceeded at 30 °C in MeCN as the solvent, using *fac*-$(Irppy)_3$ (0.3 mol%) as the photoredox catalyst, K_2CO_3 (2.0 equiv.) as the base and *N*-cyclohexyl-*N*-isobutylcyclohexanamine (0.5-2.0 equiv.), under irradiation with a blue LED.[299] Interestingly, no arene-contaning by-products were observed, suggesting that the method might be useful for late-stage azolylation of pharmaceuticals, in which the major goal is the derivatization of molecules with minimal time and effort.

Evano *et al.* described in 2017 the use of a copper photoredox catalyst, $[(DPEphos)(bcp)Cu]PF_6$, to activate the carbon-halogen bond of aryl halides at room temperature under irradiation with 420 nm light, thus making possible several reactions, including the direct *ortho*-arylation of variously substituted arenes.[300] Despite the photochemical approach allowed for mild experimental conditions, the need of a large excess (20 equiv.) of the arenes and of a large loading (10 mol%) of the copper catalysts, in combination with very long reaction times (3 days), makes the present protocol of low interest from the sustainability point of view.
Among organic photoredox catalysts, eosin Y is the most studied in direct C-H *ortho*-arylation of arenes. Selected examples were reported in 2016 by König and co-workers for the *ortho*-arylation of substituted arenes with perfluoroaryl bromides,[295] performed in acetonitrile under irradiation at 535 nm and in the presence of Et_3N (2.0 equiv.) as the base and 5 mol% of the organocatalyst.

A more extended study was carried out in 2017 by Balaraman *et al.*: they reported a base- and oxidant-free strategy for the direct C-H bond *ortho*-arylation of anilides **252** with aryldiazonium salts, performed at room temperature in MeOH under irradiation with a 3 W green LED for 12 h, in the presence of $Pd(OAc)_2$ (10 mol%) as catalyst and eosin Y (1 mol%) as photoredox organocatalyst.[202] Reactions proceeded under very mild and sustainable conditions, affording *ortho*-arylated products **253** in most cases in yields > 75% (**Scheme 96**). On one hand, the use of diazonium salts as arylating agents is highly desirable in terms of high atom economy and waste prevention; however, on the other hand the typical advantages of the use of organocatalysts cannot be found in this specific case, since eosin Y was here used in combination with a large amount of a palladium catalyst.



R = H, 2-*i*-Pr, 2-OMe, 3-OMe, 4-OMe, 4-Et, 2-Cl, 3,4-Cl_2, 4-Cl, 3-F, 4-F, 2-Br, 3-Br, 4-Br, 4-OPiv
Ar = Ph, *o*-$OMeC_6H_4$, *o*-BrC_6H_4, *m*-MeC_6H_4, *m*-$CF_3C_6H_4$, *m*-$NO_2C_6H_4$, *m*-CNC_6H_4, *m*-$OPhC_6H_4$, *p*-MeC_6H_4, *p*-$OMeC_6H_4$, *p*-FC_6H_4, *p*-BrC_6H_4, *p*-$NO_2C_6H_4$, *p*-CNC_6H_4

Scheme 96. Direct C-H *ortho*-arylation of anilides **252** with aryldiazonium salts, performed under irradiation with a 3 W green LED and eosin Y (1 mol%) as photoredox catalyst.

In 2019, Yadav *et al.* proposed a simple approach to 2-aminobiphenyls by visible light-promoted direct *ortho*-arylation of anilines using aryl diazonium salts (3.0 equiv.), in acetonitrile/water (10:1 v/v) mixture and with eosin Y (1 mol%) as the only catalyst, under irradiation of a green LED for 12-18 h at room temperature.[301] Compared to the previous work of Balaraman *et al.*, such protocol appears in our opinion more appealing: the use of a fully organocatalyzed approach, with the removal of any metal catalyst, is highly desirable.

Very recently, Rao and co-workers reported the photocatalytic *ortho*-arylation of *p*-xylene and mesitylene with aryl diazonium salts, carried out in DMSO as the solvent, using the naturally occurring cercosporin as bioorganic photoredox catalyst; the main advantage of the procedure is that it worked under irradiation with sunlight, thus making it very advantageous and highly sustainable from the point of view of *Green*

Chemistry.[297] Moreover, the combined use of a natural photocatalyst and a completely free source of energy made the overall protocol highly convenient and cheap.

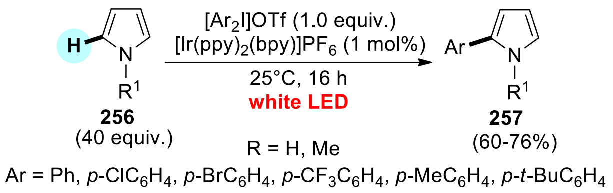
Pyrroles are definitely the most investigated substrates in the context of photochemical direct C-H arylation of *N*-heteroarenes. Among metal photoredox catalysts, ruthenium-, iridium- and copper-based species were successfully used. In 2013, Xiao and co-workers reported the C2 regioselective direct arylation of *N*-methylpyrrole with diaryliodonium salts, performed at room temperature under blue LED irradiation in acetonitrile and in the presence of $Ru(bpy)_3Cl_2$ (1 mol%) as a catalyst; the main limitation of the procedure is represented by the high excess of *N*-methylpyrrole (100 equiv.), which can hardly make it convenient and highly sustainable.[302]

The same photoredox catalyst was also used by Natarajan *et al.* for C2 direct coupling of *N*-methylpyrroles **254** with arylsulfonyl chlorides, performed at room temperature in MeCN as solvent, in the presence of $Ru(bpy)_3Cl_2$ (3 mol%) and under irradiation with blue LED lamp (425 nm).[303] Interestingly, in this case no excess of pyrroles was required, and the corresponding α-arylated pyrroles **255** were obtained in 56-89% yields (**Scheme 97**). In our opinion the present investigation is very appealing, since it represents to date the only example of direct C-H bond arylation which combined the advantages of photochemical processes with those of sulfonyl chlorides as arylating agents. As we already pointed out in other points of the manuscript, these substrates typically show many appealing features, including broad availability and easy handling, as well as high waste prevention, due to the formation of gaseous SO_2 as by-product.

Scheme 97. Photochemical C2 regioselective direct C-H arylation of of *N*-methylpyrroles **254** with arylsulfonyl chlorides, performed with $Ru(bpy)_3Cl_2$ photocatalyst under irradiation with blue LED lamp, reported in 2016 by Natarajan *et al.*[303]

The $Ru(bpy)_3Cl_2$ photocatalyst was also used in 2017 by König and co-workers in combination with pyrene (5.0 mol%) as the photocatalytic system for the C2 regioselective arylation of *N*-methylpyrrole with aryl bromides or chlorides as suitable arylating reagents, performed in the presence of a slight excess of DIPEA (1.4 equiv), in DMSO as the solvent and at room temperature.[304] This protocol was really fast (2.5 h) and afforded the corresponding products in modest to good yields (41-86%), although the need of 10 equiv. of the pyrrole is a clear limit to its sustainability.

Chatani *et al.* proposed in 2013 the use of $[Ir(ppy)_2(bpy)]PF_6$ (1 mol%) as the photoredox catalyst for the direct C2 arylation of pyrroles **256** with diaryliodonium salts: the reactions, performed at room temperature under irradiation with white LED, afforded the desired coupling products **257** in modest to good yields (48-75%), but unfortunately also in this case high amounts of heteroarenes (that is, 40 equiv.) were required, thus limiting the interest of the process in the context of the *Green Chemistry* (**Scheme 98**).[305]

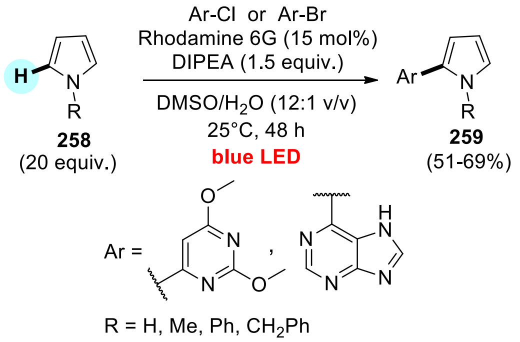


Scheme 98. Photochemical C2 regioselective direct C-H bond arylation of of pyrroles **256** with diaryliodonium salts, performed with $[Ir(ppy)_2(bpy)]PF_6$ photocatalyst under irradiation with white LED, reported in 2013 by Chatani *et al.*[305]

A more sustainable protocol was proposed by Weaver *et al.*, who described a C2 arylation of NH-free and *N*-substituted pyrroles with bromoazoles: reactions, carried out in acetonitrile at 30 °C under blue LED irradiation using *fac*-$(Irppy)_3$ as photocatalyst, did not required a large excess of heteroarene and did not afford large amounts of by-products, thus making the products purification quite simple.[299] No arene-contaning by-products were observed, thus suggesting that the method might be useful for late-stage azolylation of pharmaceuticals, in which the major goal is the derivatization of molecules with minimal time and effort.

The $[(DPEphos)(bcp)Cu]PF_6$ complex was described by Evano *et al.* as a general and broadly applicable copper-based photoredox catalyst: it allowed the C2 regioselective arylation of *N*-substituted pyrroles with aryl halides under very mild conditions, although once again a large excess (20 equiv.) of the arene is required, together with quite long reaction times (3 days).[300,306]

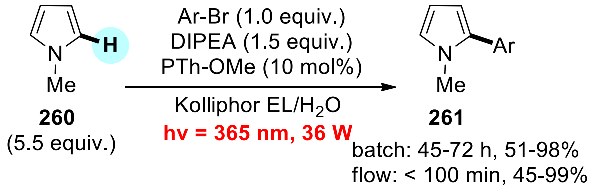
Moving on organic photocatalysts, few examples of the photochemical direct C-H bond arylation of pyrroles were described by König *et al.* in the context of more extended investigations on several (hetero)arenes, based on the use of the above mentioned eosin Y, occurring quickly at room temperature with aryldiazonium salts[307] or fluoroaryl bromides[295] as arylating agents. In a following study, the C2 arylation of pyrroles was treated by the same group in more details: NH-free and *N*-substituted pyrroles **258** were treated with (hetero)aryl bromides and chlorides using Rhodamine 6G (15 mol%) as the photoredox catalyst and *N,N*-diisopropylethylamine (1.5 equiv.) as sacrificial electron donor, at room temperature in a DMSO/water mixture (12:1 v/v) under irradiation with blue LEDs (455 nm): the synthetic method afforded the corresponding coupling products **259** generally in good yields, thus providing a metal-free alternative for the synthesis of biologically interesting nucleobases under mild conditions (**Scheme 99**).[143]



Scheme 99. C2 regioselective direct arylation of pyrroles **258** with heteroaryl chlorides and bromides, performed under blue LED irradiation with rhodamine 6G as photoredox catalyst.

The photochemical direct C-H bond arylation reactions of pyrroles with aryldiazonium salts under mild and sustainable conditions were also achieved by using other organo-photocatalysts: the NADH coenzyme model 9,10-dihydro-10-methylacridine[296] and in particular the naturally occurring cercosporin, having the main advantage to be able of working under irradiation with sunlight.[297]

In 2021, Beverina *et al.* reported an interesting study, where the C2 photochemical direct arylation of *N*-methylpyrrole **260** with (hetero)aryl bromides was carried out for the first time in water under the micellar catalysis approach into a microfluidic system, thanks to the use of PEGylated castor oil derivative Kolliphor EL as surfactant: the reactions were carried out under irradiation with a 36 W lamp (λ = 365 nm) at room temperature, using 10-(4-methoxy)phenyl-10*H*-phenothiazine (PTh-OMe, 10 mol%) as photocatalyst, in combination with DIPEA (1.5 equiv.).[144] The corresponding C2 arylated products **261** were obtained in good yields, while the use of microfluidic photo-reactor improved reaction time (< 100 min) with respect to batch conditions, without reducing the yields and selectivity (**Scheme 100**). In our opinion, this study reports one of the most sustainable and environmental friendly protocols in the context of photochemical direct C-H bond arylation of (hetero)arenes: the combination of a photochemical process with the advantages of micellar catalysis and the features of flow chemistry perfectly fits with most of the Twelve Principles of the *Green Chemistry*.

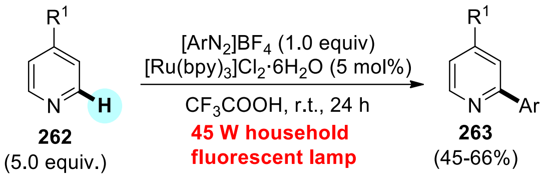


Ar = *p*-COOEtC_6H_4, *p*-CNC_6H_4, 2-thienyl, 2-benzothiazolyl

Scheme 100. C2 regioselective direct C-H arylation of *N*-methylpyrrole **260** with (hetero)aryl chlorides, performed at 365 nm irradiation using 10-(4-methoxy)phenyl-10*H*-phenothiazine (PTh-OMe) as photocatalyst, in batch and continuous flow conditions.

The photochemical direct C-H bond arylation of pyridines has been less investigated to date. An interesting study was described in 2014 by Xue and co-workers, with the photocatalytic direct arylation of pyridine hydrochlorides in water with aryldiazonium tetrafluoroborates as the arylating agents: working in the presence of $[Ru(bpy)_3]Cl_2{\cdot}6H_2O$ as the photocatalyst under irradiation with a 45 W fluorescent bulb, the direct arylation reactions were performed at room temperature, giving final products in good to excellent yields (48-92%) and generally high C2 regioselectivity, although after 80 h.[162] In this protocol, the application of a photochemical approach was coupled with the choice of water as an environmental friendly solvent and the use of aryldiazonium salts as arylating agents with high atom economy and waste prevention: all these features were in our opinion well favourable from the point of view of the *Green Chemistry*.

In 2015, Su *et al.* described a similar transformation: pyridines **262** (5.0 equiv.) were treated with aryldiazonium salts (1.0 equiv.) using once again the $[Ru(bpy)_3]Cl_2{\cdot}6H_2O$ photocatalyst (5 mol%) under visible light irradiation (45 W household fluorescent compact bulb lamp), at room temperature using trifluoroacetic acid as solvent. The corresponding 2-aryl pyridines **263** were obtained in 45-66% yields (**Scheme 101**).[298] It is worth to emphasize that the use of trifluoroacetic acid as the solvent represents a severe limit to the process sustainability, since it is highly irritant and harmful to the environment.



R^1 = *t*-Bu, CF_3, CN

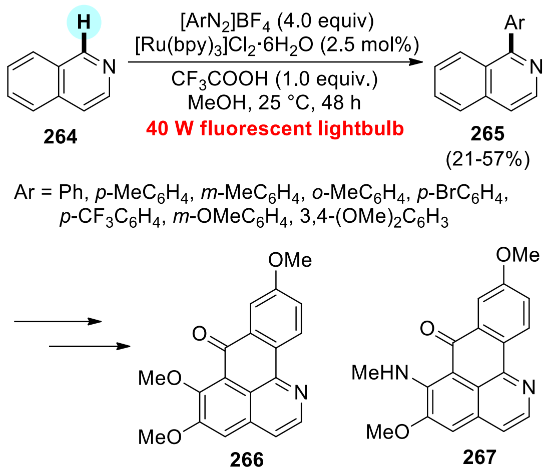
Ar = *p*-BrC_6H_4, *p*-FC_6H_4, *p*-MeC_6H_4, *p*-OMeC_6H_4

Scheme 101. Photochemical direct C-H bond arylation of pyridines **262** with aryldiazonium salts, performed in the presence of $[Ru(bpy)_3]Cl_2{\cdot}6H_2O$ photocatalyst under visible light irradiation, reported in 2015 by Su *et al.*[298]

In 2017, in the context of the above-mentioned photocatalytic Minisci-type reactions of unactivated arenes with aryl carboxylic acids, Glorius *et al.* also reported few examples of C2 regioselective direct arylation of pyridines: reactions involved the $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ catalyst (3 mol%), Cs_2CO_3 (2 equiv.) as base and a bromomalonate derivative (3.5 equiv.), under blue LED irradiation (455 nm) at 55 °C for 22 h.[291] The only example of photochemical direct C-H bond arylation of pyridines organocatalyzed was reported in 2019 by Rao *et al.*, who described the use of natural cercosporin under sunlight.[297]

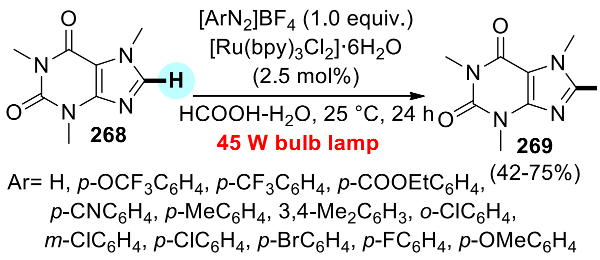
In addition to these procedures involving homogeneous photo-redox catalysts, some examples of recoverable photoredox catalysts have also been reported, which we already described in the previous section 2.2. In 2015, Rueping *et al*. proposed a C2 regioselective photocatalytic direct C-H arylation of pyridines with aryldiazonium salts, carried out in EtOH as the solvent, promoted by the easily accessible and recyclable TiO_2 as the catalyst.[106] In 2016, Wang and co-workers described the use of a three-dimensional porous $Cu_{2-x}S$-MoS_2 framework as recoverable and efficient photocatalyst for a similar direct C-H arylation of pyridines with diazonium salts as arylating agents, performed for 1 h at room temperature under irradiation with a Xenon lamp.[89] Interestingly, both protocols were particularly convenient from the point of view of the *Green Chemistry*, as they were performed at room temperature with ethanol as a green reaction medium, affording the desired coupling products after short reaction time.

Moving on bicyclic *N*-heteroarenes, only few examples were described involving metal photoredox catalysts. Lei and co-workers reported the photoredox direct C-H arylation of isoquinoline **264** with aryldiazonium salts (4.0 equiv.), performed in MeOH at room temperature under irradiation with a 40 W fluorescent lightbulb and in the presence of $[Ru(bpy)_3]Cl_2{\cdot}6H_2O$ (2.5 mol%) as photocatalyst and trifluoroacetic acid (1.0 equiv.) as additive.[216] Such protocol, affording the corresponding C1 arylated products **265** in modest to good yields (21-57%) after 48 h, was very interesting not only from a synthetic point of view, since it was successfully applied for the synthesis of biologically active alkaloids menisporphine **266** and daurioxoisoporphine C **267**, but also in the context of sustainability, since it worked under mild conditions and in the absence of the large excess of heteroarene, as typically occurred for many other photocatalytic processes described above (**Scheme 102**).



Scheme 102. Photochemical direct C-H arylation of isoquinoline **264** with aryldiazonium salts, performed with [Ru(bpy)$_3$]Cl$_2$·6H$_2$O as photocatalyst under irradiation with a 40 W fluorescent lightbulb.

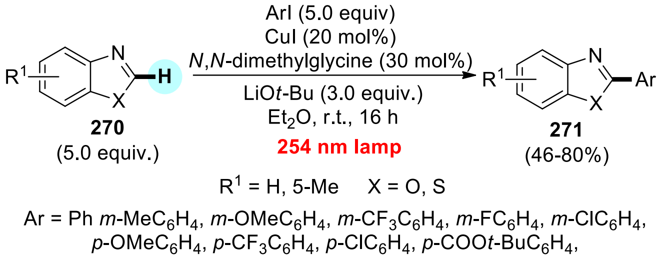
The [Ru(bpy)$_3$]Cl$_2$·6H$_2$O photocatalyst was also used by Xue *et al.* for the development of a highly effective visible light-promoted protocol on caffeine **268** with aryldiazonium salts: reactions were performed at room temperature in H$_2$O as the solvent, with [Ru(bpy)$_3$]Cl$_2$·6H$_2$O (2.5 mol%) and formic acid as additive, under irradiation with a 45 W bulb lamp, to give the arylated products **269** after 24 h (**Scheme 103**).[162] In this protocol, which is one of the very few studies on the direct C-H bond arylation of the caffeine heterocyclic scaffold, the application of a photochemical approach was coupled with the choice of water as an environmental friendly solvent and the use of aryldiazonium salts as arylating agents with high atom economy and waste prevention: all these features were in our opinion well favourable from the point of view of the *Green Chemistry*.



Scheme 103. Visible light-promoted direct C-H arylation of caffeine **268** with aryldiazonium salts, performed in the presence of [Ru(bpy)$_3$]Cl$_2$·6H$_2$O (2.5 mol%) under irradiation with a 45 W bulb lamp.

Only few selected examples of *fac*-(Irppy)$_3$ assisted C2 regioselective direct C-H bond azolylation of NH-free and *N*-substituted indoles were reported in 2016 by Weaver *et al.* in a more extended work involving several (hetero)arenes.[299] The reaction were carried out under mild conditions, at 30 °C in acetonitrile as the solvent, using 0.3 mol% of the *fac*-(Irppy)$_3$ photoredox catalyst, K$_2$CO$_3$ (2.0 equiv.) as the base and *N*-cyclohexyl-*N*-isobutylcyclohexanamine (0.5-2.0 equiv.), under blue LED irradiation.

In 2016, Ackermann *et al.* described a photocatalyzed direct C-H bond arylation of benzoxazoles or benzothiazoles **270** with iodoarenes (5.0 equiv.), performed with the use of CuI (20 mol%) as the catalyst and *N*,*N*-dimethylglycine (30 mol%) as ligand.[308] More in detail, reactions required lithium *t*-butoxide (3.0 equiv.) as base and Et$_2$O as a solvent, under irradiation at 254 nm, at room temperature for 16 h, affording the corresponding C2 arylated products **271** in 46-80% yields (**Scheme 104**). Despite the use of a copper species as the photocatalytic system was appealing in terms of costs (as they are typically cheaper than ruthenium and iridium complexes), the sustainability of the process appeared quite limited, in particulat due to the need of large amounts of the metal catalyst.

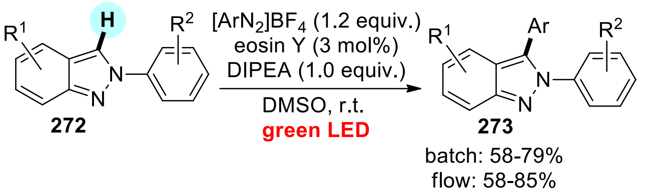


Scheme 104. Photochemical direct C-H bond arylation of benzoxazoles or benzothiazoles **270** catalyzed by CuI/*N*,*N*-dimethylglycine under irradiation at 254 nm, reported in 2016 by Ackermann *et al.*[308]

Very recently, Baeg and co-workers proposed the use of a ruthenium-graphene nanosheet photocatalyst for regioselective C3 arylation of imidazo[1,2-*a*]pyrimidines with bromoarenes (1.0 equiv.), performed in acetonitrile as the reaction medium and in the presence of Et$_3$N (2.0 equiv.) as the base.[309] This protocol can be considered sustainable, since it worked very efficiently at room temperature with no need for an excess of the starting heteroarenes, as well as for the possibility to be performed under sunlight irradiation, which is a totally sustainable cost-free source of energy.

The study of organocatalyzed-photochemical direct C-H arylations of bicyclic *N*-heteroarenes has been quite limited to date. In 2016, Yang *et al.* described a very simple and fast method for the C3 regioselective direct C-H arylation of NH-free indoles with aryldiazonium salts: by simply using 1 mol% of rhodamine B as the organocatalyst and under irradiation with a 25 W white lamp, reactions were performed in 1 h at room temperature in DMSO as the solvent, affording 3-aryl indoles in modest to good yields (up to 73%).[310] Interestingly, this protocol is one of the fastest examples of all the photochemical direct C-H arylation of (hetero)arenes reported to date in the literature: this aspect, in combination with all the other above mentioned features (metal-free conditions, use of arylating agents with high waste prevention, room temperature) makes in our opinion such investigation of high interest in the frame of the *Green Chemistry*.

In 2019, Kim and co-workers reported a very appealing approach for the photocatalytic C3 direct arylation of 2*H*-indazoles **272** with aryldiazonium salts in batch and continuous flow-conditions: reactions were carried out in DMSO at room temperature, using eosin Y (3 mol%) under irradiation of a green LED and in the presence of DIPEA (1.0 equiv.) as the base, affording the desired 3-aryl-2*H*-indazoles **273** in most cases in good yields (**Scheme 105**).[311] The possibility of combining the typical advantages of organophotocatalyzed processes (*i.e.*, metal-free conditions and room temperature) with the appealing technology of flow chemistry made this protocol highly appealing in the perspective of green and sustainable chemistry, opening the way to very fast synthesis of drug molecules (liver X receptor inhibitor drugs) with very good yields. In a following study, authors performed the same reactions under continuous flow conditions in capillary microreactors where eosin Y was immobilized.[312]

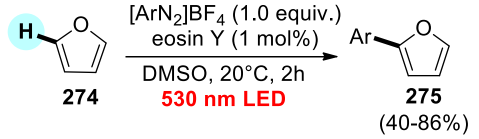


R^1= H, 7-OMe, 6-F, 6-Br R^2 = H, 4-Me, 2-Me
Ar = *o*-MeC_6H_4, *p*-MeC_6H_4, *p*-$OMeC_6H_4$, *o*-CNC_6H_4,
p-CNC_6H_4, *m*-FC_6H_4, *m*-ClC_6H_4, *p*-BrC_6H_4, *p*-ClC_6H_4,
p-$NO_2C_6H_4$, 4-OMe-3-ClC_6H_3, 2,4,6-$Me_3C_6H_2$

Scheme 105. Photocatalytic C3 direct arylation of 2*H*-indazoles **272** reported in 2019 by Kim and co-workers,[311] using eosin Y as photoredox catalyst under irradiation of a green LED.

Among all the *O*-heteroarenes, furans are the only substrates which have been investigated in photocatalytic direct C-H arylation processes, often in more extended studies involving other heteroarenes. Only one study involving an homogeneous metal photocatalyst has been described: in 2016, Natarajan *et al.* used $[Ru(bpy)_3]Cl_2$ photocatalyst (3 mol%) for the C2 regioselective arylation of furans with arylsulfonyl chlorides, at room temperature under irradiation with blue LED lamp (425 nm) and in acetonitrle as solvent.[303]

A larger number of investigations were carried out with homogeneous photoredox organocatalysts. In 2012, König and co-workers reported the first, pioneering study in this context, with the direct C-H bond arylation of furan **274** with aryldiazonium salts simply in the presence of eosin Y (1 mol%) under irradiation with a 530 nm LED: working at 20 °C in DMSO as the solvent, the C2 arylated products **275** were obtained in 2 h (**Scheme 106**).[307] The only factor limiting the sustainability of this process is the use of a quite large excess (10 equiv.) of furan.



Ar = Ph, *p*-ClC_6H_4, *o*-$NO_2C_6H_4$, *m*-$NO_2C_6H_4$,
p-$NO_2C_6H_4$, *p*-CNC_6H_4, *p*-$COOEtC_6H_4$,
p-BrC_6H_4, *p*-$OMeC_6H_4$, *p*-OHC_6H_4, *p*-MeC_6H_4

Scheme 106. Photocatalytic C2 regioselective direct C-H bond arylation of furan **274** with aryldiazonium salts, performed under 530 nm LED irradiation in the presence of eosin Y.

In addition to the above mentioned NADH coenzyme model 9,10-dihydro-10-methylacridine[296] and natural perylenequinonoid pigment cercosporin,[297] which were used in the photochemical direct C-H bond arylation of several (hetero)arenes, including few selected examples of furans, an interesting study was described in 2017 by Gryko and co-workers, based on the use of porphyrins as organic photocatalysts: they reported the direct C2 arylation of furans with diazonium salts, at room temperature in DMSO under irradiation with a 455 nm LED, using 1 mol% of several porphyrins.[313] These macrocycles have finely tunable physico-chemical properties, thanks to their chemical functionalization with suitable substituents; in particular, they found that electron-poor tetra(pentafluorophenyl)porphyrin was the most effective photoredox organocatalyst in promoting these reactions, affordind the 2-aryl furans in 40.81% yields.

A significant number of examples of recoverable photoredox catalysts have also been reported for the direct C-H arylation of furans, which we already considered in the previous section 2.2. In 2015, Rueping *et al.* proposed the C2 regioselective direct C-H bond arylation of furan with aryldiazonium salts in the presence of recyclable TiO_2 catalyst, working under irradiation with a 11 W household lamp and in ethanol as a solvent.[106] Despite the advantages related to the use of a recoverable catalyst, a sustainable solvent and an photochemical approach, the need of sub-stoichiometric amounts of TiO_2 (between 0.1 and 1 equiv.), and above all the need of a large excess of furans represent severe limits to the development of an highly sustainable protocol.

In 2016, Wang and co-workers described the use of three-dimensional porous $Cu_{2-x}S$-MoS_2 framework as recoverable and efficient photoredox catalyst for a similar direct C-H arylation of furans with diazonium salts as arylating agents, performed for 1 h at room temperature under irradiation with a Xenon lamp working with a 700 nm light.[89] The 2-aryl furans were obtained in 72-98% yields, although also in this case a large excess of the heteroarene was mandatory for achieving high yields of the products.

In 2017, Wang and co-workers reported two very interesting works of photochemical direct C-H bond arylation of furans with diazonium salts as arylating agents, based on the use of graphitic C_3N_4 (*g*-C_3N_4). In a first study, they used graphitic carbon nitride/reduced graphene oxide (*g*-C_3N_4/rGO) nanocomposite, which was active under visible light irradiation (λ = 450 nm);[108] in the other, a carbon nitride/polypyrrole (C_3N_4-PPy) heterojuction aerogel, acting as efficient photocatalyst under a while LED, was successfully applied.[109]

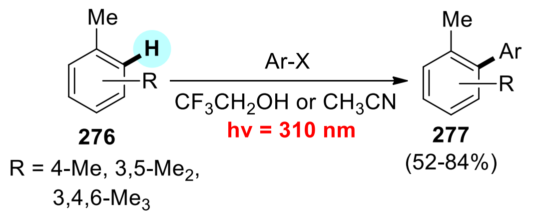
In 2020, Metin *et al.* proposed the first application of black phosphorus as heterogeneous and recoverable photoredox catalyst for the direct C-H bond arylation of furan with aryl diazonium salts, working efficiently in the presence of white light, at 25 °C for 2 h in DMSO as the solvent.[111] If the use of black phosphorus was definitely highly interesting from the point of view of photochemical processes, which could open the way to more sustainable protocols, in this specific case the need for an excess of furan (10 equiv.) and the modest recyclability of the photocatalyst still represent severe limitations in the context of the *Green Chemistry*.

Very recently, Yadav and co-workers proposed the use of a graphitic carbon nitride-based fluorescein isothiocyanate (*g*-C_3N_4–FITC) thin film as an excellent photocatalyst, having the great advantage to be active under sunlight, for the direct C-H bond arylation of furans performed in DMSO at room temperature for 6 h.[110]

All the above mentioned photochemical protocols for direct C-H bond arylation of furans were actually also performed on thiophenes, in most cases with similar yields: in fact, given their similar chemical structure, photochemical processes on thiophenes were often considered as an extension of protocols first developed for furans.

4.1.2. Photochemical direct C-H arylation of (hetero)arenes without photoredox catalysts. From the point of view of *Green Chemistry*, the development of photochemical direct C-H arylation protocols which occur without the presence of photoredox catalysts is generally more appealing, since the purification of the final products is easier to be performed thanks to the minor contamination.

The first study in this context was published in 2007 by Fagnoni and co-workers: they described the direct C-H arylation of alkyl benzenes **276** with aryl halides (chlorides, fluorides) or esters (mesylates, triflates, phosphates) as arylating agents: reactions were performed in 2,2,2-trifluoroethanol (although acetonitrile was a greener alternative in some cases) under irradiation with lamps at λ = 310 nm, affording the corresponding *ortho*-aryl products **277** after 1-8 h at room temperature (**Scheme 107**).[314] Despite the use of a poorly sustainable solvent, this pioneering study demonstrated the possibility of photochemical direct C-H arylations under metal-free and very mild conditions, opening the door to new possibilities in the context of sustainable organic synthesis.



X = Cl, F, OMs, OTf, $O(PO)(OEt)_2$
Ar = p-$NH_2C_6H_4$, p-$NMe_2C_6H_4$, p-OHC_6H_4, o-$MeOC_6H_4$, m-$MeOC_6H_4$, p-$MeSC_6H_4$, 4-NH_2-2-MeC_6H_3, 4-MeO-2,6-$Me_2C_6H_2$, 4-(Me_2t-Bu)SiO-2-MeC_6H_3, 4-(Me_2t-Bu)SiO-2,6-$Me_2C_6H_2$

Scheme 107. Photochemical direct C-H arylation of alkyl benzenes **276** with aryl halides or esters as arylating agents, performed under irradiation at λ = 310 nm in 2007 by Fagnoni *et al.*[314]

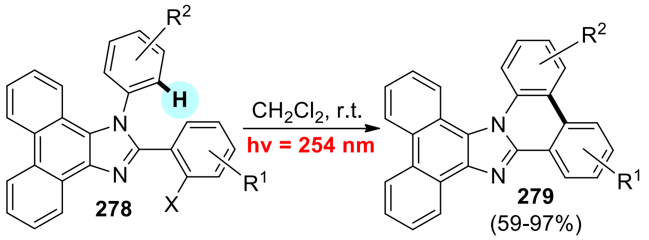
In a following study, they proposed the arylation of unactivated arenes with electron-rich aryl nonaflates ($ArO-SO_2C_4F_9$) as non-conventional arylating agents, which can be generated *in situ* from the corresponding phenols, working in protic reaction media (often 2,2,2-trifluoroethanol) and in presence of cesium carbonate as base under irradiation at 310 nm for 24 h.[315] If aryl nonaflates represent a class of highly reactive arylating agents, from the point of view of the *Green Chemistry* their use is actually poorly favourable, especially in terms of atom economy and waste prevention, since they produced perfluorinated nonaflates as by-products, thus making it necessary not only a purification of the coupling products, but also expensive waste disposal procedures.

In 2013, Rossi *et al.* reported the photoinduced direct C-H arylation of benzene with several aryl iodides and bromides, performed in DMSO under irradiation with two HPI-T 400 W lamps and only in the presence of *t*-BuOK (3.0 equiv.).[316] Although reactions were carried out in 1 h at room temperature, the protocol was not useful from an environmental friendly point of view: despite the absence of transition metal catalyst, the use of a strong base and above all a very large excess of benzene (150 equiv.) inevitably limited the sustainability of the process.

In 2013, Baumgartner *et al.* proposed the photochemical direct C-H arylation of phenols and other hydroxyaryl derivatives (2-napthol, 4-hydroxycoumarin, sesamol) with several aryl iodides and bromides, performed in DMSO with a strong base (*t*-BuOK) and under irradiation with two 400 W halogen lamps emitting at a maximum of 350 nm.[317] If this study was of high interest as a proof-of-concept, in a following, work they instead focused the attention on the development of more sustainable experimental conditions: on one hand, the same reactions were carried out in water as more environmental friendly solvent, used in combination with KOH as base; on the other, they demonstrated that the halogen lamp could be efficiently replaced by a high-efficient and less expensive LED.[318]

In 2017, König *et al.* described a very straightforward method for the direct *ortho*-(hetero)arylation of anilines, performed with (hetero)aryl bromides under irradiation with blue LED light (λ = 455 nm) at room temperature, in the presence of DIPEA (0.5 equiv.) as a base and in acetonitrile as the solvent.[319]

Gryko's research group has also investigated photochemical direct C-H bond arylation processes, in the context of intramolecular *ortho*-arylations of arenes for the synthesis of polycyclic systems. In particular, they discovered that phenanthro[9,10-*d*]imidazoles **278**, bearing a 2-halogenoaryl substituent at C2 position, can undergo a photochemically driven direct C-H bond arylation at room temperature simply under irradiation at 254 nm, affording phenanthro[9′,10′:4,5]imidazo[1,2-*f*]phenanthridines **279** in very high yields, up to 97% (**Scheme 108**).[320] Interestingly, here the same reactions were also performed in the solid crystalline state, again upon simple irradiation with UV light (254 nm), affording products **279** quantitatively in 48-72 h.[321] Performing organic reactions in the solid state has clear advantages over more traditional synthesis in solution, especially from the point of view of the *Green Chemistry*; however, the benefits are even greater in the case of planar π-conjugated aromatics, due to their low solubility in most organic solvents. A similar photocatalytic direct C-H bond arylation protocol was extended by the same authors to the synthesis of imidazo[1,2-*f*]phenanthridine skeletons.[322]

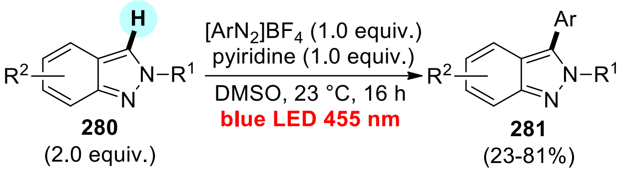


X= Cl, Br, I, TfO R^1= H, 6-F, 4-CN, 4,5-OMe_2
R^2= 4-t-Bu, 3,5-(t-Bu)$_2$, 4-n-octyl, 4-NO_2, 4-SF_5,
4-COOEt, 4-CN, 3,4,5-F_3, 3,4,5-OMe_3

Scheme 108. Photochemically driven (λ = 254 nm) intramolecular direct C-H bond arylation of phenanthro[9,10-*d*]imidazoles **278**, performed at room temperature with no photocatalyst.

The catalyst-free photochemical direct C-H bond arylation of *N*-, *O*- and *S*-heteroarenes is very uncommon. A metal- and additive-free photochemical direct C-H arylation of boron BODIPYs at their C3 and C5 positions with aryldiazonium salts was reported in 2019 by Jiao *et al.*: the reactions were carried out in acetone at room temperature, under irradiation with a 450 nm LED, affording the corresponding 3,5-diaryl BODIPYs in modest to good yields (28-68%).[323]

In the same year, Lee *et al.* reported a mild visible-light-mediated, photocatalyst-free C3 regioselective direct C-H bond arylation of 2H-indazoles **280** with aryldiazonium salts as arylating agents, performed at room temperature in DMSO and in the presence of pyridine (1.0 equiv.) as the base, under blue LEDs irradiation (455 nm) for 15 h, which afforded the corresponding 3-arylated indazoles **281** in 23-81% yields (**Scheme 109**). [324] In our opinion, the present protocol seems to be quite appealing in the context of the *Green Chemistry*, since no large excess of the heteroarenes were required: only 2.0 equiv. of indazoles **280** were used here.



R^1= Ph, *o*-$MeOC_6H_4$, *m*-$MeOC_6H_4$, *p*-$MeOC_6H_4$, *o*-FC_6H_4, *m*-FC_6H_4, *p*-FC_6H_4, *p*-MeC_6H_4, 2-pyridyl, 1-naphthyl, Me, *i*-Pr, CH_2Ph

R^2= H, 5-F, 7-MeO

Ar = Ph, *o*-$MeOC_6H_4$, *m*-$MeOC_6H_4$, *p*-$MeOC_6H_4$, *o*-FC_6H_4, *m*-FC_6H_4, *p*-FC_6H_4, *p*-MeC_6H_4, *p*-ClC_6H_4, *p*-BrC_6H_4, 1-naphthyl, 3-quinolinyl

Scheme 109. Visible-light-mediated photocatalyst-free C3 regioselective direct C-H arylation of 2*H*-indazoles **280** with aryldiazonium salts, performed under blue LEDs irradiation (455 nm).

Rossi and co-workers reported few selected examples of photoinduced direct arylation of thiophene with aryl iodides and bromides; reactions were carried out in DMSO as the solvent under irradiation with two HPI-T 400 W lamps and only in the presence of *t*-BuOK (3.0 equiv.), affording the corresponding mono-arylated products with good C2 selectivity (although non-negligible amounts of the C3 products were also isolated).[316] Although reactions were carried carried out in 1 h at room temperature, the need of a large excess of heteroarene limited the overall sustainability of this protocol.

4.2. Microwave-assisted direct C-H bond arylation of (hetero)arenes

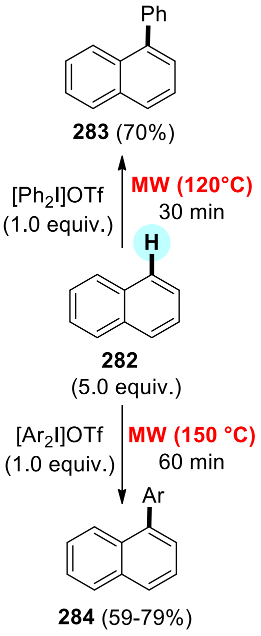
In the last twenty years, considerable attention has been focused on the use of microwave (MW) irradiation in organic synthesis, as an efficient alternative to conventional thermal heating.[325] Depending on convection currents, the traditional heating is slow and ineffective in transferring energy to reagents into a reaction vessel (in particular, the temperature of the vessel surface needs to be higher than that of the reaction mixture). On the contrary, microwave irradiation produces an efficient internal heating due to the ability of specific materials (solvent or reagent with a permanent dipole moment) to convert electromagnetic energy into heat, thus allowing for reaction temperature higher with respect to solvent reflux temperatures and for minimized wall effects (the temperature of vessel surface in this case is lower than that of the reaction mixture). The homogeneous and rapid increase in temperature into the microwave-irradiated reaction vessel often results in a dramatic enhancement of reaction rate. The observed rate acceleration is believed to be a consequence of a purely thermal/kinetic effect, but also “non-thermal” microwave effects were sometime claimed to rationalize some microwave-assisted reaction outcomes. The elimination of the wall effect is also reported to be beneficial in metal-catalyzed reactions since it may lead to increased catalyst lifetime.

The microwave irradiation has been explored as energy source in a wide variety of chemical processes, including direct C-H bond arylation reactions of (hetero)arenes, that typically require high temperatures and prolonged reaction time.[9] Drastically reduced reaction time and enhanced reaction yields compared to those achieved under thermal heating were often observed, thus suggesting the microwave irradiation to be a useful tool to improve the sustainability of direct C-H bond arylation approach.

4.2.1. Microwave-assisted direct C-H bond arylation of arenes.

Few examples of microwave-assisted intermolecular direct C-H arylation of simple arenes have been reported in the literature. In 2008, during their investigation on rhodium-catalyzed microwave-assisted direct arylation of heteroarenes with aryl iodides, Itami *et al.* found that direct C-H bond arylation of monosubstituted benzenes also takes place with a good *ortho-para* selectivity.[326]

In 2012, Rodríguez *et al.* reported the MW-assisted direct C-H arylation of unbiased arenes with diaryliodonium triflates in a very appealing process where the use of a metal catalyst, solvent or additives is not required.[278] For the direct C-H arylation of naphthalene **282** with diphenyliodonium triflate, a clear improvement in both the reaction yield (70% *vs.* 57%) and α-selectivity (7:1 *vs.* 1.2:1) of coupling product **283** was detected under microwave irradiation at 120°C with respect to conventional thermal heating, while reaction time was remarkably reduced from 72 hours to 30 minutes. Various diaryliodonium triflates were then tested for the direct arylation of naphthalene affording the corresponding arylated naphthalenes **284** in good yields (59-79%) and moderate selectivity (α:β ratio from 3:1 to 10:1) in short reaction times (60 minutes at 150°C) (**Scheme 110**). Although the metal- and solvent-free conditions as well as the short reaction times under MW irradiation are greatly beneficial, the use of diaryliodonium triflates clearly does not satisfy the atom-economy principle decreasing the sustainability of this approach.

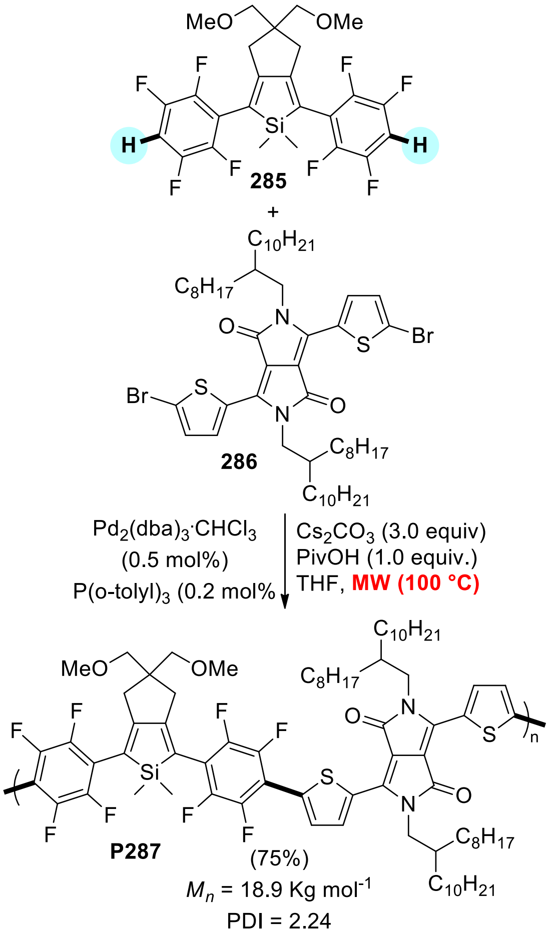


Ar = *p*-FC_6H_4, *p*-ClC_6H_4, *p*-BrC_6H_4, *p*-MeC_6H_4, *p*-*t*-BuC_6H_4

Scheme 110. Base- and metal-free direct C-H bond arylation of naphthalene **282** performed under MW irradiation, reported in 2012 by Rodríguez *et al.*[278]

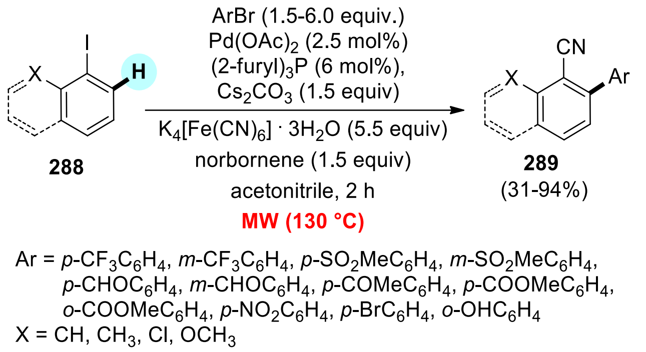
In 2012, Kappe and co-workers reported a direct C-H bond arylation of benzene with aryl bromides, under high-temperature and high-pressure; reactions were performed in the presence of $Co(acac)_3$ as the catalyst and lithium bis(trimethylsilyl)amide as the base, under MW irradiation at 200 °C (15 bar) for 5 min.[327] Under conventional heating at 80°C, higher catalyst and base loadings and a prolonged reaction times of 48 h were found to be necessary to achieve the complete consumption of the aryl bromides. Despite the short reaction times, the sustainability of the protocol was quite low, due to the need of large excess of the arene to produce satisfying results, as well as the need of high temperature despite the use of microwave irradiation.

In 2019, microwave-assisted direct C-H arylation polymerization of a polyfluorinated arene monomer **285** with a diketopyrrolopyrrole-based dibromide **286** was described by Scott and co-worker, working at 100 °C under microwave irradiation for 24 h.[328] A blue colored polymer **P287** with moderate molecular weight (M_n = 18.9 Kg mol^{-1}) and a polydispersity of 2.24 was isolated in 75% yield after Soxhlet purification (**Scheme 111**). The effect of microwave irradiation on both yield and polymer properties by comparison with the analogous thermal process was not evaluated. In fact, this study was mainly focused on the synthesis of conjugated polymers with selected electro-optical features, rather than to the development of highly sustainable direct C-H bond arylation polymerization protocols.



Scheme 111. Microwave-assisted direct C-H bond arylation polymerization of polyfluoroarene monomer **285** with diketopyrrolopyrrole-based dibromide **286** , described in 2019 by Scott and co-worker.[328]

The lack of regioselectivity represents one of the major drawbacks in the intermolecular direct C-H bond arylation of arenes; therefore, many diverse approaches have been developed to promote the regioselective direct C-H bond *ortho*-arylation of these reactants. In 2007, Lautens and co-workers developed a microwave-assisted Catellani-type protocol, consisting in a tandem Palladium-catalyzed direct C-H *ortho*-arylation of iodoarenes **288** with aryl bromides as arylating agents, followed by cyanation on the C-I bond mediated by norbornene, to give *ortho*-aryl aromatic nitriles **289** in 31-94% yields (**Scheme 112**).[329] Aryl iodides mono-substituted in *ortho* position were used to avoid the formation of multiple products since only one C-H functionalization can occur when one of the *ortho* positions of the aryl iodide is substituted. Furthermore, an excess of aryl bromides is required to minimize the homo-coupling product deriving from the competitive *ortho* arylation by another molecule of aryl iodide.



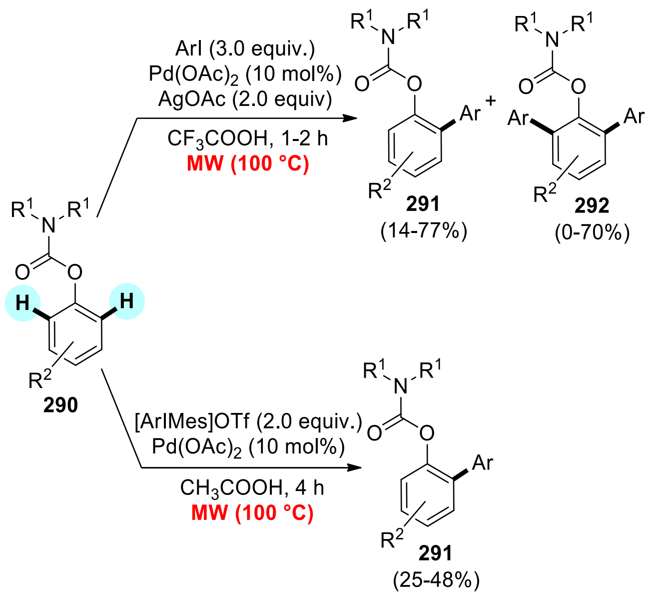
Scheme 112. Synthesis of *ortho*-aryl aromatic nitriles **289** *via* microwave-assisted Pd-catalyzed Catellani-type protocol.

Crabtree *et al.* developed in 2008 a protocol for the microwave-assisted decarboxylative coupling of aromatic acids with aryl halides or arenes, performed in the presence of $Pd(OAc)_2$ and *t*-Bu-XPhos as the catalytic system and Ag_2CO_3 as the base, in a 9 : 1 mixture of DMF and DMSO as the solvent, under MW heating at 200 °C for only 5 min.[330] Reactions of carboxylic acids with a variety of functionalized aryl iodides afforded the target products in high regioselectivity (coupling occurs at the site of decarboxylation). When carboxylic acids were reacted with arenes, the corresponding coupling products were obtained in good regioselectivity only in the presence of *ortho*-directing groups on arenes.

Therefore, the introduction of *ortho*-directing groups on arenes is an efficient strategy to improve regioselectivity and reaction rates in direct C-H bond arylation reactions of these substrates. Indeed, the proximity between the directing group and the metal complex forces the *ortho* aromatic C-H bond activation and increases the rate of metalation. In this contest, the use of *N*-containing heterocyclic directing groups is an attractive synthetic tool. Ruthenium-catalyzed *ortho*-arylation of 2-phenylpyridine and 2-phenyl-2-oxazoline with (hetero)aryl bromides under conventional thermal heating was reported in 2008 by Inoue *et al.*, demonstrating that MW-assisted reactions gave similar yields with respect to those under conventional thermal heating in dramatically shorter reaction times (30 min at 160 °C *vs.* 20 h at 120 °C), by using $[RuCl_2(\eta^6\text{-}C_6H_6)]_2-4PPh_3$ as the catalyst, K_2CO_3 as the base and NMP as the solvent.[331]

In 2013, Gimeno *et al.* showed that the inexpensive catalytic system $RuCl_3$-nH_2O-Zn-NaOAc is active for the selective *ortho* mono-arylation of 2-phenylpyridine with aryl and heteroaryl chlorides in H_2O; the reaction can be accelerated using microwave irradiation instead of conventional thermal heating (1 h *vs.* 20 h), although a slightly increase of the *ortho*-diarylated product with respect to the monoarylated one was found.[137] The protocol, using commercially available components, inexpensive aryl chlorides and a green solvent, is of particular interest from the point of view of *Green Chemistry*, and it was also scaled up to a multi-gram scale with excellent isolated yields.

In 2009, Bedford and co-workers reported a Pd-catalyzed direct *ortho*-arylation of carbamate-protected phenols **290** with either aryl iodides or diaryliodonium salts.[332] More in detail, reactions with aryl iodides were carried out using 10 mol% of $Pd(OAc)_2$ as the catalyst and 2.0 equiv. of silver acetate as the base, in trifluoroacetic acid as solvent for 1-2 h under microwave irradiation, affording a mixture of both mono-arylated **291** and bi-arylated **292** products; reactions with iodonium salts were instead carried out with only $Pd(OAc)_2$ (10 mol%), in acetic acid as solvent, under MW for 4 h, affording exclusively the desired mono-arylated products **291** (**Scheme 113**). Despite the use of MW is favourable in promoting these reactions, in our opinion the present protocol is characterized by many issues which hardly fit with the Twelve Principles of the *Green Chemistry*: the need of high palladium loading; the use of hardly sustainable reaction media (in particular, in the case of trifluoroacetic acid); the use of iodonium salts as arylating agents with low atom economy.

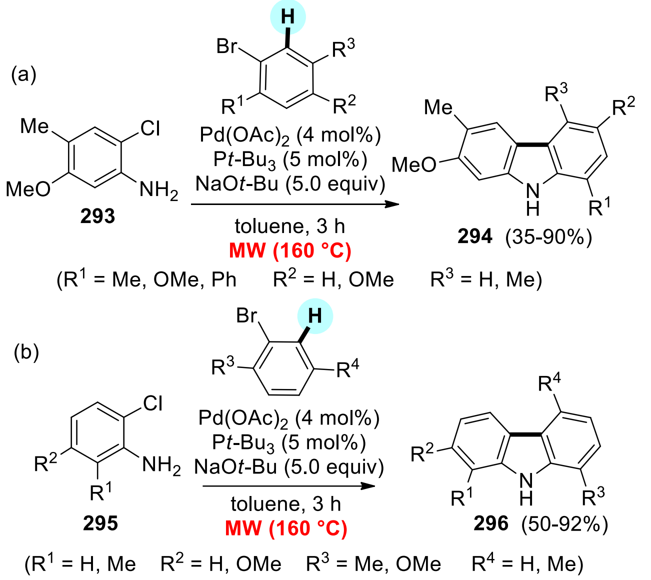


Ar = *p*-BrC$_6$H$_4$, *m*-BrC$_6$H$_4$, *p*-COOMeC$_6$H$_4$, *m*-COOEeC$_6$H$_4$,
p-MeC$_6$H$_4$, *p*-COMeC$_6$H$_4$, *p*-OMeC$_6$H$_4$, *m*-OMeC$_6$H$_4$,
o-MeC$_6$H$_4$, *o*-OMeC$_6$H$_4$,
R^1 = Me, Et, i-Pr, Ph R^2 = 4-*t*-Bu, 3-Me, 3-OMe

Scheme 113. Pd-catalyzed direct *ortho*-arylation of carbamate-protected phenols **290** with aryl iodides or diaryliodonium salts assisted by microwave irradiation, reported in 2009 by Bedford and co-workers.[332]

In contrast with the usually observed *ortho*-selectivity deriving from the effect of directing groups, *meta*-selective C-H bond arylation based on the use of copper catalysts have been also developed. In 2017, Hong and co-workers described efficient copper catalysts for direct C-H bond *meta*-arylation of pivanilide substrates with diaryliodonium triflate under microwave heating: homogeneous $Cu(OTf)_2$ and heterogeneous Cu(II)-β zeolite catalysts were used, affording the desired products in very short times (30 min and 1-4 h, respectively), while a typical reaction time for the same transformation reported in the literature was about 24 h under conventional heating conditions.[87] Despite shorter reaction times were demonstrated under MW irradiation, the use of DCE as the solvent and the need of an excess of diaryliodonium triflate (2 equiv.) negatively impact on the sustainability of the protocol.

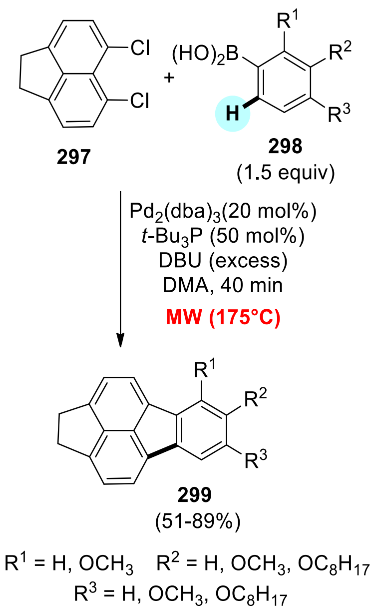
MW-assisted intramolecular direct arylation, entropically favored with respect to the related intermolecular reactions, are useful synthetic protocol in the synthesis of benzo-fused (hetero)cycles. Examples based on the formation of five-membered rings are detailed below. In 2006, Bedford *et al.* reported the synthesis of NH-free carbazoles, including carbazole-based natural alkaloids, from 2-chloroanilines by a tandem microwave-assisted Buchwald-Hartwing amination/direct C-H arylation process.[333] The microwave-assisted one-pot protocol appears to be general to produce the NH-free carbazoles **294** and **296** from the reaction of, respectively, 2-chloroanilines **293** and **295** with 2-substituted aryl bromides (**Scheme 114**). This microwave-assisted, one-pot protocol was also extended to the synthesis of indoles and, in a following study, to the synthesis of fluorinated carbazoles.[334]



Scheme 114. Synthesis of carbazoles **294** and **296** by one-pot, microwave-assisted tandem Buchwald-Hartwing amination/direct C-H arylation process.

Maes and co-workers reported some examples of palladium-catalyzed intramolecular direct C-H bond arylation at high temperature and under microwave irradiation, where 5*H*-pyrido[3,2-*b*]indoles were synthesized from 2-chloro-pyridin-3-amines.[335] Due to the low reactivity of C-Cl bond the high catalyst loading of $PdCl_2(PPh_3)_2$ (8 mol%) was needed to achieve full conversion under microwave irradiation at 180°C for 10 min. Clearly, this high amount of the homogeneous palladium catalyst, in combination with the use of DMA as a solvent, clearly limited the interest of this approach in the frame of the *Green Chemistry*.

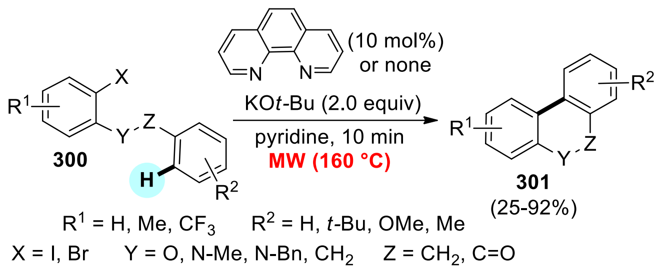
In 2009, Scott *et al.* developed the synthesis of fluoranthene derivatives **299** from 5,6-dichloroacenaphthene **297** and arylboronic acids **298** by a Pd-catalyzed sequence involving an intermolecular Suzuki-Miyaura cross-coupling followed by an intramolecular direct C-H bond arylation reaction of arene rings (**Scheme 115**).[336] Interestingly, they showed that the reactions carried out under microwave irradiation required shorter time than those carried out with thermal heating (40 min *vs.* 36 h for reaction of **297** with benzeneboronic acid). However, if such protocol was highly appealing from a synthetic point of view since it allowed for the preparation of highly functionalized polycyclic compounds, the need of a high palladium loading (20 mol%) and of a quite expensive ligand (that is, *t*-Bu$_3$P, 50 mol%) makes it of only limited interest from a sustainability point of view.



Scheme 115. Synthesis of fluoranthenes **299** from 5,6-dichloroacenaphthene **297** and arylboronic acids **298** by a MW-assisted Pd-catalyzed sequence involving an intermolecular Suzuki-Miyaura cross-coupling followed by an intramolecular direct C-H bond arylation.

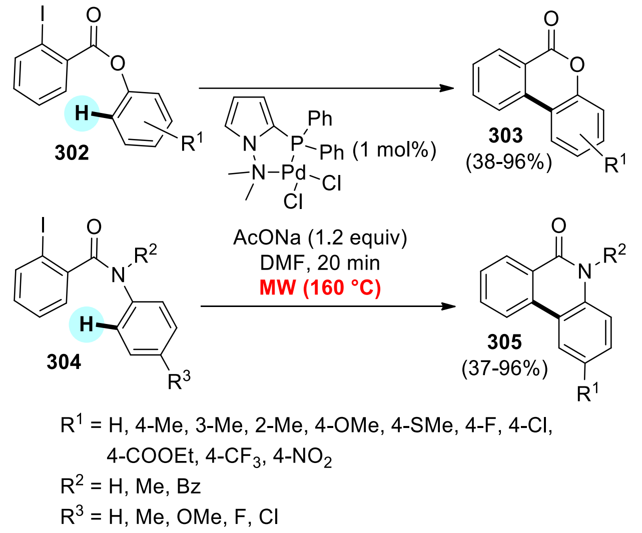
MW-promoted intramolecular direct C-H arylation reactions of arenes affording five-membered rings were also used to synthesize many biologically active compounds: Overman and co-workers proposed the Palladium-catalyzed enantioselective cyclization of a dienyl aryl triflate to dihydrocarbazole derivative, an intermediate in total synthesis of the *Strychnos* alkaloid (+)-minfiensine;[337] Harding and co-workers described a route to azafluoranthene alkaloids and azafluoranthene-like isoquinoline alkaloids based on intramolecular direct C-H bond arylation reactions of functionalized arenes.[338]

Microwave-assisted intramolecular direct C-H bond arylation of arenes leading to the formation of six-membered ring have also been studied. In 2011, Charette *et al*. developed a *t*-BuOK-mediated intramolecular cyclization of *ortho*-halo-substituted aryl ether, aniline and amide derivatives **300** in the absence of a transition metal catalyst; substrates were treated in pyridine under microwave irradiation at 160 °C for 10 min, affording the target molecules **301** in yields ranging from 25% to 92% (**Scheme 116**).[339] A longer reaction time (16 h) was instead required to achieve high conversions under conventional thermal heating at 80 °C. The regioselectivity of cyclization was influenced by the substitution on the benzyl moiety of the aryl system and the formation of a mixture of regioisomeric products was observed in most cases.



Scheme 116. Microwave-assisted, transition metal catalyst-free intramolecular direct C-H bond arylation of *ortho*-halo-substituted aryl ether, aniline and amide derivatives **300** described in 2011 by Charette *et al.*[339]

In 2016, López-Cortés *et al.* reported the MW-assisted intramolecular direct C-H bond arylation of iodoesters **302** and iodoamides **304** to give, respectively, benzopyrones **303** and phenanthridinones **305**.[340] Reactions were carried out using a non commercial [N,P]-pyrrole $PdCl_2$ complex (1 mol%), in the presence of 1.2 equiv. of sodium acetate as a base: working for only 20 minutes under microwave irradiation in DMF, the desired coupling products were obtained in moderate to excellent yields (38-96% for **303**; 37-96% for **305**) (**Scheme 117**). The rapid and easy preparation of these tricyclic lacton and lactam derivatives, only possible thanks to the use of microwave irradiation, is very appealing for synthetic organic chemists; however, the use of harmful DMF as the solvent, as well as the need of a non-commercial Pd complex as catalyst (which need to be *ad hoc* synthesized), represent severe limitation in terms of the process sustainability.

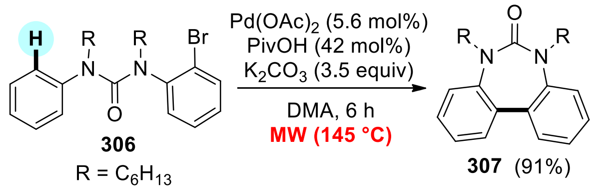


Scheme 117. Microwave-assisted intramolecular direct C-H bond arylation of iodoesters **302** and iodoamides **304** to give, respectively, benzopyrones **303** and phenanthridinones **305**, reported in 2016 by López-Cortés *et al.*[340]

For the sake of completeness, we feel compelled to report that the Pd-catalyzed intramolecular direct C-H bond arylation reactions of arenes involving the formation of a six-membered ring under MW irradiation were successfully used also for the synthesis of several other polycyclic compounds: tetracyclic heterocycles with a fused ring system of 1,4-oxazine or 5*H*-phenanthridine;[341] pyridazino-fused phenanthrenes;[335] benzopyran-fused flavones;[342] naphthalene-fused quinolinol ligands;[343] aporphine alkaloids.[344] In all these cases, the application of microwave irradiation as non-conventional energy source definitely allowed for the development of fast protocols (typically ranging between few minutes and 1 h). However, we will not consider these protocols in detail below: if from a merely synthetic point of view they could be quite appealing, allowing for an easily and fast preparation of many highly functionalized polycyclic compounds, in most cases these procedures were associated to the need of high loading of homogeneous metal catalysts, the use of toxic and harmful solvents, the production of co-products and/or by-products thus requiring tedious purification procedures of the desired coupling products.

The microwave irradiation was also found to promote some examples of intramolecular direct C-H arylation of arenes leading to the formation of seven-membered rings. In 2011, Harding *et al.* used a MW-assisted strategy based on a intramolecular direct arylation of arenes as the key step for the synthesis of *C*-homoaporphine alkaloids.[345] More in detail, after a fine tuning of the experimental conditions, the intramolecular direct C-H arylation step was carried out with $Pd(OAc)_2$ (10 mol%) as the catalyst, Cy_3P (40 mol%) as the ligand, K_2CO_3 (4.0 equiv.) as the base and pivalic acid (40 mol%) as an additive, in DMSO as the solvent for 15 minutes under microwave irradiation. Once again, despite the use of MW allowed for very fast reactions, high catalytic loading was required for obtaining products in good yields. On the other hand, this specific work was mainly focused on the optimization of the preparation of *C*-homoaporphine alkaloids, rather than on the development of highly sustainable synthetic protocols.

Takagi, Mikami and co-workers reported in 2019 the preparation of non-planar, urea-bridged oligophenylenes with a seven-membered ring endowing the chiral groups. The main backbone **307** was synthesized by intramolecular Pd-catalyzed direct C-H arylation of *N*,*N*′-dihexyl-*N*-(2-bromophenyl)-*N*′-phenylurea **306** in the presence of $Pd(OAc)_2$ as catalyst, K_2CO_3 as base and pivalic acid as additive.[346] The best yield was obtained after 6 h for ligand-free reaction under MW irradiation; under similar conditions, lower yield was observed after 24 h working in the presence of the sole thermal heating at 145 °C (**Scheme 118**).



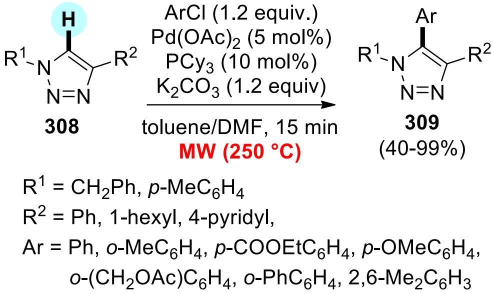
Scheme 118. Intramolecular Pd-catalyzed direct arylation of *N*,*N*′-dihexyl-*N*-(2-bromophenyl)-*N*′-phenylurea **306** assisted by microwave irradiation: synthesis of **307**, intermediate in the preparation of urea-bridged oligophenylenes.

4.2.2. Microwave-assisted direct C-H bond arylation of *N*-heteroarenes.

Among five-membered monocyclic *N*-heteroarenes, only few examples of microwave-assisted direct C-H bond arylation of pyrroles have been reported in the literature, performed in the context of more extended investigations of MW-assisted arylation of several heteroarenes, using palladium,[347] rhodium[326,348] or manganese[197] catalysts.

Triazoles and imidazoles have been more investigated as substrates for MW-assisted direct arylation reactions. In 2007, Oshima et *al.* reported the C5 regioselective direct C-H arylation of 1,4-disubstituted 1,2,3-1*H*-triazoles **308** with aryl chlorides as arylating agents, carried out in the presence of $Pd(OAc)_2/PCy_3$ as the catalytic system, K_2CO_3 as the base and a toluene/DMF mixture as the reaction medium, affording under microwave the desired 5-arylated products **309** in good yields after only 15 minutes (**Scheme 119**).[349] Interestingly, the application of microwave irradiation was here very appealing, since it allowed to activate the less reactive aryl chlorides,whose use in organic synthesis is more favourable than other typical arylating agents, because they are less expensive and readily available compared to the corresponding aryl bromides and iodides.

Very recently, Liu and co-workers developed an appealing route to 1,5-disubstituted-1,2,3-1*H*-triazoles, which are less accessible than more common 1,4-disubstituted-1*H*-1,2,3-triazoles (which instead are easily prepared by Cu(I)-catalyzed Huisgen 1,3-dipolar cycloaddition). Their synthetic approach was based on the direct C-H arylation of 1-benzyl-1,2,3-triazoles with functionalized aryl bromides in the presence of $Pd(OAc)_2/P(t\text{-}Bu)_3\text{-}HBF_4$ as the catalytic system, K_2CO_3 as the base and DMF as the reaction solvent under microwave irradiation at 100 °C for 30 minutes.[350]

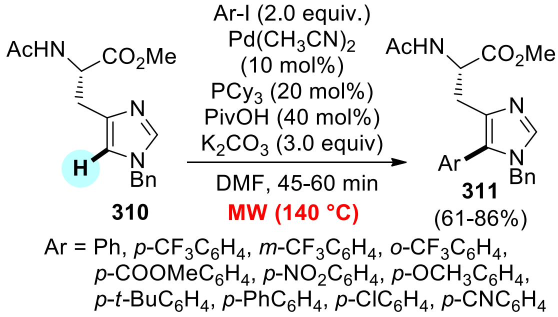


Scheme 119. Microwave-assisted C5 regioselective direct C-H arylation of 1,4-disubstituted 1,2,3-1*H*-triazoles **308** with aryl chlorides, reported In 2007 by Oshima et *al.*[349]

Few examples of rhodium-catalyzed C2 regioselective direct C-H bond arylation of 4,5-diaryl-1*H*-imidazoles under microwave irradiation at 250 °C for 40 min was reported in 2006 by Ellman and co-workers.[351] Actually, despite the appealing use of microwave irradiation, authors were not interested here in the development of a highly sustainable synthetic method, as demonstrated by the use of *o*-dichlorobenzene as reaction medium.

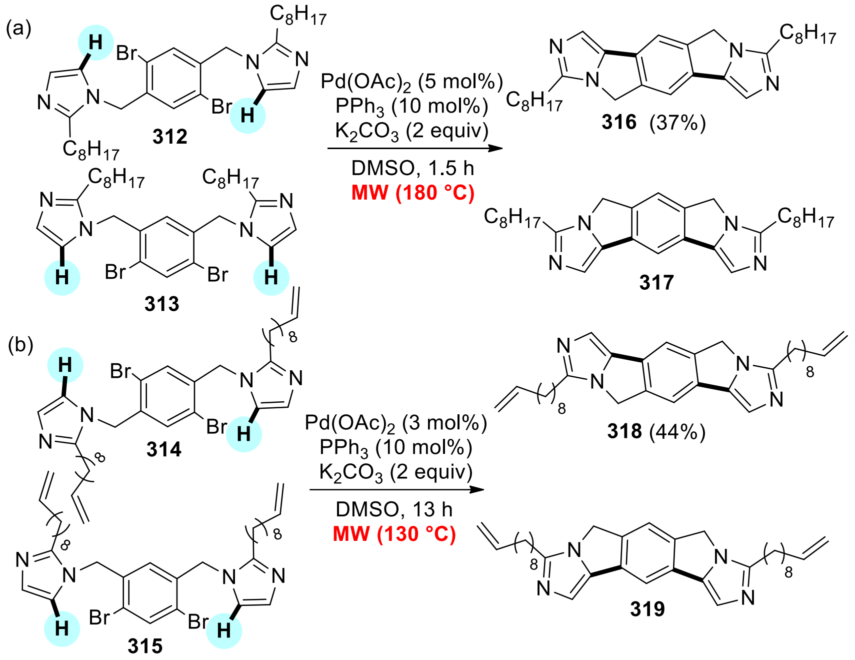
In more recent examples, palladium catalysis has found applications in microwave-assisted direct C-H bond arylation reactions of imidazole derivatives. In 2011, Lee *et al.* developed a C5 regioselective direct C-H arylation of imidazoles with aryl bromides and chlorides using a moderate loading (2.5 mol %) of a preformed electron-rich palladium acetate complex bearing both phosphine and *N*-heterocyclic carbene ligands, KOAc as the base and DMA as the solvent under microwave irradiation at 140 °C.[352] The microwave irradiation effectively promoted reactions, affording C5 arylated products in comparable or slightly higher yields but in markedly shorted reaction times (2 h *vs.* 18 h) with respect to conventional thermal heating.

In the same year, Kappe and co-workers showed that the reactivity of imidazole ring in the C5 regioselective Palladium-catalyzed direct C-H bond arylation increased significantly using microwave heating at 180 °C compared to previous literature conditions based on thermal heating ($Pd(OAc)_2/PCy_3$ was used as the catalytic system in the presence of K_2CO_3 as the base, pivalic acid as additive in DMF).[353]



Scheme 120. Palladium-catalyzed C5 regioselective direct C-H bond arylation of the *L*-histidine derivative **310** under microwave irradiation.

In 2013, Jain *et al.* described the C5 regioselective direct C-H arylation of fully protected L-histidine **310** with aryl iodides: reactions were performed in DMF under microwave irradiation at 140°C for 45-60



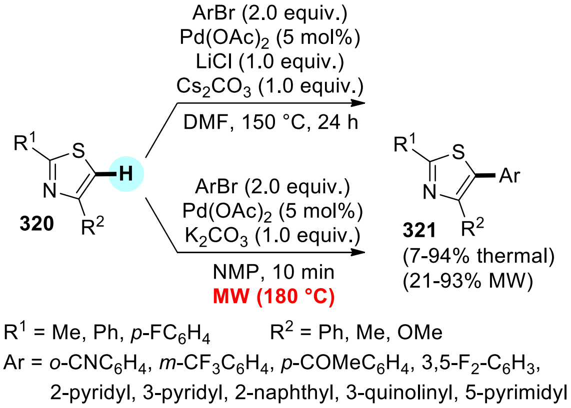
Scheme 121. Microwave-assisted synthesis of fused imidazole monomers **316-319** by palladium-catalyzed intramolecular direct C-H bond arylation of derivatives **312-315**.

minutes, using $Pd(CH_3CN)_2$ (10 mol%) as the catalytic precursor, PCy_3 (20 mol%) as the ligand, K_2CO_3 (3.0 equiv.) as the base and pivalic acid (40 mol%) as additive, thus affording 5-aryl-L-histidines **311** in 61-86% yields.[354] From a synthetic point of view, the present protocol was very appealing: excellent C5-regioselectivity and total chiral integrity were reported in addition to high yields, functional groups tolerance and short reaction times. However, some issues still remain in the frame of the *Green Chemistry*, in particular the need of high catalytic loading, the use of DMF as harmful reaction medium and the need of an excess of aryl iodide. Moreover, very low yields were obtained when the aryl bromides were used as coupling partners (**Scheme 120**).

In 2016 Takagi *et al.* reported the synthesis of π-conjugated polymers whose basic building blocks were the fused imidazole monomers **316-319**; these were synthesized by microwave-assisted intramolecular direct C-H arylation of derivatives **312-315**, performed in DMSO at 180 °C (for 1.5 h) or at 130 °C (for 13 h) using $Pd(OAc)_2$, PPh_3 and K_2CO_3 (**Scheme 121**).[355]

Microwave-assisted direct C-H arylation protocols of five-membered *N*-heterocycles including O or S atoms have been also developed. In 2008, Piguel *et al.* reported a ligand-free palladium/copper co-mediated direct C2 arylation of 5-aryloxazoles with aryl bromides under MW irradiation, affording a variety of 2,5-diaryloxazole derivatives in good yields (57-76%) and very short reaction time (4-15 minutes).[356] Very low yield was found for the coupling of 5-phenyloxazole with bromobenzene in the same experimental conditions ($Pd(OAc)_2$/CuI as the catalytic system, in the presence of K_2CO_3 as the base and DMF as the solvent) but under thermal heating at 150 °C instead of microwave irradiation (11% *vs.* 81%).

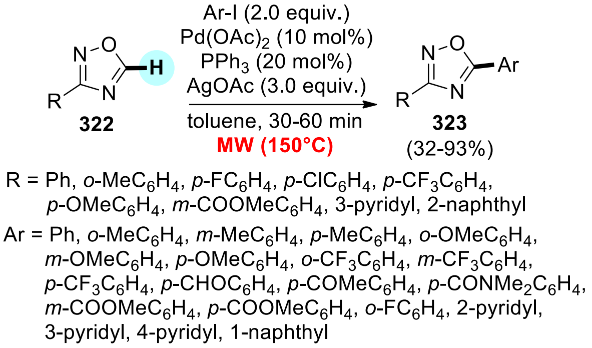
In 2013, Yum *et al.* reported an appealing comparative work, where the ligand-free C5 regioselective Pd-catalyzed direct C-H bond arylation of 2,4-disubstituted thiazoles **320** were carried out under conventional or MW-assisted heating.[357] In the first case, reactions were performed in $Pd(OAc)_2$ (5.0 mol%) as the catalytic system, in the presence of LiCl (1.0 equiv.) as additive and Cs_2CO_3 (1.0 equiv.) as base, in DMF as the solvent under thermal heating at 150 °C, affording the corresponding 5-arylated thiazoles products **321** after 24 h in 7-94% yields. In the other case, the reactions were performed with $Pd(OAc)_2$ (5 mol%) as the catalyst, K_2CO_3 (1.0 equiv.) as the base, in NMP under microwave irradiation at 180 °C, affording the same products **321** after only 10 minutes in 21-93% yields (**Scheme 122**). As expected, the products yields of the microwave-assisted reactions were slightly higher but the reaction time dramatically shorter with respect to the reactions under conventional thermal heating.



Scheme 122. Ligand-free C5 regioselective Palladium-catalyzed direct C-H bond arylation of 2,4-disubstituted thiazoles **320**, carried out under conventional or MW-assisted heating.

A C5 regioselective Pd-catalyzed direct C-H bond arylation of thiazoles with iodoarenes, performed at 115 °C under MW irradiation, in H_2O as a solvent for 1.5 h, was reported by Wünsch *et al.*[152] In 2017, Hu *et al.* described a MW-assisted, C5 regioselective direct C-H arylation of 3-substituted 1,2,4-oxadiazoles **322** with aryl iodides, in the presence of $Pd(OAc)_2/PPh_3$ as catalytic system and silver acetate as base, affording

3,5-diaryl-1,2,4-oxadiazole derivatives **323**, obtained in most cases in high yields (**Scheme 123**).[358] If the application of microwave irradiation allowed for high yields in short reaction times, the use of large amounts of palladium and, above all, silver species (respectively 20 mol% and 3.0 equiv.) represent a severe issue in terms of sustainability, since they could easily contaminate the coupling products.



Scheme 123. C5 regioselective direct C-H arylation of 3-substituted 1,2,4-oxadiazoles **322** with aryl iodides assisted by microwave irradiation.

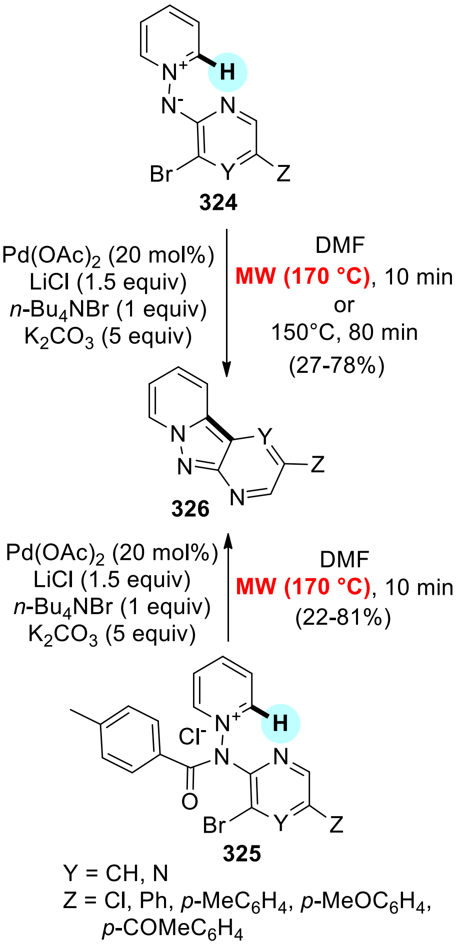
A tandem S_NAr reaction/MW-assisted direct C-H arylation protocol for the synthesis of several pyrazolofuropyrazine scaffolds starting from 5-hydroxypyrazoles and 2,3-dichloropyrazine was reported in 2018 by Nakamura and co-workers.[359] After the first S_NAr step, $PdCl_2(PPh_3)_2$ and NaOAc were added and the resulting reaction mixture was kept under MW at 160 °C for 1 h, affording the expected products in very low yields (10-32%). Therefore, in this case the use of microwave was not of particular help in achieving high yields of the direct arylation products.

Moving to six-membered monocyclic *N*-heteroarenes, direct C-H bond arylation reactions of pyridine and diazine-based derivatives have been deeply investigated under microwave irradiation. In 2008, Itami *et al.* demonstrated that the coupling of electron-deficient *N*-heterocycles (pyridine, pyridazine, pyrimidine and pyrazine derivatives) with aryl iodides can be promoted by potassium *t*-butoxide under microwave irradiation without the need of transition metal catalysts.[360] Despite the very short reaction time to achieve fully conversion (5 min at 50°C), reactions required a large excess of the *N*-heteroarene (40 equiv.), thus limiting its effective sustainability, and can afford mixtures of different regioisomers.

In 2010, Guchhait *et al.* developed a microwave-assisted protocol for the oxidative direct C-H bond arylation of a variety of heteroarenes, including pyridine and pyrimidine derivatives, with (hetero)arylboronic acids in the presence of $Mn(OAc)_3$.[197] Despite the use of boronic acids as arylating agents did not represent the best choice in terms of the *Green Chemistry*, the choice of ethanol, which is the the result of a quite extensive solvent screening, in combination with the use of microwave irradiation, confirmed a general sustainability for this method.

In 2020, Kozak and co-workers investigated the oxidative direct C-H bond arylation of pyrazine, pyridazine and pyridine derivatives with arylboronic acids using $K_2S_2O_8$ as the oxidant and $FeSO_4$ as the catalyst, in a H_2O/CH_2Cl_2 solvent mixture under microwave heating at 70 °C for 25 min.[161] The use of an iron species as catalyst (which is typically less expensive than palladium and other more common metal catalysts for direct C-H arylation protocols), in combination with the choice of microwave irradiation is definitely favourable; however, on the other hand several issues in the frame of the *Green Chemistry* still remain: the use of dichlorometane as not sustainable co-solvent; the need of high loading of the homogeneous iron catalyst (20 mol%), which could contaminate coupling products; the use of boronic acids as arylating agents with modest waste prevention.

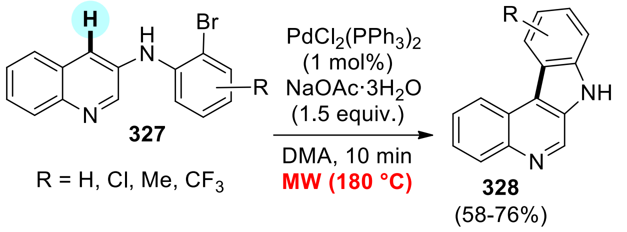
More frequently, Palladium-based catalysts were used in microwave-assisted direct arylation reactions of pyridine and diazine derivatives. In 2008 Alvarez-Builla *et al.* studied the synthesis of a new class of pyrazolopyridines **326** by palladium-catalyzed intramolecular direct C-H arylation of pyridinium *N*-aminides **324** or related *N*-acyl salts **325**, performed with $Pd(OAc)_2$ as the catalyst, K_2CO_3 as the base, LiCl and *n*-Bu_4Br as additives, under microwave irradiation at 150 °C for 80 min or at 170°C for 10 min.[361] MW irradiation was crucial for obtaining the final products **326** in higher yields and shorter times compared with the use of the sole thermal heating. In fact, compound **326** (Y = CH, Z = Cl) was obtained in good yield (72%) at 170 °C under MW irradiation after only 10 minutes, while it was isolated in lower yield (47%) after 48 h under conventional thermal heating (**Scheme 124**).



Scheme 124. Synthesis of pyrazolopyridines **326** by Pd-catalyzed intramolecular direct C-H arylation of pyridinium *N*-aminides **324** or related *N*-acyl salts **325** assisted by microwave irradiation.

In 2009, Beccalli *et al.* reported a palladium-catalyzed intramolecular direct C-H bond arylation of functionalized nicotinamides, leading to polyazacyclic systems using ligand-free conditions, carried out using $Pd(OAc)_2$ as the catalyst, KOAc as the base and Bu_4NCl as additive, in DMA as the solvent.[362] Interestingly, authors reported that, by keeping the same experimental conditions, MW irradiation could considerably shorten the reaction time with respect to conventional heating (45 min under MW heating at 120 °C *vs.* 24 h under thermal heating at 100°C). In 2012, Hanna Jr. *et al.* reported the direct C-H bond arylation of pyridine *N*-oxide with 2-bromoacetanilides, carried out in the presence of $Pd(OAc)_2/P(t\text{-}Bu_2Me)\cdot HBF_4$ as the catalytic system and K_2CO_3 as the base in toluene under microwave heating at 140 °C for 1-3 h, giving the corresponding C2 arylated products in 51-76% yields.[363]

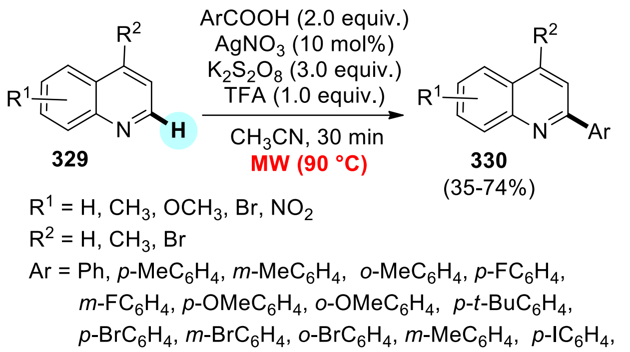
Among bicyclic *N*-heteroarenes, quinoline and indole derivatives have been largely investigated as substrates for direct C-H bond arylation reactions under microwave irradiation. In 2006, Maes *et al.* reported the synthesis of 5-methyl-5*H*-indolo[2,3-*c*]quinolines starting from 3-bromoquinoline and 2-bromoanilines by a three step protocol involving a Buchwald-Hartwig amination, a regioselective intramolecular direct arylation and a final methylation.[364] The intramolecular direct C-H bond arylation step was performed at 180 °C under microwave irradiation: *N*-(2-bromophenyl)quinolin-3-amines **327** afforded the final 7*H*-indolo[2,3-*c*]quinolines **328** in good yields, allowing to reduce both the reaction time (10 min *vs* 1h) and the catalyst loading (1 mol% *vs* 23 mol%) with respect to thermal heating at 160 °C (**Scheme 125**). Few years later, the same protocol was extended to the synthesis of 11*H*-indolo[3,2-*c*]isoquinolines.[365]



Scheme 125. Microwave irradiation-assisted intramolecular direct C-H bond arylation of *N*-(2-bromophenyl)quinolin-3-amines **327**: synthesis of 7*H*-indolo[2,3-*c*]quinolines **328**, described In 2006 by Maes *et al.*[364]

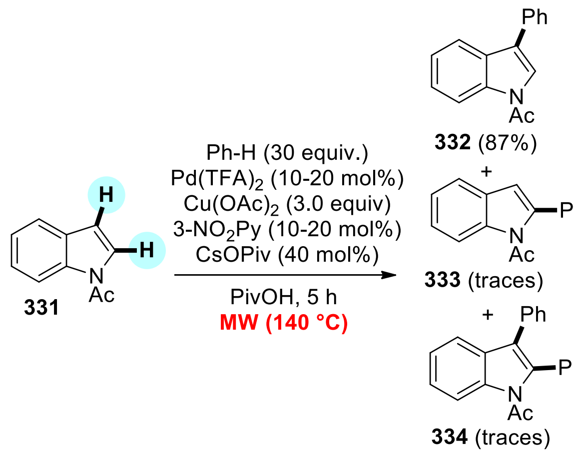
A very appealing investigation was reported in 2017 by Yuan *et al.*, who reported a straightforward microwave-assisted protocol for the Minisci reaction of quinolines **329**, that is a Ag(I)-catalyzed radical coupling with aromatic carboxylic acids, performed in the presence of a suitable oxidizing agent; in fact, the coupling typically occurred through the decarboxylation of the aryl carboxylic acids to give the corresponding radicals, which are the real arylating species, thanks to the synergistic action of the silver catalyst and the oxidant.[366] In this case, reactions were carried out by using $AgNO_3$ (10 mol%) as the catalyst, $K_2S_2O_8$ (3.0 equiv.) as the oxidant and trifluoroacetic acid (1.0 equiv.) as additive, in acetonitrile under microwaves irradiation at 90 °C. The present protocol exhibited broad substrate scope and good functional group tolerance on both carboxylic acids and quinolines **329**, affording the 2-arylquinoline derivatives products **330** in moderate to good yields (35-74%). However, it is worth to emphasize that a mixture of 2-substituted and 4-substituted quinoline derivatives was obtained starting from quinolines unsubstituted in the C4 position (**Scheme 126**).

The microwave-assisted direct arylation of quinoline and isoquinoline with phenylboronic acid catalyzed by $Mn(OAc)_3$, performed in ethanol as a sustainable solvent, was reported in 2010 by Guchhait *et al.*[197] Itami and co-workers instead described the MW-assisted direct C-H bond arylation of quinoxaline with iodobenzene in the presence of potassium *t*-butoxide (1.5 equiv.) as base, although it required a large excess (40 equiv.) of the starting heteroarene.[360]



Scheme 126. Microwave-assisted Minisci reaction of quinolines **329** for the preparation of 2-arylquinoline derivatives **330**.

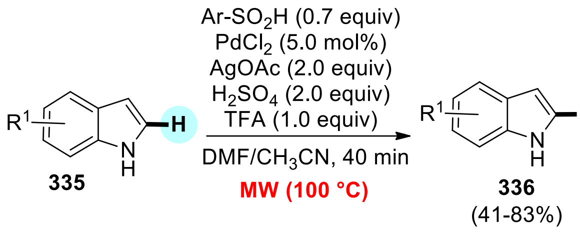
In 2007, Fagnou *et al.* reported that palladium, in the presence of a copper oxidant, can catalyze the oxidative direct C-H arylation of *N*-acetylindoles with benzenes.[367] Under thermal heating a prolonged reaction time (24 h) was necessary to get to completation the reaction of *N*-acetylindole **331** with benzene affording **332-333-334** in overall 61% yield (**332**:**333**:**334** = 27:1:0.3) with 10 mol% of $Pd(TFA)_2$; on the contrary, microwave heating at 140°C provided **332** in 87% yield in only 5 h (**Scheme 127**).



Scheme 127. Microwave-assisted protocol for the oxidative direct C-H bond arylation of *N*-acetylindole **331** with benzene described in 2007 by Fagnou and co-workers.[367]

In 2012, James and co-workers developed an efficient macrocyclization reaction by the intramolecular, microwave-assisted Palladium-catalyzed C2 regioselective direct C-H bond arylation of tryptophan indole moiety with iodophenyl-containing amino acids.[368] More in detail, from 15- to 25-membered peptidic macrocycles were obtained in 40-75% yield by treatment of the starting materials with $Pd(OAc)_2$, *ortho*-nitrobenzoic acid and $AgBF_4$ under microwave irradiation at 130 °C for 30 min. Using the same catalytic system, conventional thermal heating required longer reaction times (12 h) at higher temperature (150 °C), confirming the high efficiency of MW irradiation as an highly efficient source of energy in promoting direct C-H bond arylation of highly functionalized substrates.

A general protocol for the C2 regioselective direct C-H bond arylation of NH-free indoles **335** with arylsulfinic acids as non-conventional arylating agents was presented in 2013 by Wang *et al.*: reactions were carried with $PdCl_2$ (5 mol%) as the catalyst, silver acetate (2.0 equiv.) as the oxidant and H_2SO_4 (2.0 equiv.) as additive, for 40 minutes under MW irradiation at 100 °C, affording 2-arylindoles **336** in moderate to high yields (41-83%).[369] The microwave irradiation had a beneficial effect on reaction time and yields: under thermal heating at 100 °C, the reaction of indole with phenysulfinic acid afforded 2-pheylindole in lower yield (61% *vs*. 82%) and longer reaction time (24 h *vs.* 40 min) compared to under microwave irradiation (**Scheme 128**).

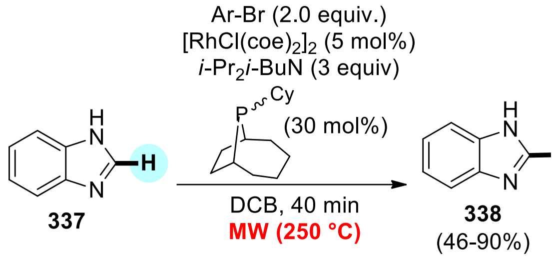


R^1 = H, 5-Me, 7-Me, 5-OMe, 6-F, 5-Cl, 5-Br, 5-CN, 4-COOMe
Ar = Ph, *p*-MeC_6H_4, *m*-MeC_6H_4, *o*-MeC_6H_4, *p*-ClC_6H_4, *o*-ClC_6H_4, *p*-$OMeC_6H_4$, *p*-FC_6H_4, *p*-BrC_6H_4, *p*-*t*-BuC_6H_4, 1-naphthyl, 2-naphthyl

Scheme 128. Microwave-assisted C2 regioselective direct C-H bond arylation of NH-free indoles **335** with arylsulfinic acids, reported in 2013 by Wang *et al.*[369]

In 2016, Marsden and co-workers studied a MW-assisted intramolecular direct C-H arylation of 2-(*N*-Indolyl) amides decorated with bromoaryl moieties to give indole-fused benzodiazepines.[370] Working under MW irradiation with typical direct C-H bond arylation conditions, *i.e.*, in the presence of $Pd(OAc)_2$ as the catalytic precursor, PPh_3 as the ligand, potassium acetate as the base and TBAB as additive, in toluene as the solvent, the target molecules were obtained in 36-87% yields after only 15 minutes. In this case, no comparative studies between MW and thermal heating have been performed: in fact, authors were here mainly interested in the development of an efficient method for the preparation of indole-fused benzodiazepines, in order to achieve the synthesis of the hexahydropyrrolindole core of psychotrimine, rather than to study more environmental friendly conditions.

Microwave-assisted protocols for the direct C-H arylation of bicyclic *N*-heteroarenes with two or more nitrogen atoms were also developed. Two studies involving rhodium catalysis have been reported by Ellman and co-workers. In 2006, they developed a microwave-promoted direct C-H bond arylation protocol between 1*H*-benzo[*d*]imidazole **337** and aryl halides, using Rh catalysts[371] in the presence of 9-cyclohexylbicyclo-[4.2.1]-9-phosphanonane ligand and *ortho*-dichlorobenzene as the solvent, affording the corresponding C2 arylated products **338**.[351] The same products can also be obtained in good yields by thermal heating of the reaction mixtures in [D_8]THF in sealed tubes (150°C for 24 h), but the microwave irradiation allowed to reduce reaction times to only 40 minutes and eliminated the safety hazards associated with sealed-tube conditions (**Scheme 129**). The microwave protocol was then also extended to the direct C-H arylation of diverse other *N*-heterocycles including 1-methyl-1*H*-benzo[*d*]imidazole and benzo[*d*]oxazole. The same group in 2008 also developed a set of phosphepine ligands and investigated their activity in the Rh-catalyzed direct C-H arylation of many heteroarenes, including 1*H*-benzo[*d*]imidazole, benzo[*d*]oxazole and benzo[*d*]thiazole, with aryl bromides under MW irradiation.[348] With respect to their previous protocol, performed under MW at 250 °C for 40 min, temperature was here reduced to 200 °C but extending the reaction time to 2 h, using a THF/*ortho*-dichlorobenzene solvent mixture. If in both these works the use of microwave irradiation was very efficient, especially if compared with the conventional thermal heating, we do not feel like considering these two works of particular interest in the frame of the *Green Chemistry*: first of all, the use of toxic and harmful ortho-dichlorobenzene as a solvent hardly fit with the sustainability criteria; moreover, the need for not commercial Rh ligands could definitely impact on the overall cost of the process.



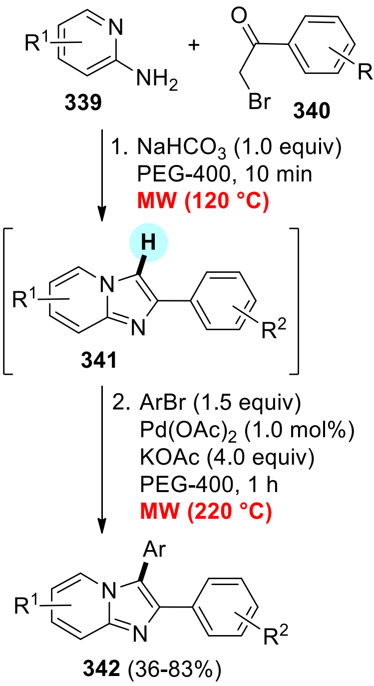
coe = cyclooctene

Ar = Ph, *p*-MeC_6H_4, *p*-$CF_3C_6H_4$, *p*-ClC_6H_4, *p*-CNC_6H_4, *p*-PhC_6H_4, *p*-$OCH_3C_6H_4$, *p*-$COEtC_6H_4$, *m*-MeC_6H_4, *p*-$CONH_2C_6H_4$, *m*-$OEtC_6H_4$, *m*-$COOEtC_6H_4$,

Scheme 129. Microwave-promoted direct C-H arylation protocol of 1*H*-benzo[*d*]imidazole **337** with aryl bromides, reported in 2006 by Ellman and co-workers.[351]

In the frame of palladium-mediated processes, in 2006 Berteina-Raboin *et al.* reported an interesting comparative study between thermal and microwave heating for the Pd-catalyzed C3 regioselective direct C-H arylation of imidazo[1,2-*a*]pyridines with aryl bromides, demonstrating that the use of MW significantly shortened reaction times.[372] More in detail, reactions were carried out in the presence of $Pd(OAc)_2$ as the catalyst, Ph_3P as the ligand and K_2CO_3 as the base: 3-aryl imidazo[1,2-*a*]pyridine products were obtained when both reagents were warmed at 100°C for 4 h using dioxane as the solvent, or irradiated at 130-150 °C for only 1-3.5 h in a mixture of dioxane-ethanol. On one hand, if the use of MW here allowed for a reduction of the reaction times, on the other similar products yields were found with both heating.

The synthesis of 2,3-diarylimidazo[1,2-*a*]pyridines **342** was reported in 2014 by the same group through a MW-assisted one-pot process in PEG-400 medium, which is more interesting from the point of view of *Green Chemistry* as it used a more sustainable reaction medium.[264] The protocol was based on the formation of 2-arylimidazo[1,2-*a*]pyridines **342** by a condensation step of 2-aminopyridines **339** with α-bromo ketones **340**, followed by Palladium-catalyzed direct C-H arylation of the resulting intermediate **341** with aryl bromides at the C3 position. After the first condensation step, performed in only 10 minutes under basic conditions thanks to use of microwave, bromoarene (1.5 equiv.), $Pd(OAc)_2$ (1 mol%) and KOAc (4.0 equiv.) were added, and the resulting mixture was left for 1 h under microwave irradiation, affording the final 2-arylimidazo[1,2-*a*]pyridines **342** in 36-83% yields (**Scheme 130**). In our opinion, such protocol was quite appealing in the context of the *Green Chemistry*: in addition to the use of microwave as efficient source of energy, able of drastically reducing the energy requirements of both condensation and direct arylation step, the use of PEG-400 as sustainable solvent was highly favourable; moreover, the development of one-pot processes, allowing for a reduction of the isolation and/or purification steps, is a further highly desirable feature which perfectly fits with the principles of the *Green Chemistry*.



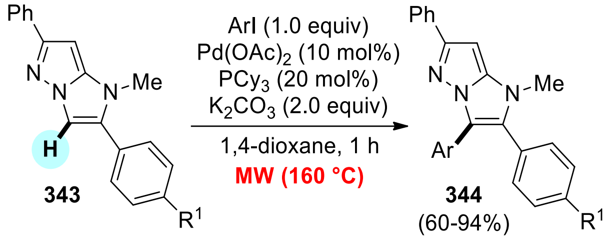
R^1 = H, Me, CF_3, Cl, COOMe
R^2 = H, OMe, Cl, F, NO_2
Ar = Ph, o-C_6H_4, m-C_6H_4, p-MeC_6H_4, p-$MeOC_6H_4$,
m-NO_2, p-$NO_2C_6H_4$, p-$CF_3C_6H_4$, p-FC_6H_4,
p-$COOMeC_6H_4$, p-$CHOC_6H_4$

Scheme 130. Synthesis of 2,3-diarylimidazo[1,2-*a*]pyridines **342** by microwave-assisted one-pot condensation/direct C-H arylation process in PEG-400 as the solvent.

Examples of microwave-assisted C3 arylation on the imidazolyl[1,2-*a*]pyridine moiety with non-commercially available Pd catalysts, such as preformed palladium acetate complex bearing phosphine and *N*-heterocyclic carbene ligands[352] and (SIPr)Pd(allyl)Cl complex [SIPr: (*N*,*N*'-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazol-2-ylidene)][373] were also reported. As can be easily foreseen, if on one hand in all these studies the use of microwave offered the possibility of reducing the energy requirements, on the other the choice of non-commercially available catalysts, which are often the result of quite long and tedious synthetic procedures, may have a negative impact on the overall cost of these direct C-H bond arylation.

In 2006, Van der Eycken and co-workers developed a Pd-catalyzed, microwave-assisted direct C-H arylation of 2-substituted imidazo[1,2-*a*]pyrimidines with aryl bromides affording 2,3-substituted imidazo[1,2-*a*]pyrimidines; switching the energy source from thermal heating to microwave irradiation, while keeping equal all other experimental conditions (*i.e.*, $Pd(OAc)_2$ as the catalyst, PPh_3 as the ligand, Cs_2CO_3 as the base in 1,4-dioxane as the solvent) a relevant increase of yield (96% *vs.* 56%) and a drastic reduction of reaction time (30 min *vs.* 72h) was found in the arylation of 2-phenylimidazo[1,2-*a*]pyrimidine with bromobenzene.[374] A similar conclusion was found in 2010 by Berteina-Raboin and co-workers for the C3 regioselective direct C-H bond arylation of imidazo[1,2-*b*]pyridazines with aryl bromides.[375]

In 2012, Guillaumet *et al.* developed a protocol for the C3 regioselective direct C-H bond arylation of imidazo[1,2-*b*]pyrazoles **343** with aryl bromides as arylating agents, carried out with 10 mol% of $Pd(OAc)_2$ and 20 mol% of Cy_3P as the catalytic system, 2.0 equiv. of K_2CO_3 as the base in 1,4-dioxane as the solvent.[376] A preliminary comparative study on selected substrates clearly showed that MW irradiation allowed to obtain higher yields in shorter reaction time (1 h *vs.* 41 h) with respect to the conventional thermal heating (reflux). Therefore, the use of such MW-assisted protocol was extended to a variety of aryl bromides with both electron-withdrawing and electron-donating groups also in the *ortho* position, affording the corresponding 3-arylated imidazo[1,2-*b*]pyrazole products **344** in good to excellent yields (60-94%); however, the use of heteroaryl bromides resulted instead in low yields of the desired coupling products (**Scheme 131**).



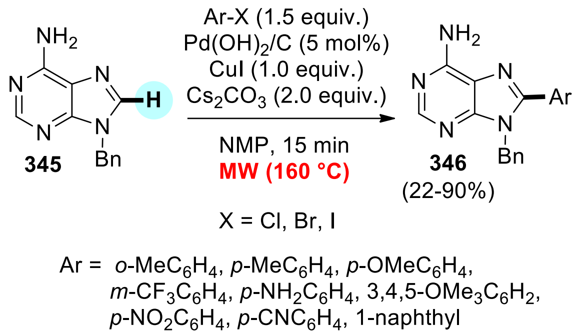
R^1 = Me, OMe, CF_3
Ar = Ph, o-MeC_6H_4, m-MeC_6H_4, p-MeC_6H_4, p-$MeOC_6H_4$,
p-$CF_3C_6H_4$, p-$MeCOOC_6H_4$, o-CNC_6H_4, m-CNC_6H_4,
p-CNC_6H_4

Scheme 131. Microwave-assisted direct C-H bond arylation of imidazo[1,2-*b*]pyrazoles **343** with aryl bromides, described in 2012 by Guillaumet *et al.*[376]

In 2013, the same authors reported a similar protocol for C7 or C3/C7 regioselective direct C-H bond arylation of imidazo[1,2-*b*]pyrazole derivatives with aryl bromides and chlorides; the method is based on use of $Pd(OAc)_2$ and PCy_3HBF_4 as the catalytic system and Cs_2CO_3 as the base in 1,4-dioxane for 4 h under microwave irradiation at 160 °C.[377] In general, the use of aryl chlorides in organic synthesis is more favourable than other typical arylating agents, because they are less expensive and readily available compared to the corresponding bromides and iodides. The possibility of activation of the less reactive Ar-Cl bond was here possible thanks to the use of microwave irradiation, thus confirmating its high efficiency in promoting some direct C-H arylation protocols which hardly could be performed under conventional thermal heating.

In 2016, Nakamura *et al.* reported the direct arylation of imidazo[1,5-*a*]pyridines with 5-iodofuran-2-carbaldehyde or 5-bromothiophene-2-carbaldehyde in the presence of $Pd(OAc)_2$ and CsOAc in DMA under microwave irradiation at 100 °C for 1.5 h.[378] Authors demonstrated that the microwave heating could accelerate reactions: with lower temperature (100 °C *vs.* 150 °C) and shorter reaction time (1.5 h *vs.* 12 h) the coupling products were obtained with improved yields with respect to conventional thermal heating (47% *vs* 30%), when 1-(4-(trifluoromethyl)phenyl)imidazo[1,5-*a*]pyridine was reacted with 5-iodofuran-2-carbaldehyde.

In the context of microwave-assisted protocols for the direct C-H bond arylation of bicyclic *N*-heteroarenes with two or more nitrogen atoms, examples of palladium catalysis in the presence of copper-based co-catalysts have also been developed. A protocol for the direct C-H bond arylation of free-(NH_2) adenines **345** with aryl halides under MW activation was reported in 2008 by Alami *et al.*: starting substrates were selectively arylated at the C8 position by reaction with aryl halides (iodides, bromides and chlorides) using $Pd(OAc)_2$/C as the catalyst in association with CuI and Cs_2CO_3 as the base in NMP for 15 min at 160 °C under MW, to give the corresponding products **346** (**Scheme 132**).[59] The benefit of microwave irradiation was demonstrated: the reaction between 9-benzyl-9*H*-purin-6-amine and *p*-iodoanisole under thermal heating (160 °C, 15 min) resulted in a low conversion, while in the presence of microwave the coupling product was obtained in high yield (90%).



Scheme 132. Direct C-H bond arylation of free-(NH_2) adenines **345** with aryl halides under MW activation, reported in 2008 by Alami and coworkers.[59]

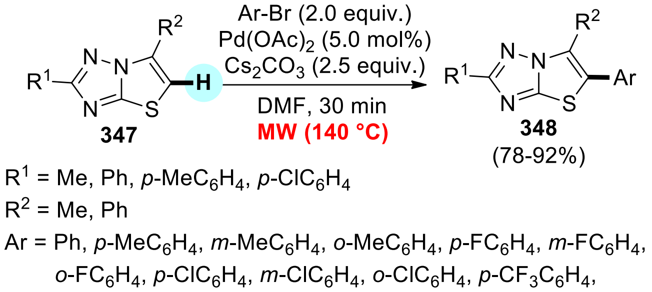
A Pd-Cu complex was also used as catalyst in the microwave-assisted synthesis of C8-(hetero)aryl inosines, reported in 2014 by Pérez-Pérez *et al.*[379] The target molecules were obtained in good yields (46-61%) by the reaction of 2',3'-*O*-isopropylideneinosine with a variety of aryl iodides under microwave conditions (120 °C, 1 h) using $Pd(OAc)_2$ (5 mol%) and CuI (3.0 equiv.) as the catalytic system, in the presence of Cs_2CO_3 and piperidine, in DMF as the solvent. The possibility of easily achieving the direct arylation on highly functionalized heteroarenes, thanks to microwave irradiation, is highly desirable. However, the use of harmful DMF as a solvent, as well as the need of a large amount of CuI as the co-catalyst, represent severe issues in the context of the *Green Chemistry*.

Bicyclic *N*-heteroarenes also containing sulfur or oxygen atoms were also investigated as substrates for direct C-H bond arylation reactions under microwave irradiation. Few examples of Rh-catalyzed direct C-H arylation of benzo[*d*]oxazole and benzo[*d*]thiazole with aryl bromides were reported by Ellman and co-workers in 2008.[348] Actually, despite the use of microwave irradiation was definitely appealing, authors were not interested here in the development of a highly sustainable synthetic method, demonstrated by the use of *ortho*-dichlorobenzene as reaction medium.

Lee *et al.* studied in 2012 the palladium-catalyzed direct C-H arylation of thieno[3,4-*b*]pyrazines with bromothiophenes using $Pd(OAc)_2/Bu_4NBr$ as the catalytic system and potassium acetate as the base, in DMFas the solvent under MW heating at 80°C: they found that a mixture of di- and tri-arylated products was generated by arylation of both C5 and C7 positions of thiophene moiety and C2 position of pyrazine core.[380] Under microwave irradiation the same arylated products (in the same molar ratio) were obtained in shorter reaction time (5 min *vs.* 12 h) with respect to the thermic conditions.

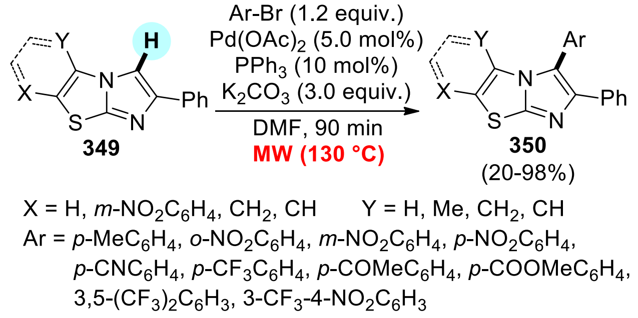
2-Arylbenzothiazoles were synthesized in good yields (73-85%) by Kumar *et al.* in 2014 by the C2 regioselective direct C-H bond arylation of benzo[*d*]thiazole with diaryliodonium triflates, performed in the presence of CuI and *t*-BuOLi, in 1,4-dioxane as a solvent and under microwave irradiation, at 130 °C for 30 min.[381] Unfortunately, control experiments using conventional heating in the same experimental conditions have not been carried out. Moreover, the use of iodonium salts as arylating agents was poorly favourable in the context of the *Green Chemistry*, since they are typically characterized by a low atom economy and waste prevention.

Liu, Zhan and co-workers reported in 2013 the microwave-assisted $Pd(OAc)_2$-catalyzed direct arylation of thiazolo[3,2-*b*]-1,2,4-triazoles **347** with aryl bromides under ligandless conditions: optimization studies on selected substrates showed that the microwave irradiation allowed to markedly improve yields of the coupling products **348** and to reduce reaction time (30 min *vs.* 16 h) compared to conventional heating at 160°C (**Scheme 133**).[382] The combination of MW with the use of ligandless condition is certainly appealing, but the choice of DMF as a solvent represent a severe limit to the sustainability of the method, as well as the need of a quite high loading of an homogeneous metal catalyst.

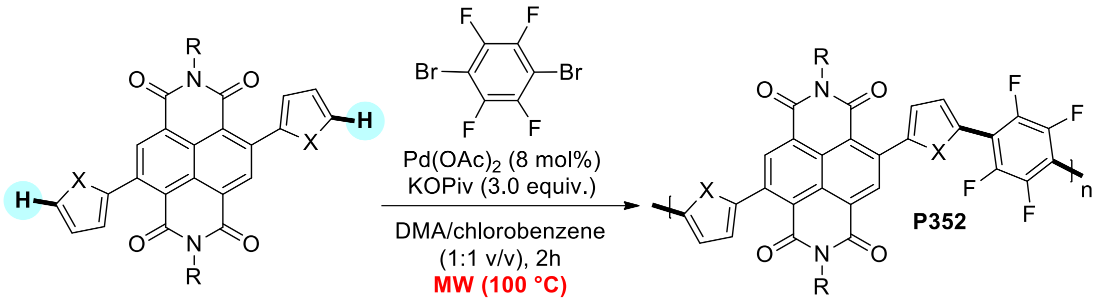


Scheme 133. Microwave-assisted $Pd(OAc)_2$-catalyzed direct arylation of thiazolo[3,2-*b*]-1,2,4-triazoles **347** with aryl bromides under ligandless conditions reported in 2013 by Liu, Zhan and co-workers.[382]

In 2014, Jing *et al.* described a Pd-catalyzed C5 regioselective direct C-H arylation of 6-phenyl substituted imidazo[2,1-*b*]thiazoles **349** with a range of aryl bromides under microwave irradiation.[383] The protocol was based on the use of $Pd(OAc)_2/PPh_3$ as the catalytic system and K_2CO_3 as the base, in DMFas the solvent, under microwave irradiation at 130 °C for 90 minutes, affording the 5-arylated imidazo[2,1-*b*]thiazole products **350** in 20-98% yields (**Scheme 134**). By using conventional thermal heating, only lower yields of products **350** in longer times (13 h) were detected.



Scheme 134. Microwave-assisted Pd-catalyzed direct C-H arylation of imidazo[2,1-*b*]thiazoles **349** with aryl bromides.



351

P352a: X = O, R = 2-octyldodecyl, M_n = 6.6 Kg mol^{-1}
P352b: X = S, R = 2-octyldodecyl. M_n = 7.2 Kg mol^{-1}
P352c: X = S, R = 2-decyltetradecyl, M_n = 7.8 Kg mol^{-1}

Scheme 135. Synthesis of naphthalene diimide co-polymers **P352a-c** by direct C-H bond arylation polymerization of furan- and thiophene-flanked naphthalene diimides monomers **351** under microwave irradiation.

Finally, Routier and co-workers reported a direct arylation protocol to functionalize 2,6-bisarylimidazo[2,1-*b*]-[1,3,4]thiadiazoles at the C5 position using aryl bromides, based on the use of microwave irradiation as essential energy source to allow high yields of the desired coupling products.[384] Reaction were carried out in dioxane or toluene using an excess of aryl bromide (1.5 equiv.), Pd(OAc)$_2$-Xantphos as the catalytic system and Cs_2CO_3 as the base under microwave irradiation at 150 °C for 1 h.

4.2.3. Microwave-assisted direct C-H bond arylation of *O*-heteroarenes.

A limited number of studies of microwave-mediated direct C-H bond arylation of *O*-heteroarenes have been described in the literature. For the sake of completeness we feel compelled to report that, in the field of more extended investigations of MW-assisted arylation of several heteroarenes, few examples of the application of furan and benzofuran derivatives as starting materials in protocols involving palladium,[347,353] rhodium[326,385] or manganese[197] catalysts under microwave irradiation have been successfully performed, leading to the corresponding 2-arylated products in moderate to good yields.

A more appealing investigation was reported in 2014 by Sommer and co-workers, who described the synthesis and properties of naphthalene diimide copolymers **P352** prepared by selective direct α-arylation of furan- and thiophene-flanked naphthalene diimides **351** and 1,4-dibromo-2,3,5,6-tetrafluorobenzene (**Scheme 135**).[386] The reactions were carried out in the presence of Pd(OAc)$_2$ and potassium pivalate under microwave irradiation at 100 °C for 2 h, affording materials which displayed high electron mobilities despite their oligomeric character (**P352a**: M_n = 6.6 Kg mol^{-1}, **P352b**: M_n = 7.2 Kg mol^{-1}, **P352c**: M_n = 7.8 Kg mol^{-1}).

4.2.4. Microwave-assisted direct C-H bond arylation of *S*-heteroarenes.

Large efforts have been devoted to the development of protocols for the microwave-assisted direct arylation of thiophene derivatives, due to their importance as structural moieties in the synthesis of biologically active compounds and functional materials for organic electronics.

Examples of microwave-assisted rhodium-catalyzed direct C-H arylation reactions of thiophenes and bithiophenes with aryl iodides as arylating agents were reported by Itami and co-workers.[326,385] Unfortunately, these protocols were associated to the use of large amounts of silver carbonate as base, which could easily be responsible of a severe metal contamination of the coupling products, as well as to the need of *ortho*-xylene as a poorly environmentally friendly reaction medium.

More frequently, palladium species were used as catalysts for direct C-H bond arylation reactions of thiophene derivatives. In 2005, Beccalli *et al.* synthesized tricyclic fused quinolones and naphthyridones by intramolecular Pd-catalyzed direct C-H arylation of several heterocycles, including thiophene-2-carboxylic acid and thiophene-3-carboxylic acid derivatives, assisted by microwave irradiation.[347] More in detail, these reactions were performed with Pd(PPh$_3$)$_4$ as the catalyst and KOAc as the base, in DMA under microwave irradiation at 140°C, affording the target molecules in very shorter times with respect to conventional heating (12-30 min vs. 24h).

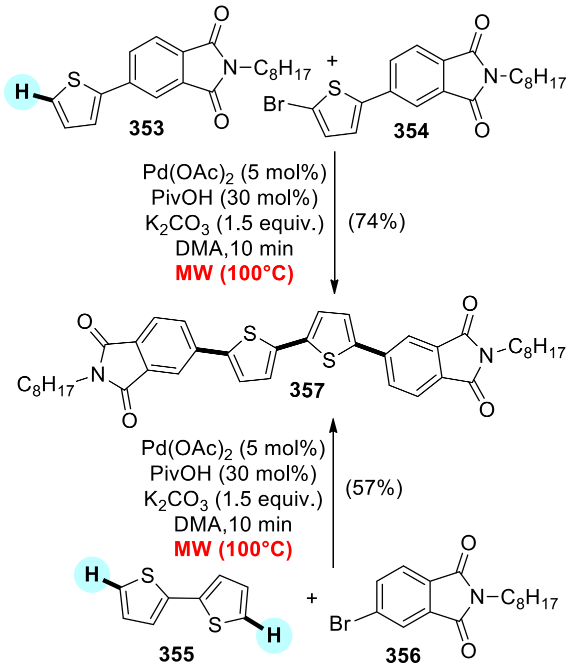
In 2011, Kappe *et al*. developed a microwave-assisted procedure for the Pd-catalyzed direct C-H arylation of thiophenes and benzothiophenes with (hetero)aryl bromides.[353] From a sustainability point of view, on one hand the protocol was quite appealing as it required low catalyst and ligand loadings (1 mol% of Pd(OAc)$_2$ and 2 mol% of PCy$_3$) and short reaction time (10-60 min) under microwave irradiation at 180 °C; however, on the other hand the use of toxic DMF as the solvent was a severe issue. The procedure appeared more interesting from a merely synthetic point of view, since it allowed to isolate products in good yields also in the case of systems that were reported as unsuccessful in the literature with conventional thermal heating procedures.

In 2017, Cravotto and coworkers reported an eco-friendly protocol for the direct C-H arylation of thiophenes with aryl iodides and bromides as arylating agents, performed in GVL as non-toxic and biomass-derived solvent, in ligand-free conditions and under microwave irradiation.[258] The procedure required a very low catalyst loading (Pd(OAc)$_2$ 0.2 mol% in the presence of KOAc as the base), but an excess of the thiophene derivative (2.0 equiv. with respect to the aryl halide) and the microwave irradiation at 140 °C for 2 h were needed to afford the desired coupling products. In particular, modest to good yields were reported by using electron-deficient aryl bromides (8-82%), while the use of aryl iodides and the addition of pivalic acid as additive were required for electron donating groups (42-52%). In our opinion the present protocol is quite appealing in the frame of *Green Chemistry*, thanks to the combination of the typical advantages of microwave heating with the use of GVL as a highly sustainable solvent and the need of very low metal loading, under ligand-free conditions.

Microwave-assisted direct C-H bond arylation of thiophene derivatives were also applied for the synthesis of π-conjugated oligomers with intriguing optoelectronic properties. In 2014, Melucci *et al.* prepared 9,10-dithienylanthracene-based materials by using MW-assisted direct

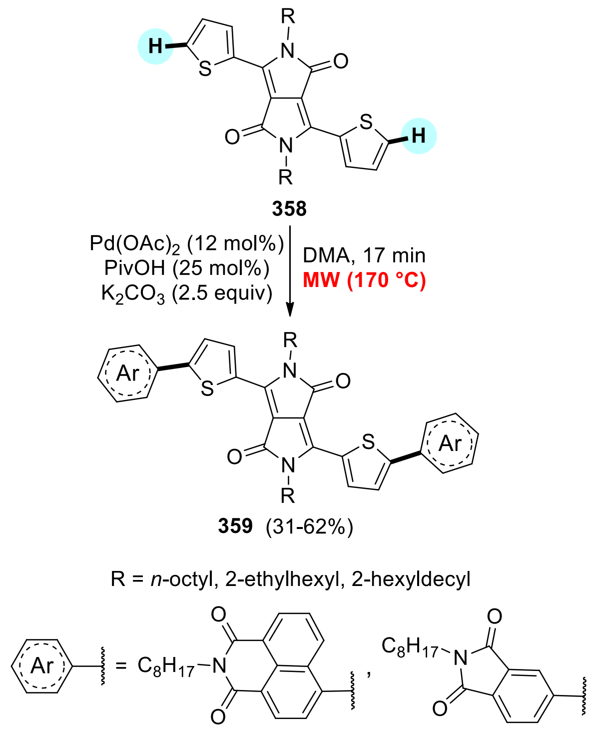
C-H arylation reactions of thiophene, bithiophene or end-substituted analogues with 9,10-dibromoanthracene.[387] The target molecules were obtained in yields ranging from 31% to 81% in only 5 minutes under microwave irradiation at 150°C, in the presence of $Pd(OAc)_2$ as the catalyst and PCy_3HBF_4 as the ligand, K_2CO_3 as the base, pivalic acid as additive and DMF as the solvent. For comparison, the same reactions were also performed under thermal heating, affording comparable yields only after 24 h at 110 °C

In 2014, Welch and co-workers synthesized a *H*-aggregated thiophene-phthalimide based small molecule **357** by two different synthetic pathways, based on a microwave-assisted palladium-catalyzed direct C-H bond arylation protocol, performed with $Pd(OAc)_2$ (5 mol%) as the catalyst, K_2CO_3 (1.5 equiv.) as the base, PivOH (30 mol%) as additive, in DMA as the solvent, under MW heating for only 10 minutes.[388] In one case, mono-arylation reaction of the thiophene derivative **353** with bromothiophene **354** afforded the desired π-conjugated product **357** in 74% yield; in the other case, bis-arylation of bithiophene **355** with the bromophthalimide **356** gave the same product **357** in 57% yield (**Scheme 136**). As a comparison, the same reactions carried out under conventional thermal heating produced yields similar to those obtained under microwave heating (84 and 68% *vs*. 74 and 57%), but in longer reaction times (2 h *vs.* 10 min). In a following study, the use of MW irradiation in combination with the recoverable commercial SiliaCat® DPP-Pd catalyst was successfully applied by the same authors to the synthesis of a very similar small molecule organic semiconductor, differing only in the alkyl chains of phthalimide moieties (see section 2.1.4).[68]



Scheme 136. Synthesis of **357** by two different pathways based on a microwave-assisted palladium-catalyzed direct C-H bond arylation protocol.

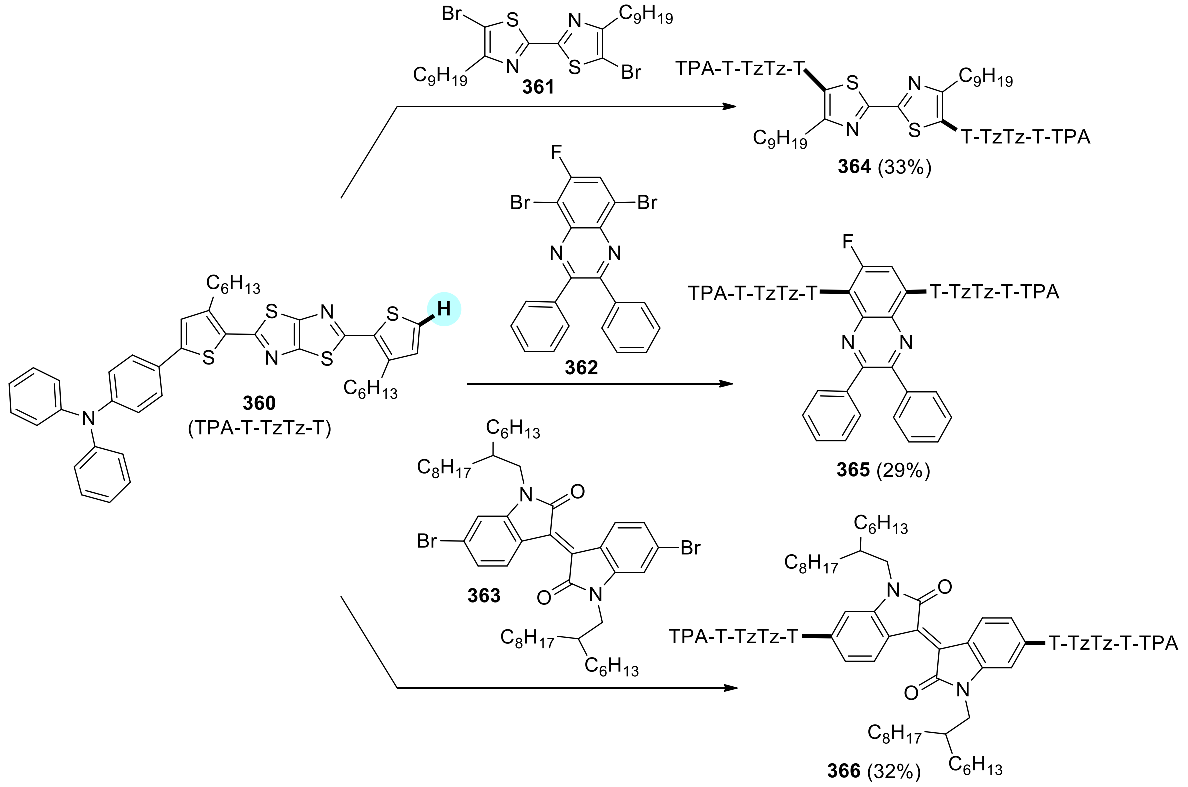
Moreover, the same group reported the synthesis and optoelectronic characterization of a series of diketopyrrolopyrrole (DPP) based small molecules **359**, bearing electron-deficient phthalimide or naphthalimide end-capping units, obtained by direct C-H bond arylation reaction of bis-thienylDPP **358** with naphthalimide and phthalimide bromides under microwave irradiation at 170 °C for 17 min (**Scheme 137**).[389] All the compounds were found to have narrow optical band gaps ranging from 1.66 to 1.73 eV, high thermal stabilities and n-type charge carrier mobilities.



Scheme 137. Microwave-assisted synthesis of diketopyrrolopyrrole-based small molecules **359** by direct C-H arylation reaction of bis-thienylDPP **358** with naphthalimide and phthalimide bromides.

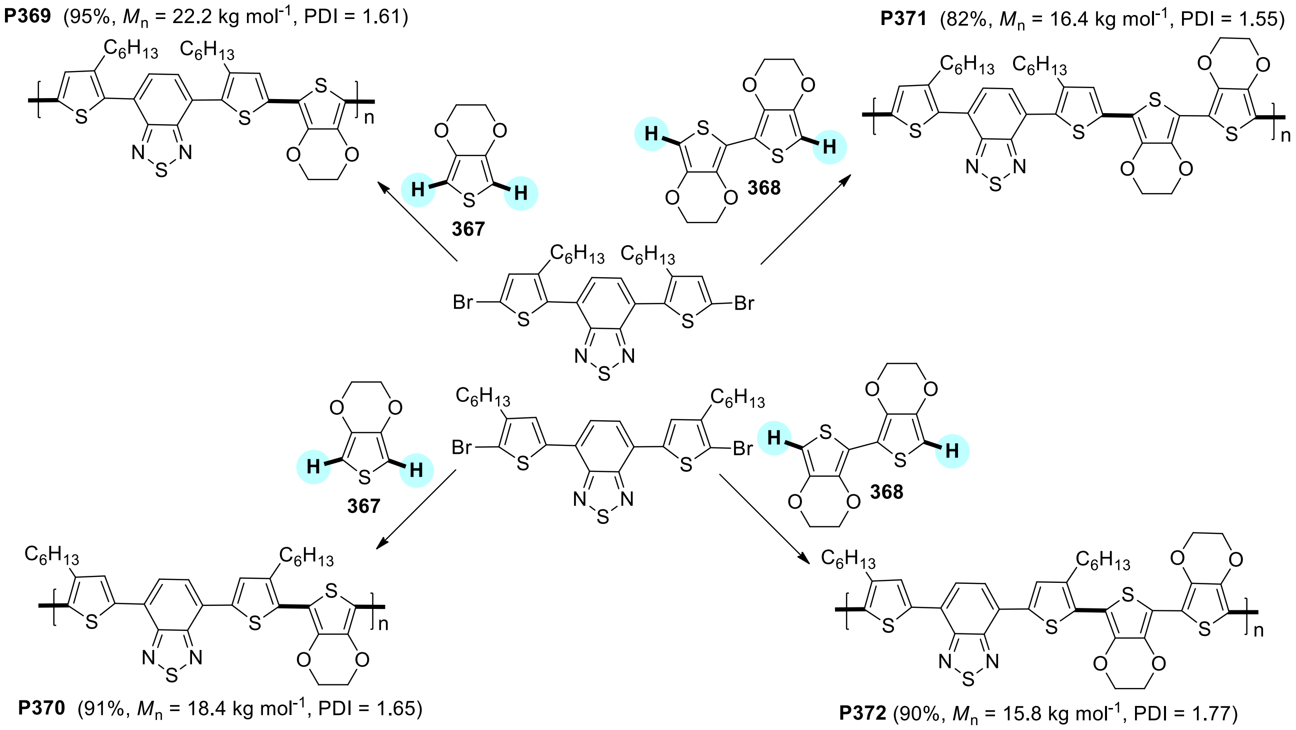
In 2016, Maes *et al.* developed a microwave-assisted protocol for the preparation of push-pull molecular chromophores **364-366** based on the C2 regioselective direct C-H bond arylation of the thiophene ring of an asymmetric triphenylamine-monosubstituted 2,5-dithienyl-thiazolo[5,4-*d*]thiazole precursor **360** with the brominated bithiazole (**361**), quinoxaline (**362**) or isoindigo (**363**) units.[390] In particular, the direct arylation reactions were carried out with $Pd(OAc)_2$ (4 mol%) as the catalyst, $PCy_3{\cdot}HBF_4$ (8 mol%) as the ligand, K_2CO_3 (3.0 equiv.) as the base, PivOH (1.0 equiv.) as additive, in toluene under MW irradiation (**Scheme 138**). In 2017, they extended the same direct C-H arylation protocol to the synthesis of new 2,5-dithienylthiazolo[5,4-*d*]thiazole-based small molecules.[391] It is worth to emphasize that, despite the use of MW as non-conventional and highly efficient source of energy, in both these studies authors were not interested in the development of a sustainable synthetic protocol, but rather to the characterization of the obtained π-conjugated materials.

3,4-Ethylenedioxythiophene (EDOT) has been often used as a monomer in direct C-H bond arylation polymerization reactions under microwave irradiation. In 2013, Lee and co-workers synthesized several conjugated copolymers *via* direct C-H arylation of EDOT **367** or bis-EDOT **368** with dithienyl-benzothiadiazole derivatives: polymerization reactions were performed in DMF in the presence of $Pd(OAc)_2$, KOAc and Bu_4NBr affording the target polymers **P369-P372** in yields comparable to those obtained by Stille reactions, *i.e.*, 82-95% *vs* 88-97% (**Scheme 139**).[392]



Conditions: $Pd(OAc)_2$ (4.0 mol%), PCy_3HBF_4 (8.0 mol%), PivOH (1.0 equiv.), K_2CO_3 (3.0 equiv.), toluene, 18 h, **MW (150 °C)**

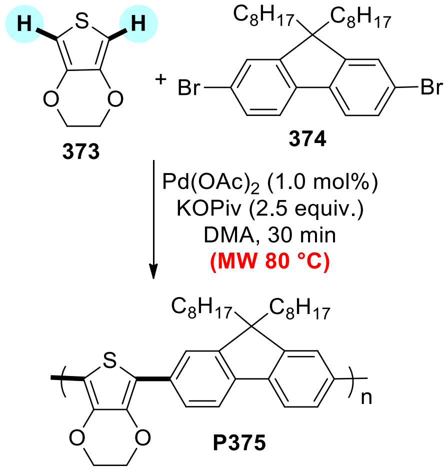
Scheme 138. Synthesis of chromophores **364-366** based on the microwave-assisted C2 regioselective direct C-H bond arylation of the thiophene ring of **360** with brominated bithiazole (**361**), quinoxaline (**362**) or isoindigo (**363**) units.



Conditions: $Pd(OAc)_2$ (20 mol%), KOAc (6.0 equiv.), $n Bu_4NBr$ (2.0 equiv.), DMF,
5 min **MW (100 °C)**, 5 min **MW (120 °C)**, 30 min **MW (150 °C)**

Scheme 139. Synthesis of π-conjugated copolymers *via* direct C-H bond arylation polymerization of EDOT **367** or bis-EDOT **368** with dibrominated dithienyl-benzothiadiazole derivative, performed under microwave irradiation.

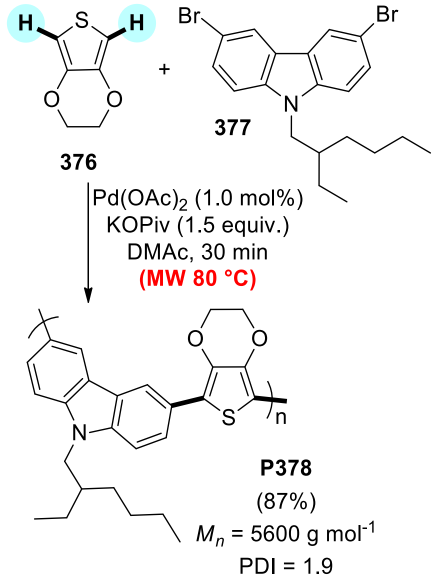
Kanbara *et al.* reported in 2013 the direct C-H bond arylation-based co-polymerization of EDOT **373** with 9,9-dioctyl-2,7-dibromofluorene **374**, performed under typical direct C-H bond arylation conditions (1.0 mol% of $Pd(OAc)_2$ as the catalyst, 2.5 equiv. of potassium pivalate as the base and DMA as the solvent), assisted by microwave irradiation as an efficient energy source, affording poly[(3,4-ethylenedioxythiophene-2,5-diyl)-(9,9-dioctylfluorene-2,7-diyl)] (PEDOTF) **P375** in high yield (**Scheme 140**)[393]. In general, an increase of molecular weight (M_n) was detected on decreasing the concentration of the monomers; moreover, a dramatic decrease in the molecular weight of **P375** was observed when conventional thermal heating was used instead of microwave irradiation.



Scheme 140. Microwave-assisted co-polymerization of EDOT **373** with 9,9-dioctyl-2,7-dibromofluorene **180b** by direct C-H bond arylation reaction, reported in 2013 by Kanbara *et al.*[393]

In a following study, the same group investigated also the effects of different synthetic methods (that is, Suzuki-Miyaura coupling under thermal heating; direct C-H arylation under thermal heating; direct C-H bond arylation under microwave irradiation) on the purity and optical features of **P375** co-polymers; once again, the MW-assisted direct C-H bond arylation polymerization was found to afford pure and high-molecular-weight PEDOTF co-polymers with improved optoelectronic performances.[394] For the last class of polymers, the effects of terminal groups, residual amount of palladium catalyst and molecular weight (M_n) on the photovoltaic characteristics were also explored.[395] In 2016, the same group reported the synthesis of π-conjugated polymers by microwave-assisted direct C-H bond arylation co-polymerization of EDOT with dibrominated phenyl-, pyridyl- and thiazolyl-flanked DPPs.[396] Reactions were carried out using $Pd(OAc)_2$ (1 mol%) as the catalyst and potassium pivalate as the base in DMA under microwave irradiation at 100 °C for 1 h, affording the target polymers in 37-94% yields. As for most of the investigation related to the synthesis of π-conjugated systems, also in these works the authors were not mainly focused on the development of sustainable protocols: reactions were typically carried out with homogeneous $Pd(OAc)_2$ (although often under ligand-less conditions) and in poorly sustainable solvents, therefore their overall interest in the frame of the *Green Chemistry* appears in our opinion quite low.

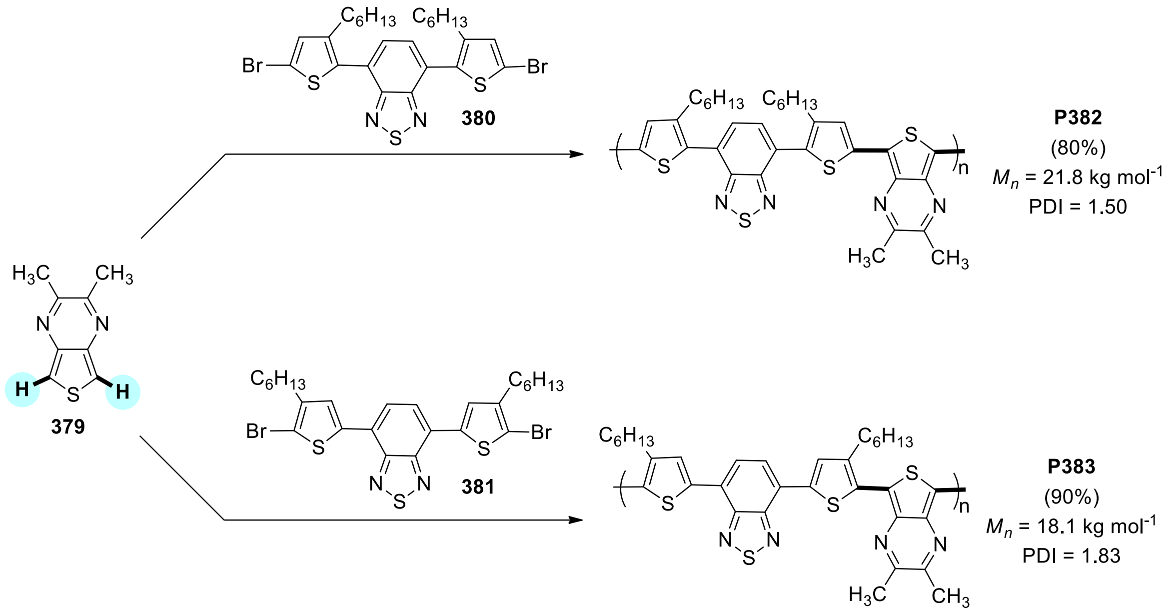
In 2016, Michinobu *et al.* investigated the co-polymerization of **376** with a series of 3,6-dibromocarbazoles **377** by a ligand-free and MW-assisted direct C-H arylation polymerization; as in the previous cases, microwave irradiation dramatically shortened reaction times compared to thermal heating.[397] Under the optimized conditions (1.0 mol% of $Pd(OAc)_2$ as the catalyst, 2.5 equiv. of potassium pivalate as the base and DMA as the solvent, MW at 80 °C for 30 min), polymer **P378** was obtained in 87% yield, with a molecular weight Mn = 5600 g mol^{-1} and a PDI of 1.9 (**Scheme 141**). Microwave heating dramatically shortened the reaction time compared to conventional heating: indeed, the polymer **P378** was obtained in 72% yield with a molecular weight Mn = 3000 g mol^{-1} and PDI = 1.6 under conventional heating at 100 °C for 6 h.



Scheme 141. Co-polymerization of **376** with 3,6-dibromocarbazoles **377** by a ligand-free, microwave-assisted direct C-H bond arylation polymerization.

In addition to EDOT, only a few other *S*-heteroarene-based monomers have been used as C-H substrates in the microwave-assisted direct C-H bond arylation polymerization. Lee *et al.* synthesized donor-acceptor co-polymers by direct arylation reactions of thieno[3,4-*b*]pyrazines with dibrominated thiophene and bithiophene derivatives, performed in the presence of $Pd(OAc)_2$ as the catalyst, KOAc as the base and Bu_4NBr as additive in DMF as the solvent, under microwave heating (5 min at 100 °C, 5 min at 120 °C, and 30 min at 150 °C).[380] In a following study, the authors also reported the MW assisted co-polymerization of 2,3-dimethylthieno[3,4-*b*]pyrazine monomer **379** with 4,7-bis(5-bromo-3-hexylthiophen-2-yl)benzo[c][1,2,5]thiadiazole **380** and 4,7-bis(5-bromo-4-hexylthiophen-2-yl)benzo[*c*] [1,2,5]thiadiazole **381**, leading to the desired co-polymers **P382-P383** in high yields after short reaction time (**Scheme 142**).[392]

In 2014, Sommer *et al.* used thiophene-flanked naphthalene diimides as monomers in microwave assisted direct C-H arylation with 1,4-dibromo-2,3,5,6-tetrafluorobenzene.[386] In 2016 Yang *et al.* investigated the use of MW for promoting the polymerization of indacenodithiophene with dibrominated dithienoquinoxalines via direct C-H arylation, carried out under phosphine-free conditions using $Pd(OAc)_2$ as the catalyst and K_2CO_3 as the base in DMA as the solvent.[398] Interestigly, they found that the microwave irradiation greatly accelerates the reaction rate, but simultaneously stimulates the formation of insoluble cross-linked ill-defined structures with respect to conventional heating.



Conditions: $Pd(OAc)_2$ (20 mol%), KOAc (6.0 equiv.), $(n\text{-}Bu)_4NBr$ (2.0 equiv), DMF,
5 min **MW (100 °C)**, 5 min **MW (120 °C)**, 30 min **MW (150 °C)**

Scheme 142. Co-polymerization of 2,3-dimethylthieno[3,4-b]pyrazine **379** with dibrominated monomers **380** and **381** by microwave-assisted direct C-H bond arylation reactions, reported in 2013 by Lee *et al.*[392]

Cravotto and co-workers reported the MW assisted direct C-H bond arylation homo-polymerization of 2-bromo-3-hexylthiophene, using low catalyst loading ($Pd(OAc)_2$, 0.2 mol %), K_2CO_3 as the base and pivalic acid as additive, in GVL as sustainable solvent at 100 °C for 3h; under these conditions, poly(3-hexyl)thiophene was isolated in 75% yield with M_n = 25 kDa.[258] In our opinion this protocol is very appealing in the frame of the *Green Chemistry*, thanks to the combination of the typical advantages of microwave heating with the use of GVL as highly sustainable solvent and the need of very low palladium loading, under ligand-free conditions.

The valuable support of microwave irradiation in promoting direct C-H bond arylation polymerization of *S*-hereroarenes under sustainable conditions was further testified in the last years. In 2018, Michinobu *et al.* reported the synthesis of hole-transporting π-conjugated polymers by microwave-assisted direct C-H bond arylation of the thiophene rings of *bis*-thienylDPP derivatives with dibrominated electron-donating co-monomers, using $Pd(OAc)_2$ as the catalyst, KOAc as the base in DMA as the solvent, under MW irradiation at 120 °C for 1 h.[399]

In 2019, Drozdov and co-workers used three monomers (bithiophene, cyclopenta[2,1-*b*:3,4-*b*']dithiophene and *bis*-thienylDPP derivatives) as C-H substrates in the microwave assisted direct C-H bond arylation polymerization with suitable dibromo(hetero)arenes, using $Pd(OAc)_2$, K_2CO_3, pivalic acid in NMP under MW irradiation at 110 °C for 10-12 h.[400]

As shown in this section, in many of the synthetic protocols reported in the literature until now microwave irradiation offered the possibility to obtain the desired coupling products under milder experimental conditions and shorter reaction times than to those of the conventional thermal heating. Conseguently, the MW irradiation confirmed its utility in the development of direct C-H arylation reactions which comply essential prerogatives dictated by *Green Chemistry*. However, the use of environmentally not benign solvents (in particular, DMF, DMA, NMP) additives (silver salts) and coupling partners (e.g. diaryliodonium salts) and/or the need of a large excess of reactants still represent critical points in the context of the *Green Chemistry*.

4.3. Other non-conventional energy sources in direct C-H bond arylation of (hetero)arenes

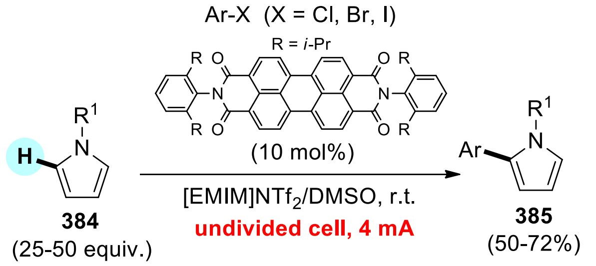
As described above, photochemical protocols and microwave-assisted methods have been widely used in the context of direct C-H bond arylation of (hetero)arenes as an alternative to conventional thermal heating. However, in the last decade new appealing approaches based on the use of other non-conventional energy sources have started to be explored for direct C-H bond arylation of (hetero)arenes. These include: electrochemical- ultrasound-, mechanochemical- and infrared irradiation-promoted protocols, which aim to reduce the energy requirements and to shorten the reaction time, in compliance with the Principle 6 of *Green Chemistry*. Although these studies are still limited, their interest in sustainable organic chemistry is large, and interesting development can be predicted.

4.3.1. Electrochemical direct C-H bond arylation of (hetero)arenes.

Electrochemical organic synthesis has been recognized as a sustainable approach for the oxidation and reduction of organic compounds: in fact, the toxic oxidizing and reducing agents used in traditional redox reactions are replaced by the electric current; in other words, voltage-applied electrodes represent a green and more eco-friendly source of electrons with respect to classic redox reagents.[401]

However, recently organic synthesis discovered a significant interest in indirect electrochemical processes, *i.e.*, reactions involving the use of suitable redox mediators to achieve indirect processes.[402] In particular, the possibility to apply indirect electrochemical methods for the carbon-carbon bond formation is very appealing: electrochemical processes can favour different mechanistic pathways with respect to the same reactions performed under the sole thermal heating, sometimes resulting in different selectivities. However, very little has been studied so far concerning indirect electrochemical processes for the carbon-carbon bond, especially in the specific case of direct C-H bond arylation of (hetero)arenes.

The first example of electrochemical direct C-H arylation was reported in 2016 by Zhu and co-workers: they described the C2 regioselective direct C-H arylation of *N*-substituted and NH-free pyrroles **384** with aryl halides (iodides, bromides and also a few examples of chlorides), carried out in an electrochemical cell with a glassy carbon cathode and a zinc anode, in 1-ethyl-3methyl-imidazolium bis((trifluoromethyl)sulfonyl) imide/DMSO mixture as a reaction medium, using a catalytic amount (10 mol%) of perylene-3,4,9,10-tetracarboxylic acid diimide derivatives as the redox mediator.[403] Interestingly, working at room temperature and under constant-current electrolysis conditions (4 mA), α-arylated products **385** were obtained in 50-72% yields (**Scheme 143**). Although the protocol showed the advantage of working at room temperature and the presence of an organic redox mediator, the need for a large excess of the starting pyrroles (25-50 equiv.) clearly limited its actual sustainability.



R^1= H, Me, Ph

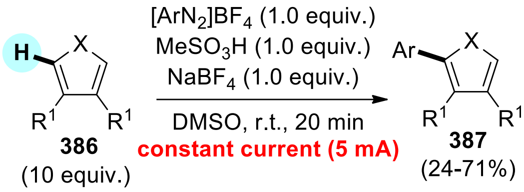
Ar = *p*-COMeC$_6$H$_4$, *p*-COOMeC$_6$H$_4$, *p*-CNC$_6$H$_4$, *o*-CNC$_6$H$_4$

Scheme 143. Electrochemical C2 regioselective direct C-H arylation of pyrroles **384** with aryl halides, developed in 2016 by Zhu and co-workers in 2016.[403]

Looking for sustainable experimental conditions for the synthesis of asymmetrical bi(hetero)aryl scaffolds via direct C-H functionalization, in 2017 Chupakhin *et al.* reported the first electrochemical oxidative direct arylation of *N*-heteroarenes (*N*-methylacridinium, quinazoline, pyrimidine, [1,2,5]oxadiazolo[3,4-*b*]pyrazine) with nucleophilic arenes, performed in a two-compartment cell, wherein anode and cathode (both consisting of a platinum wire) were separated by a membrane of a tracing paper, at room temperature in acetonitrile as the solvent, in the presence of NEt$_4$BF$_4$ as the supporting electrolyte and of potassium *t*-butoxide (1.0 equiv.) in order to increase the nucleophilic character of the arenes.[404] This protocol was very attractive from the point of view of the *Green Chemistry*, for several reasons: first, both coupling parters did not require any preactivation, thus reducing the synthetic steps; second, the electrochemical oxidative process did not require stoichiometric amounts of oxidants (typically represented by silver-based species); third, working at room temperature, the asymmetrical bi(hetero)aryl products were obtained in good yields (63-90%).

More recently, Amaya *et al.* reported the electrochemical direct C-H arylation of heteroarenes **386** (*N*-Boc-pyrrole, furan and thiophene) with aryldiazonium salts as arylating agents, performed in a sample tube containing a stainless steel plate cathode and a carbon anode under constant current electrolysis (5 mA), in DMSO as the solvent and in the presence of sodium tetrafluoroborate (1.0 equiv.) and MeSO$_3$H (1.0 equiv.), at room temperature under air for 20 min.[405] The reactions, which afforded the corresponding C2 arylated products **387** in good yields, were quite convenient as they did not require the use of metal catalyst but only of organic additives, although an excess (10 equiv.) of the heteroarene was required (**Scheme 144**).

4.3.2. Ultrasound-assisted direct C-H bond arylation of (hetero)arenes. Ultrasound is the part of the sonic spectrum which ranges from about 20 kHz to 10 MHz. Ultrasound has been used in various fields, from the industrial engineering to the medical diagnostics, and they have been successfully applied also in the context of organic synthesis. In fact, this non-conventional energy source represents a cleaner, safer and cheaper method for reagents activation in a chemical reaction with respect to conventional thermal heating; moreover, it has also been proved to be effective in terms of selectivity, reaction time and operational simplicity.[406]



R^1= H, OMe X= NHBoc, O, S

Ar = Ph, *p*-CNC$_6$H$_4$, *p*-BrC$_6$H$_4$, *p*-ClC$_6$H$_4$, *p*-IC$_6$H$_4$, *p*-OMeC$_6$H$_4$, *p*-NO$_2$C$_6$H$_4$, *o*-NO$_2$C$_6$H$_4$

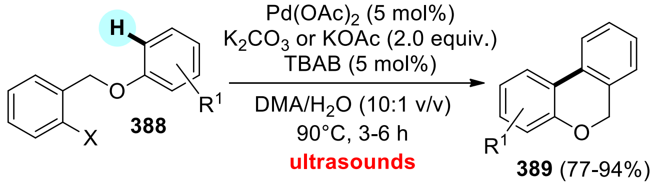
Scheme 144. Electrochemical direct C-H arylation of heteroarenes **386** with aryldiazonium salts as arylating agents, performed under constant current electrolysis (5 mA), described by Amaya *et al.*[405]

Ultrasonic waves require an elastic medium for the propagation: when ultrasound propagates, particles in this medium oscillate and transfer their energy along the direction of propagation. In particular, in the presence of a liquid medium, the longitudinal vibrations of molecules generate compressions and rarefactions, *i.e.*, an alternation of high pressure and low pressure, giving rise to the formation of microbubbles which expand and finally collapse during the compression phase, thus generating shock waves. Their collapse can generate, although only locally and for microseconds, temperatures > 2000 K and pressures > 500 bar. This phenomenon of microbubbles formation and collapse, known as cavitation, is responsible for most of the beneficial effects of ultrasound on the chemical reactions.[407]

The advantagious effects of ultrasound in organic synthesis can occur with different mechanisms depending on the use of homogeneous or heterogeneous experimental conditions. In the case of homogeneous systems, sonication is able to affect reactions proceeding via radical formations (mostly they do not affect ionic reactions); under these conditions, microbubbles generated during the cavitation process act as microreactors, where reagents can enter and react under high temperature and pressure. In heterogeneous systems, the reactions are mostly influenced by mechanical effects of cavitation, such as surface cleaning, particle size reduction and improved mass transfer; moreover, close to the solid-liquid interface, microbubbles collapse can generate jets of liquid, which hit the solid surface with force.[408]

To the best of our knowledge, only one example of ultrasound-assisted direct C-H bond arylation of (hetero)arenes has been reported in the literature: in 2012, Li *et al.* proposed a mild and efficient intramolecular direct arylation of **388** in a continuous flow capillary microreactor with the assistance of ultrasonic irradiation; reactions were performed with $Pd(OAc)_2$ (5 mol%) as the catalyst, in the presence of K_2CO_3 or KOAc (2.0 equiv.) as the base, in DMA/H_2O (10:1 v/v) mixture at 90 °C, affording the corresponding coupling products **389** in good yields after 3-6 h (**Scheme 145**).[409]

Despite the use of relatively milder reaction conditions, we believe that there is little room for improvement of ultrasound-assisted direct C-H arylation in the context of sustainability. In fact, the above mentioned study clearly showed that ultrasound did not represent an energy source intense enough to promote these reactions on its own, but its combination with thermal heating is mandatory. Probably, further improvements in ultrasound-assisted direct C-H bond arylation in terms of sustainability may be obtained by using more reactive arylating agents (aryldiazonium salts, diaryliodonium salts, etc.).



X = I, Cl, Br

R^1 = *o*-*t*-Bu, *m*-*t*-Bu, *o*-NO_2, *m*-NO_2, *p*-Ph, *p*-Cl, *p*-CHO, *p*-COOMe, *p*-COMe, 2-MeO-4-CHO

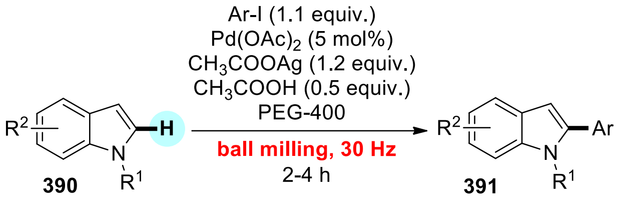
Scheme 145. Ultrasound-assisted intramolecular direct C-H bond arylation of haloethers **388**, reported in 2012 by Li and co-workers.[409]

4.3.3. Mechanochemical direct C-H bond arylation of (hetero)arenes. Mechanochemistry is concerned with chemical reactions accomplished by the application of mechanical energy, typically by means of high-energy ball milling, which provides green, clean and high sustainable synthetic methods for the preparation of target molecules and for the improvement of the efficiency in complex processes.[410]

The effects of mechanical action are quite different from those of the conventional thermal heating: by milling two or more solid substances the break of their ordered crystalline structures occurs; at the collision points, these solids deform and even melt, forming hot points where molecules can reach very high vibrational excitation states leading to bond breakage. These phenomena typically take place in intervals of about 10^{-7} seconds, known as plasma phase, followed by a longer post-plasma phase (of ~ 10^{-6} seconds) where relaxation processes dissipate the energy responsible for most of the products formed.[411]

Mechanical milling responsible for mechanochemical-assisted chemical transformations can be performed in different ways. The simplest is the manual grinding with the laboratory mortar and pestle: however, these hand milling processes can only support a limited number of mechanochemical reactions, which do not require to overcome a high-energy barrier; moreover, their reproducibility is limited. For this reason, a more appealing approach is the use of dedicated instrumentations: high-energy vibrators such as high-speed attritors or stainless steel ball mills of high impact are typically used for prolonged high energy mechanochemical-assisted processes.[412]

Despite the increasing interest towards greener and more sustainable protocols for direct C-H arylation of (hetero)arenes, the number of studies based on the use of mechanochemical methods is still very low, and limited to indoles and 1*H*-indazoles as substrates. In 2019, Banerjee and co-workers described a mechanochemical protocol for the C2 regioselective direct C-H bond arylation of indoles **390** with aryl iodides as arylating agents.[413] In particular, reactions were carried out with $Pd(OAc)_2$ (5 mol%) as the catalyst, silver acetate (1.2 equiv.) as the base, acetic acid (0.5 equiv.) as an additive and PEG-400 as the grinding auxiliary, in a mixer mill working at 30 Hz frequency for 2-4 h. The protocol was very clean, fast and sustainable, affording the desired 2-arylated indoles **391** in very good yields (**Scheme 146**).



R^1 = H, Me, Boc, CH_2Ph

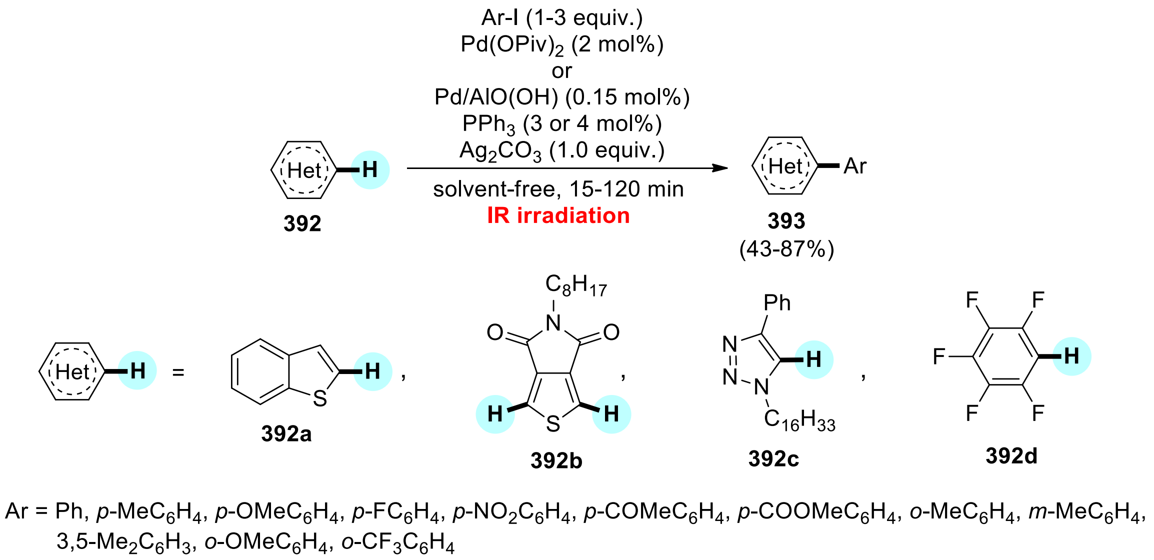
R^2 = 5-CN, 5-Br, 5-MeO

Ar = Ph, *p*-CNC_6H_4, *m*-$CF_3C_6H_4$, *p*-BrC_6H_4, *p*-$OMeC_6H_4$, *o*-$OMeC_6H_4$, *p*-OHC_6H_4, *o*-MeC_6H_4, *m*-MeC_6H_4, *p*-MeC_6H_4, *p*-*t*-BuC_6H_4

Scheme 146. Mechanochemical C2 regioselective direct C-H bond arylation of indoles **390** with aryl iodides developed in 2019 by Banerjee and co-workers:[413] reactions were performed in a mixer mill working at 30 Hz frequency.

In 2020, Su and co-workers reported a C3 regioselective oxidative direct C-H heteroarylation of *N*-substituted 1*H*-indazoles with unactivated heteroarenes as arylating agents, performed with $Pd_2(dba)_3$ (20 mol%) as the catalyst, $Cu(OAc)_2{\cdot}H_2O$ (1.5 equiv.) as sacrificial oxidant, Na_2SO_4 as both the base and the grinding auxiliary in a planetary mill working at 900 rpm; after 4 cycles of 30 min of milling and 2 min of break, the desired 3-heteroaryl-1*H*-indazoles were obtained in moderate yields (25-45%) and good regioselectivity.[414]

4.3.4. Infrared irradiation-assisted direct C-H bond arylation of (hetero)arenes. Most of the above mentioned non-conventional energy sources, despite their invaluable advantages in the context of *Green Chemistry*, often requires the access to dedicated and quite expensive instrumentations (*e.g.*, microwave reactors, apparatus for ultrasound sonication, ball mill machines for mechanochemical processes, etc.). The infrared (IR) irradiation has been very recently demonstrated as an appealing and powerful alternative to them: it is a highly efficient form of heating emitted from an inexpensive lamp (*i.e.*, a tungsten filament sealed in a quartz envelope with a halogen gas), characterized by high heat transfer rate, good heating homogeneity, low energy consumption and short heating time.[415] Thanks to these properties, the application of IR irradiation to organic reactions could provide relevant advantages, including reduced energy requirements, shortened reaction times and even access to new mechanistic pathways, in addition to its potential compatibility with solvent-free protocols. Therefore, IR irradiation could soon become a very useful tool for fast, cheap and sustainable synthesis respecting the Principle 6 of *Green Chemistry*,[416] whose true potential to date is still almost unexplored, especially in the field of Palladium-catalyzed coupling chemistry.



Scheme 147. First application of IR irradiation as non-conventional and highly efficient source of energy in the direct C-H bond arylation of hetero(arenes), under solvent-free and non-anydrous conditions, reported in 2021 by our group:[282] reactions of benzo[*b*]thiophene **392a**, thieno[3,4-*c*]pyrrole-4,6-dione **392b**, 1,2,3-1*H*-triazole **392c** and pentafluorobenzene **392d** with aryl iodides.

Very recently our group explored for the first time the application of IR irradiation as non-conventional, eco-friendly and efficient source of energy for promoting the direct C-H arylation of (hetero)arenes **392** (benzo[*b*]thiophene **392a**, thieno[3,4-*c*]pyrrole-4,6-dione **392b**, 1,2,3-1*H*-triazole **392c**, pentafluorobenzene **392d**) with aryl iodides.[282] Reactions were performed with low amounts of a palladium catalyst (homogeneous Pd(OPiv)$_2$ or supported Pd/AlO(OH)), PPh$_3$ as the ligand and Ag$_2$CO$_3$ as the base, in solvent-free and non-anhydrous conditions and under air, affording the corresponding coupling products **393** in good yields and very short reaction time, ranging from 15 minutes to 2 h depending on the specific (hetero)arene (**Scheme 147**). A comparative study of solvent-free direct arylation protocols energy consumption under IR irradiation or under conventional thermal heating confirmed that the IR irradiation is a more efficient and less expensive source of energy, in compliance with the Principle 6 of *Green Chemistry* (Design for energy efficiency).

We are convinced that the use of IR irradiation in organic reactions in the place of traditional thermal heating can provide general advantages in the context of *Green Chemistry*, *i.e.*, reduced energy consumption, shortened reaction times and even access to different mechanistic pathways, in addition to its compatibility with solvent-free conditions. Therefore, IR irradiation may become a precious tool for fast, cheap and sustainable synthesis: a powerful enabling technology which can help to usher in a greener era of organic synthesis.

5. Conclusions

In conclusion, in the present review we have reported an up-to-date overview of all the sustainable protocols adopted in the context of direct C-H bond arylation of (hetero)arenes, describing with a critical eye their advantages and limitations related to the Twelve Principles of *Green Chemistry*.

In the first section, we have discussed all the solid supported metal catalysts applied to direct C-H bond arylation of (hetero)arenes, giving particular emphasis to all the studies carried out to verify their reusability and heterogeneity (recycling tests, metal leaching analyses, hot filtration tests, kinetic studies, etc.). In the second part, we considered methods for the direct arylation of (hetero)arenes involving non-toxic and eco-friendly reaction media (water, alcohols, biomass-derived solvents, ILs, DESs) or under solvent-free conditions, discussing not only their impressive advancements in terms of sustainability with respect to traditional toxic solvents, but also their specific issues related to reagents solubility, need for harsh experimental conditions, residual toxicity, etc. In the third section, we gave a comprehensive overview on the application of non-conventional energy sources in direct C-H bond arylation reactions of (hetero)arenes: photochemical strategies, microwave-assisted protocols, electrochemical methods, as well as ultrasound-, mechanochemical- and infrared irradiation-promoted approaches; their advantages in the context of *Green Chemistry* were compared (when possible) with the corresponding performances of the traditional thermal heating.

Considering the central role of direct C-H bond arylation reactions in synthetic organic chemistry, significant future progress is expected in the next few years, focusing more and more on green and sustainable experimental conditions. We hope this review will encourage the wider scientific community involved in the synthesis of compounds involving the (hetero)aryl moieties for any use to pursue synthetic protocols inspired by the new paradigms of sustainable and environmental friendly production.

Conflicts of interest

There are no conflicts to declare.

References

1. (a) G. Bringmann, C. Günther, M. Ochse, O. Schupp and S. Tasler, in *Progress in the Chemistry of Organic Natural Products*, eds. W.

Herz, H. Falk, G. W. Kirby and R. E. Moore, Springer Vienna, Vienna, 2001, pp. 1-249; (b) S. V. Shevyakov, O. I. Davydova, D. G. Pershin, M. Krasavin, D. V. Kravchenko, A. Kiselyov, S. E. Tkachenko and A. V. Ivachtchenko, *Nat. Prod. Res.*, 2006, **20**, 735-741; (c) M. C. Kozlowski, B. J. Morgan and E. C. Linton, *Chem. Soc. Rev.*, 2009, **38**, 3193-3207; (d) H. Aldemir, R. Richarz and T. A. M. Gulder, *Angew. Chem. Int. Ed.*, 2014, **53**, 8286-8293.

2. (a) D. Pisignano, L. Persano, R. Cingolani, G. Gigli, F. Babudri, G. M. Farinola and F. Naso, *Appl. Phys. Lett.*, 2004, **84**, 1365-1367; (b) G. Marzano, C. V. Ciasca, F. Babudri, G. Bianchi, A. Pellegrino, R. Po and G. M. Farinola, *Eur. J. Org. Chem.*, 2014, **2014**, 6583-6614; (c) G. Marzano, D. Kotowski, F. Babudri, R. Musio, A. Pellegrino, S. Luzzati, R. Po and G. M. Farinola, *Macromolecules*, 2015, **48**, 7039-7048; (d) G. Marzano, F. Carulli, F. Babudri, A. Pellegrino, R. Po, S. Luzzati and G. M. Farinola, *J. Mater. Chem. A*, 2016, **4**, 17163-17170; (e) H. Bohra and M. Wang, *J. Mater. Chem. A*, 2017, **5**, 11550-11571; (f) A. Nitti, R. Po, G. Bianchi and D. Pasini, *Molecules*, 2017, **22**, 21; (g) G. Albano, L. A. Aronica, T. Biver, R. Detti and A. Pucci, *ChemistrySelect*, 2018, **3**, 1749-1754; (h) J. Kuwabara, *Polym. J.*, 2018, **50**, 1099-1106; (i) G. Albano, L. A. Aronica, A. Minotto, F. Cacialli and L. Di Bari, *Chem. Eur. J.*, 2020, **26**, 16622-16627; (j) O. Hassan Omar, M. Falcone, A. Operamolla and G. Albano, *New J. Chem.*, 2021, **45**, 12016-12023.
3. (a) J. K. Stille, *Pure Appl. Chem.*, 1985, **57**, 1771-1780; (b) N. Miyaura and A. Suzuki, *Chem. Rev.*, 1995, **95**, 2457-2483; (c) B. Betzemeier and P. Knochel, *Angew. Chem. Int. Ed.*, 1997, **36**, 2623-2624; (d) F. Naso, F. Babudri and G. M. Farinola, *Pure Appl. Chem.*, 1999, **71**, 1485-1492; (e) A. Operamolla, O. Hassan Omar, F. Babudri, G. M. Farinola and F. Naso, *J. Org. Chem.*, 2007, **72**, 10272-10275; (f) C. E. I. Knappke and A. Jacobi von Wangelin, *Chem. Soc. Rev.*, 2011, **40**, 4948-4962; (g) H. F. Sore, W. R. J. D. Galloway and D. R. Spring, *Chem. Soc. Rev.*, 2012, **41**, 1845-1866; (h) A. Punzi, F. Babudri and G. M. Farinola, *Eur. J. Org. Chem.*, 2020, **2020**, 3526-3541.
4. C. C. C. Johansson Seechurn, M. O. Kitching, T. J. Colacot and V. Snieckus, *Angew. Chem. Int. Ed.*, 2012, **51**, 5062-5085.
5. (a) T. Yamamoto, *J. Organomet. Chem.*, 2002, **653**, 195-199; (b) A. Biffis, P. Centomo, A. Del Zotto and M. Zecca, *Chem. Rev.*, 2018, **118**, 2249-2295.
6. (a) R. Rossi, F. Bellina, M. Lessi and C. Manzini, *Adv. Synth. Catal.*, 2014, **356**, 17-117; (b) R. Rossi, F. Bellina, M. Lessi, C. Manzini and L. A. Perego, *Synthesis*, 2014, **46**, 2833-2883; (c) C. B. Bheeter, L. Chen, J.-F. Soulé and H. Doucet, *Catal. Sci. Technol.*, 2016, **6**, 2005-2049; (d) W. Hagui, H. Doucet and J.-F. Soulé, *Chem*, 2019, **5**, 2006-2078; (e) H.-Y. Huang, A. Benzai, X. Shi and H. Doucet, *Chem. Rec.*, 2021, **21**, 343-356.
7. (a) A. Lei, W. Liu, C. Liu and M. Chen, *Dalton Trans.*, 2010, **39**, 10352-10361; (b) C. S. Yeung and V. M. Dong, *Chem. Rev.*, 2011, **111**, 1215-1292.
8. (a) D. Alberico, M. E. Scott and M. Lautens, *Chem. Rev.*, 2007, **107**, 174-238; (b) L. Ackermann, R. Vicente and A. R. Kapdi, *Angew. Chem. Int. Ed.*, 2009, **48**, 9792-9826; (c) G. P. McGlacken and L. M. Bateman, *Chem. Soc. Rev.*, 2009, **38**, 2447-2464; (d) L. G. Mercier and M. Leclerc, *Acc. Chem. Res.*, 2013, **46**, 1597-1605.
9. A. Sharma, D. Vacchani and E. Van der Eycken, *Chem. Eur. J.*, 2013, **19**, 1158-1168.
10. R. Rossi, M. Lessi, C. Manzini, G. Marianetti and F. Bellina, *Adv. Synth. Catal.*, 2015, **357**, 3777-3814.
11. S. Mao, H. Li, X. Shi, J.-F. Soulé and H. Doucet, *ChemCatChem*, 2019, **11**, 269-286.
12. (a) S. Yu, F. Liu, J. Yu, S. Zhang, C. Cabanetos, Y. Gao and W. Huang, *J. Mater. Chem. C*, 2017, **5**, 29-40; (b) R. M. Pankow and B. C. Thompson, *Polym. Chem.*, 2020, **11**, 630-640.
13. (a) L. Djakovitch and F.-X. Felpin, *ChemCatChem*, 2014, **6**, 2175-2187; (b) S. Santoro, S. I. Kozhushkov, L. Ackermann and L. Vaccaro, *Green Chem.*, 2016, **18**, 3471-3493; (c) S. Santoro, F. Ferlin, L. Luciani, L. Ackermann and L. Vaccaro, *Green Chem.*, 2017, **19**, 1601-1612; (d) C.-S. Wang, P. H. Dixneuf and J.-F. Soulé, *Chem. Rev.*, 2018, **118**, 7532-7585; (e) P. H. Dixneuf and J.-F. Soulé, in *Organometallics for Green Catalysis*, eds. P. H. Dixneuf and J.-F. Soulé, Springer International Publishing, Cham, Switzerland, 2019, pp. 225-265; (f) P. Gandeepan, N. Kaplaneris, S. Santoro, L. Vaccaro and L. Ackermann, *ACS Sustain. Chem. Eng.*, 2019, **7**, 8023-8040.
14. S. Hübner, J. G. de Vries and V. Farina, *Adv. Synth. Catal.*, 2016, **358**, 3-25.
15. (a) M. Campanati, G. Fornasari and A. Vaccari, *Catal. Today*, 2003, **77**, 299-314; (b) D. Astruc, F. Lu and J. R. Aranzaes, *Angew. Chem. Int. Ed.*, 2005, **44**, 7852-7872; (c) G. Albano, C. Evangelisti and L. A. Aronica, *ChemistrySelect*, 2017, **2**, 384-388; (d) G. Albano, S. Interlandi, C. Evangelisti and L. A. Aronica, *Catal. Lett.*, 2020, **150**, 652-659; (e) G. Rizzo, G. Albano, M. Lo Presti, A. Milella, F. G. Omenetto and G. M. Farinola, *Eur. J. Org. Chem.*, 2020, **2020**, 6992-6996; (f) G. Albano, C. Evangelisti and L. A. Aronica, *Catalysts*, 2021, **11**, 706.
16. T.-H. Park, A. J. Hickman, K. Koh, S. Martin, A. G. Wong-Foy, M. S. Sanford and A. J. Matzger, *J. Am. Chem. Soc.*, 2011, **133**, 20138-20141.
17. K. D. Collins, R. Honeker, S. Vásquez-Céspedes, D.-T. D. Tang and F. Glorius, *Chem. Sci.*, 2015, **6**, 1816-1824.
18. T. Parsharamulu, D. Venkanna, M. Lakshmi Kantam, S. K. Bhargava and P. Srinivasu, *Ind. Eng. Chem. Res.*, 2014, **53**, 20075-20084.
19. S. Vásquez-Céspedes, M. Holtkamp, U. Karst and F. Glorius, *Synlett*, 2017, **28**, 2759-2764.
20. D. Rasina, A. Kahler-Quesada, S. Ziarelli, S. Warratz, H. Cao, S. Santoro, L. Ackermann and L. Vaccaro, *Green Chem.*, 2016, **18**, 5025-5030.
21. S. Mao, X. Shi, J.-F. Soulé and H. Doucet, *Chem. Eur. J.*, 2019, **25**, 9504-9513.
22. M. Cao, D. Wu, W. Su and R. Cao, *J. Catal.*, 2015, **321**, 62-69.
23. M. Parisien, D. Valette and K. Fagnou, *J. Org. Chem.*, 2005, **70**, 7578-7584.
24. R. Cano, J. M. Pérez, D. J. Ramón and G. P. McGlacken, *Tetrahedron*, 2016, **72**, 1043-1050.
25. L. Nassar-Hardy, C. Deraedt, E. Fouquet and F.-X. Felpin, *Eur. J. Org. Chem.*, 2011, **2011**, 4616-4622.
26. S. Hernández, I. Moreno, R. SanMartin, G. Gómez, M. T. Herrero and E. Domínguez, *J. Org. Chem.*, 2010, **75**, 434-441.
27. K. Takagi, R. Kato, S. Yamamoto and H. Masu, *Polym. Chem.*, 2015, **6**, 6792-6795.
28. N. Nakamura, Y. Tajima and K. Sakai, *Heterocycles*, 1982, **17**, 235-245.
29. F. Bellina, C. Calandri, S. Cauteruccio and R. Rossi, *Tetrahedron*, 2007, **63**, 1970-1980.
30. X. Tian, F. Yang, D. Rasina, M. Bauer, S. Warratz, F. Ferlin, L. Vaccaro and L. Ackermann, *Chem. Commun.*, 2016, **52**, 9777-9780.
31. F. Ferlin, L. Luciani, S. Santoro, A. Marrocchi, D. Lanari, A. Bechtoldt, L. Ackermann and L. Vaccaro, *Green Chem.*, 2018, **20**, 2888-2893.
32. A. Punzi, N. Zappimbulso and G. M. Farinola, *Eur. J. Org. Chem.*, 2020, **2020**, 3229-3234.
33. S. Mao, X. Shi, J.-F. Soulé and H. Doucet, *Adv. Synth. Catal.*, 2018, **360**, 3306-3317.

34. S. Mao, X. Shi, J.-F. Soulé and H. Doucet, *Eur. J. Org. Chem.*, 2020, **2020**, 91-97.
35. F. Jafarpour, S. Rahiminejadan and H. Hazrati, *J. Org. Chem.*, 2010, **75**, 3109-3112.
36. P. Bizouard, C. Testa, V. A. Zinovyeva, J. Roger and J.-C. Hierso, *Synlett*, 2016, **27**, 1227-1231.
37. A.-J. Payne and G. C. Welch, *Org. Biomol. Chem.*, 2017, **15**, 3310-3319.
38. S. Keshipour and A. Shaabani, *Appl. Organomet. Chem.*, 2014, **28**, 116-119.
39. Y. Sun and T. Li, *ChemistrySelect*, 2020, **5**, 1431-1438.
40. L. Djakovitch, V. Dufaud and R. Zaidi, *Adv. Synth. Catal.*, 2006, **348**, 715-724.
41. G. Cusati and L. Djakovitch, *Tetrahedron Lett.*, 2008, **49**, 2499-2502.
42. Y. Huang, Z. Lin and R. Cao, *Chem. Eur. J.*, 2011, **17**, 12706-12712.
43. Y. Huang, T. Ma, P. Huang, D. Wu, Z. Lin and R. Cao, *ChemCatChem*, 2013, **5**, 1877-1883.
44. Y.-B. Huang, M. Shen, X. Wang, P. Huang, R. Chen, Z.-J. Lin and R. Cao, *J. Catal.*, 2016, **333**, 1-7.
45. E. V. Yarosh, A. A. Kurokhtina, E. V. Larina, N. A. Lagoda and A. F. Schmidt, *Org. Process Res. Dev.*, 2019, **23**, 1052-1059.
46. A. J. Reay, L. K. Neumann and I. J. S. Fairlamb, *Synlett*, 2016, **27**, 1211-1216.
47. P. Bhattacharjee, P. K. Boruah, M. R. Das and U. Bora, *New J. Chem.*, 2020, **44**, 7675-7682.
48. F. Campana, B. M. Massaccesi, S. Santoro, O. Piermatti and L. Vaccaro, *ACS Sustain. Chem. Eng.*, 2020, **8**, 16441-16450.
49. H. Veisi and N. Morakabati, *New J. Chem.*, 2015, **39**, 2901-2907.
50. L. Wang, W.-b. Yi and C. Cai, *Chem. Commun.*, 2011, **47**, 806-808.
51. L. Zhang, P. Li, C. Liu, J. Yang, M. Wang and L. Wang, *Catal. Sci. Technol.*, 2014, **4**, 1979-1988.
52. Y. M. A. Yamada, Y. Yuyama, T. Sato, S. Fujikawa and Y. Uozumi, *Angew. Chem. Int. Ed.*, 2014, **53**, 127-131.
53. L. Duan, R. Fu, B. Zhang, W. Shi, S. Chen and Y. Wan, *ACS Catal.*, 2016, **6**, 1062-1074.
54. C. Deraedt, R. Ye, W. T. Ralston, F. D. Toste and G. A. Somorjai, *J. Am. Chem. Soc.*, 2017, **139**, 18084-18092.
55. R. V. Hegde, T.-G. Ong, R. Ambre, A. H. Jadhav, S. A. Patil and R. B. Dateer, *Catal. Lett.*, 2021, **151**, 1397-1405.
56. J. Lee, J. Chung, S. M. Byun, B. M. Kim and C. Lee, *Tetrahedron*, 2013, **69**, 5660-5664.
57. D. Firmansyah, I. Deperasińska, O. Vakuliuk, M. Banasiewicz, M. Tasior, A. Makarewicz, M. K. Cyrański, B. Kozankiewicz and D. T. Gryko, *Chem. Commun.*, 2016, **52**, 1262-1265.
58. H. Kilic, M. Turgut, M. S. Yilmaz, O. Dalkilic and Ö. Metin, *ACS Sustain. Chem. Eng.*, 2018, **6**, 11433-11440.
59. S. Sahnoun, S. Messaoudi, J.-F. Peyrat, J.-D. Brion and M. Alami, *Tetrahedron Lett.*, 2008, **49**, 7279-7283.
60. S. Sahnoun, S. Messaoudi, J.-D. Brion and M. Alami, *Org. Biomol. Chem.*, 2009, **7**, 4271-4278.
61. A. Paul, A. Paul and S. Yadav, *Tetrahedron Lett.*, 2020, **61**, 151364.
62. V. A. Zinovyeva, M. A. Vorotyntsev, I. Bezverkhyy, D. Chaumont and J.-C. Hierso, *Adv. Funct. Mater.*, 2011, **21**, 1064-1075.
63. S. Hayashi, Y. Kojima and T. Koizumi, *Polymer*, 2017, **113**, 214-220.
64. D.-T. D. Tang, K. D. Collins, J. B. Ernst and F. Glorius, *Angew. Chem. Int. Ed.*, 2014, **53**, 1809-1813.
65. S. Hayashi, Y. Kojima and T. Koizumi, *Polym. Chem.*, 2015, **6**, 881-885.
66. S. Wang, D. Hu, W. Hua, J. Gu, Q. Zhang, X. Jia and K. Xi, *RSC Adv.*, 2015, **5**, 53935-53939.
67. K. Uegaki, K. Nakabayashi, S.-i. Yamamoto, T. Koizumi and S. Hayashi, *RSC Adv.*, 2020, **10**, 19034-19040.
68. S. M. McAfee, J. S. J. McCahill, C. M. Macaulay, A. D. Hendsbee and G. C. Welch, *RSC Adv.*, 2015, **5**, 26097-26106.
69. (a) A. Punzi, F. Nicoletta, G. Marzano, C. G. Fortuna, J. Dagar, T. M. Brown and G. M. Farinola, *Eur. J. Org. Chem.*, 2016, **2016**, 3233-3242; (b) A. Punzi, N. Zappimbulso and G. M. Farinola, *Monatsh. Chem.*, 2019, **150**, 59-66.
70. J. Areephong, A. D. Hendsbee and G. C. Welch, *New J. Chem.*, 2015, **39**, 6714-6717.
71. A.-J. Payne, N. A. Rice, S. M. McAfee, S. Li, P. Josse, C. Cabanetos, C. Risko, B. H. Lessard and G. C. Welch, *ACS Appl. Energy Mater.*, 2018, **1**, 4906-4916.
72. T. A. Welsh, M. Nazari and G. C. Welch, *Asian J. Org. Chem.*, 2020, **9**, 1291-1300.
73. P. Josse, S. Dayneko, Y. Zhang, S. Dabos-Seignon, S. Zhang, P. Blanchard, G. C. Welch and C. Cabanetos, *Molecules*, 2018, **23**, 962.
74. T. A. Welsh, A. Laventure, A. F. Alahmadi, G. Zhang, T. Baumgartner, Y. Zou, F. Jäkle and G. C. Welch, *ACS Appl. Energy Mater.*, 2019, **2**, 1229-1240.
75. V. Kandathil, M. Kempasiddaiah, S. B. S and S. A. Patil, *Carbohydr. Polym.*, 2019, **223**, 115060.
76. S. Hayashi, A. Takigami and T. Koizumi, *ChemPlusChem*, 2016, **81**, 930-934.
77. Y. Kojima, S. Hayashi and T. Koizumi, *J. Polym. Sci., Part A: Polym. Chem.*, 2017, **55**, 1183-1188.
78. S. Sreekumar, S. Xavier, A. Govindan, R. E. Thampikannu, K. Vellayan and B. González, *Res. Chem. Intermed.*, 2020, **46**, 4529-4542.
79. T. A. Welsh, A. Laventure and G. C. Welch, *Molecules*, 2018, **23**, 931.
80. D.-T. D. Tang, K. D. Collins and F. Glorius, *J. Am. Chem. Soc.*, 2013, **135**, 7450-7453.
81. A.-J. Payne, J. Song, Y. Sun and G. C. Welch, *Chem. Commun.*, 2018, **54**, 11443-11446.
82. T. A. Welsh, A. J. Payne and G. C. Welch, *New J. Chem.*, 2019, **43**, 9333-9337.
83. T. A. Welsh, A. Laventure, T. Baumgartner and G. C. Welch, *J. Mater. Chem. C*, 2018, **6**, 2148-2154.
84. J. D. B. Koenig, A. Laventure and G. C. Welch, *ACS Appl. Energy Mater.*, 2019, **2**, 8939-8945.
85. E. Y. Lee and J. Park, *ChemCatChem*, 2011, **3**, 1127-1129.
86. B. P. Mathew, H. J. Yang, H. Jeon, J. H. Lee, J. C. Kim, T. J. Shin, K. Myung, S. K. Kwak, J. H. Kwak and S. Y. Hong, *J. Mol. Catal. A: Chem.*, 2016, **417**, 64-70.
87. H. J. Yang, B. P. Mathew, D. G. Oh, K. Myung, J. H. Kwak and S. Y. Hong, *Catal. Commun.*, 2017, **90**, 83-86.
88. R. Tadikonda, M. Nakka, S. Rayavarapu, S. P. K. Kalidindi and S. Vidavalur, *Tetrahedron Lett.*, 2015, **56**, 690-692.
89. L. Zhi, H. Zhang, Z. Yang, W. Liu and B. Wang, *Chem. Commun.*, 2016, **52**, 6431-6434.
90. W. Zhang, Q. Zeng, X. Zhang, Y. Tian, Y. Yue, Y. Guo and Z. Wang, *J. Org. Chem.*, 2011, **76**, 4741-4745.
91. W. Zhang, Y. Tian, N. Zhao, Y. Wang, J. Li and Z. Wang, *Tetrahedron*, 2014, **70**, 6120-6126.
92. G. Satish, K. H. V. Reddy, B. S. P. Anil, K. Ramesh, R. U. Kumar and Y. V. D. Nageswar, *Tetrahedron Lett.*, 2015, **56**, 4950-4953.
93. H. T. N. Le, T. T. Nguyen, P. H. L. Vu, T. Truong and N. T. S. Phan, *J. Mol. Catal. A: Chem.*, 2014, **391**, 74-82.
94. T. Truong, V. T. Nguyen, H. T. X. Le and N. T. S. Phan, *RSC Adv.*, 2014, **4**, 52307-52315.

95. C. Huang, J. Wu, C. Song, R. Ding, Y. Qiao, H. Hou, J. Chang and Y. Fan, *Chem. Commun.*, 2015, **51**, 10353-10356.
96. S. Vásquez-Céspedes, K. M. Chepiga, N. Möller, A. H. Schäfer and F. Glorius, *ACS Catal.*, 2016, **6**, 5954-5961.
97. C. Rajendran and G. Satishkumar, *ChemCatChem*, 2017, **9**, 1284-1291.
98. S. H. Doan, K. D. Nguyen, T. T. Nguyen and N. T. S. Phan, *RSC Adv.*, 2017, **7**, 1423-1431.
99. R. Zhang, C.-X. Miao, S. Wang, C. Xia and W. Sun, *ChemCatChem*, 2012, **4**, 192-195.
100. N. T. S. Phan, C. K. Nguyen, T. T. Nguyen and T. Truong, *Catal. Sci. Technol.*, 2014, **4**, 369-377.
101. H. T. T. Nguyen, D. N. A. Doan and T. Truong, *J. Mol. Catal. A: Chem.*, 2017, **426**, 141-149.
102. H. Liu, B. Yin, Z. Gao, Y. Li and H. Jiang, *Chem. Commun.*, 2012, **48**, 2033-2035.
103. Z.-H. Sun, W. Chen, B.-B. Qian, L. Wang, B. Yu, Q. Chen, M.-Y. He and Z.-H. Zhang, *Appl. Organomet. Chem.*, 2020, **34**, e5482.
104. H. Miura, K. Wada, S. Hosokawa and M. Inoue, *Chem. Eur. J.*, 2010, **16**, 4186-4189.
105. R. S. Shelkar, K. E. Balsane and J. M. Nagarkar, *Tetrahedron Lett.*, 2015, **56**, 693-699.
106. J. Zoller, D. C. Fabry and M. Rueping, *ACS Catal.*, 2015, **5**, 3900-3904.
107. K. Luo, Q. Su, P. Ju, X. Li, Z. Liu, X. Sun, G. Li and Q. Wu, *Chem. Res. Chin. Univ.*, 2020, **36**, 1302-1309.
108. X. Cai, H. Liu, L. Zhi, H. Wen, A. Yu, L. Li, F. Chen and B. Wang, *RSC Adv.*, 2017, **7**, 46132-46138.
109. J. Liu, H. Wang, J. Bai, T. Li, Y. Yang, Y. Peng and B. Wang, *J. Mater. Chem. A*, 2017, **5**, 24920-24928.
110. S. Chaubey, R. K. Yadav, T. W. Kim, T. C. Yadav, A. Kumar, D. K. Dwivedi, B. K. Pandey and A. P. Singh, *Chin. J. Chem* . 2021, **39**, 633-639.
111. E. Kalay, H. Küçükkeçeci, H. Kilic and Ö. Metin, *Chem. Commun.*, 2020, **56**, 5901-5904.
112. (a) P. G. Jessop, *Green Chem.*, 2011, **13**, 1391-1398; (b) L. Moity, M. Durand, A. Benazzouz, C. Pierlot, V. Molinier and J.-M. Aubry, *Green Chem.*, 2012, **14**, 1132-1145; (c) M. Tobiszewski, S. Tsakovski, V. Simeonov, J. Namieśnik and F. Pena-Pereira, *Green Chem.*, 2015, **17**, 4773-4785.
113. A. D. Curzons, D. C. Constable and V. L. Cunningham, *Clean Prod. Process.*, 1999, **1**, 82-90.
114. C. J. Clarke, W.-C. Tu, O. Levers, A. Bröhl and J. P. Hallett, *Chem. Rev.*, 2018, **118**, 747-800.
115. C. Jimenez-Gonzalez, C. S. Ponder, Q. B. Broxterman and J. B. Manley, *Org. Process Res. Dev.*, 2011, **15**, 912-917.
116. (a) Y. Gu and F. Jérôme, *Chem. Soc. Rev.*, 2013, **42**, 9550-9570; (b) A. G. Correa, M. W. Paixao and R. S. Schwab, *Curr. Org. Synth.*, 2015, **12**, 675-695; (c) F. G. Calvo-Flores, M. J. Monteagudo-Arrebola, J. A. Dobado and J. Isac-García, *Top. Curr. Chem.*, 2018, **376**, 18.
117. (a) J. H. Clark, T. J. Farmer, A. J. Hunt and J. Sherwood, *Int. J. Mol. Sci.*, 2015, **16**, 17101-17159; (b) M. Sarmah, M. Mondal and U. Bora, *ChemistrySelect*, 2017, **2**, 5180-5188.
118. (a) A. Lubineau and J. Augé, in *Modern Solvents in Organic Synthesis*, ed. P. Knochel, Springer Berlin Heidelberg, Berlin, Heidelberg, 1999, pp. 1-39; (b) P. H. Dixneuf and V. Cadierno, *Metal Catalyzed Reactions in Water*, Wiley-VCH, Weinheim, Germany, 2013.
119. C. J. Li, *Chem. Rev.*, 1993, **93**, 2023-2035.
120. Z. Wu, F. Luo, S. Chen, Z. Li, H. Xiang and X. Zhou, *Chem. Commun.*, 2013, **49**, 7653-7655.
121. R. Long, X. Yan, Z. Wu, Z. Li, H. Xiang and X. Zhou, *Org. Biomol. Chem.*, 2015, **13**, 3571-3574.
122. L. J. Durak and J. C. Lewis, *Organometallics*, 2014, **33**, 620-623.
123. Y.-J. Lin, H.-S. Sun, H.-R. Yang, Y.-Y. Lai, K.-Y. Hou and Y.-H. Liu, *Macromol. Rapid Commun.*, 2020, **41**, 2000021.
124. A. Bruggink and A. McKillop, *Tetrahedron*, 1975, **31**, 2607-2619.
125. B. Li, C. B. Bheeter, C. Darcel and P. H. Dixneuf, *Top. Catal.*, 2014, **57**, 833-842.
126. M. Murai, H. Maekawa, S. Hamao, Y. Kubozono, D. Roy and K. Takai, *Org. Lett.*, 2015, **17**, 708-711.
127. D. Roy, H. Maekawa, M. Murai and K. Takai, *Chem. Asian J.*, 2015, **10**, 2518-2524.
128. L.-Y. Shao, L.-H. Xing, Y. Guo, K.-K. Yu, W. Wang, H.-W. Liu, D.-H. Liao and Y.-F. Ji, *Adv. Synth. Catal.*, 2018, **360**, 2925-2937.
129. O. René and K. Fagnou, *Org. Lett.*, 2010, **12**, 2116-2119.
130. F. Chen, Q.-Q. Min and X. Zhang, *J. Org. Chem.*, 2012, **77**, 2992-2998.
131. A. M. Calascibetta, S. Mattiello, A. Sanzone, I. Facchinetti, M. Sassi and L. Beverina, *Molecules*, 2020, **25**, 3717.
132. T. Miao and L. Wang, *Adv. Synth. Catal.*, 2014, **356**, 429-436.
133. L. Ackermann, J. Pospech and H. K. Potukuchi, *Org. Lett.*, 2012, **14**, 2146-2149.
134. K. S. Singh and P. H. Dixneuf, *ChemCatChem*, 2013, **5**, 1313-1316.
135. N. Kaloğlu, İ. Özdemir, N. Gürbüz, H. Arslan and P. H. Dixneuf, *Molecules*, 2018, **23**, 647.
136. A. D. Dwivedi, C. Binnani, D. Tyagi, K. S. Rawat, P.-Z. Li, Y. Zhao, S. M. Mobin, B. Pathak and S. K. Singh, *Inorg. Chem.*, 2016, **55**, 6739-6749.
137. L. A. Adrio, J. Gimeno and C. Vicent, *Chem. Commun.*, 2013, **49**, 8320-8322.
138. S. Seifert, D. Schmidt and F. Würthner, *Org. Chem. Front.*, 2016, **3**, 1435-1442.
139. S. Seifert, D. Schmidt, K. Shoyama and F. Würthner, *Angew. Chem. Int. Ed.*, 2017, **56**, 7595-7600.
140. B. S. Cho, H. J. Bae and Y. K. Chung, *J. Org. Chem.*, 2015, **80**, 5302-5307.
141. H. Brodnik, F. Požgan and B. Štefane, *Org. Biomol. Chem.*, 2016, **14**, 1969-1981.
142. Q. Yang, T. Wei, Y. He, Y. Liang and Z.-T. Zhang, *Helv. Chim. Acta*, 2015, **98**, 953-960.
143. A. Graml, I. Ghosh and B. König, *J. Org. Chem.*, 2017, **82**, 3552-3560.
144. F. Pallini, E. Sangalli, M. Sassi, P. M. C. Roth, S. Mattiello and L. Beverina, *Org. Biomol. Chem.*, 2021, **19**, 3016-3023.
145. T. Lv, X.-H. Zhang, J.-S. Han and P. Zhong, *J. Fluorine Chem.*, 2012, **137**, 44-49.
146. S. Fuse, T. Morita, K. Johmoto, H. Uekusa and H. Tanaka, *Chem. Eur. J.*, 2015, **21**, 14370-14375.
147. A. Mahindra and R. Jain, *Synlett*, 2012, **23**, 1759-1764.
148. G. L. Turner, J. A. Morris and M. F. Greaney, *Angew. Chem. Int. Ed.*, 2007, **46**, 7996-8000.
149. E. F. Flegeau, M. E. Popkin and M. F. Greaney, *Org. Lett.*, 2008, **10**, 2717-2720.
150. S. A. Ohnmacht, P. Mamone, A. J. Culshaw and M. F. Greaney, *Chem. Commun.*, 2008, 1241-1243.
151. S. M. Wales, K. A. Hammer, K. Somphol, I. Kemker, D. C. Schröder, A. J. Tague, Z. Brkic, A. M. King, D. Lyras, T. V. Riley, J. B. Bremner, P. A. Keller and S. G. Pyne, *Org. Biomol. Chem.*, 2015, **13**, 10813-10824.
152. A. Kokornaczyk, D. Schepmann, J. Yamaguchi, K. Itami and B. Wünsch, *MedChemComm*, 2016, **7**, 327-331.

153. I. B. Seiple, S. Su, R. A. Rodriguez, R. Gianatassio, Y. Fujiwara, A. L. Sobel and P. S. Baran, *J. Am. Chem. Soc.*, 2010, **132**, 13194-13196.
154. W. Mai, J. Yuan, Z. Li, G. Sun and L. Qu, *Synlett*, 2012, **2012**, 145-149.
155. L. Fang, X. Shi, L. Chen, J. Yu and L. Wang, *Synlett*, 2014, **25**, 1413-1418.
156. J. D. Galloway, D. N. Mai and R. D. Baxter, *Org. Lett.*, 2017, **19**, 5772-5775.
157. R. Wang and J. R. Falck, *Org. Chem. Front.*, 2014, **1**, 1029-1034.
158. J. Wang, S. Wang, G. Wang, J. Zhang and X.-Q. Yu, *Chem. Commun.*, 2012, **48**, 11769-11771.
159. Y. Huang, D. Guan and L. Wang, *Chin. J. Chem .* 2014, **32**, 1294-1298.
160. K. Komeyama, Y. Nagao, M. Abe and K. Takaki, *Bull. Chem. Soc. Jpn.*, 2014, **87**, 301-313.
161. K. P. Start, M. D. Wheeler and C. M. Kozak, *Can. J. Chem.*, 2020, **99**, 182-192.
162. D. Xue, Z.-H. Jia, C.-J. Zhao, Y.-Y. Zhang, C. Wang and J. Xiao, *Chem. Eur. J.*, 2014, **20**, 2960-2965.
163. L. Joucla, N. Batail and L. Djakovitch, *Adv. Synth. Catal.*, 2010, **352**, 2929-2936.
164. S. Islam and I. Larrosa, *Chem. Eur. J.*, 2013, **19**, 15093-15096.
165. P. Nareddy, F. Jordan and M. Szostak, *Org. Lett.*, 2018, **20**, 341-344.
166. G. N. Vaidya, S. Fiske, H. Verma, S. K. Lokhande and D. Kumar, *Green Chem.*, 2019, **21**, 1448-1454.
167. A. F. P. Biajoli, E. T. da Penha and C. R. D. Correia, *RSC Adv.*, 2012, **2**, 11930-11935.
168. G.-p. Lu and C. Cai, *Synlett*, 2012, **23**, 2992-2996.
169. Y. Gao, W. Zhu, L. Yin, B. Dong, J. Fu, Z. Ye, F. Xue and C. Jiang, *Tetrahedron Lett.*, 2017, **58**, 2213-2216.
170. M.-Z. Lu, P. Lu, Y.-H. Xu and T.-P. Loh, *Org. Lett.*, 2014, **16**, 2614-2617.
171. N. Thrimurtulu, A. Dey, A. Singh, K. Pal, D. Maiti and C. M. R. Volla, *Adv. Synth. Catal.*, 2019, **361**, 1441-1446.
172. S. A. Ohnmacht, A. J. Culshaw and M. F. Greaney, *Org. Lett.*, 2010, **12**, 224-226.
173. K. Gambouz, A. El Abbouchi, S. Nassiri, F. Suzenet, M. Bousmina, M. Akssira, G. Guillaumet and S. El Kazzouli, *Molecules*, 2020, **25**, 2820.
174. A. Gokanapalli, V. K. R. Motakatla and V. G. R. Peddiahgari, *Appl. Organomet. Chem.*, 2020, **34**, e5869.
175. A. Deb, S. Manna, A. Maji, U. Dutta and D. Maiti, *Eur. J. Org. Chem.*, 2013, **2013**, 5251-5256.
176. J.-W. Yuan, S.-N. Liu and L.-B. Qu, *Tetrahedron*, 2017, **73**, 2267-2275.
177. X. Ren, S. Han, X. Gao, J. Li, D. Zou, Y. Wu and Y. Wu, *Tetrahedron Lett.*, 2018, **59**, 1065-1068.
178. M. Tian, M. Yu, T. Shi, J. Hu, S. Li, J. Xu, N. Chen and H. Du, *Eur. J. Org. Chem.*, 2017, **2017**, 3415-3420.
179. S. Faarasse, S. El Kazzouli, M. Naas, J. Jouha, F. Suzenet and G. Guillaumet, *J. Org. Chem.*, 2017, **82**, 12300-12306.
180. S. Faarasse, S. El Kazzouli, F. Suzenet and G. Guillaumet, *J. Org. Chem.*, 2018, **83**, 12847-12854.
181. S. Kalari, D. A. Babar, U. B. Karale, V. B. Makane and H. B. Rode, *Tetrahedron Lett.*, 2017, **58**, 2818-2821.
182. Y.-X. Su, Y.-H. Deng, T.-T. Ma, Y.-Y. Li and L.-P. Sun, *Green Chem.*, 2012, **14**, 1979-1981.
183. B. Mu, J. Li, D. Zou, Y. Wu, J. Chang and Y. Wu, *Chin. J. Org. Chem.*, 2018, **38**, 95-102.
184. M.-j. Bu, G.-p. Lu, J. Jiang and C. Cai, *Catal. Sci. Technol.*, 2018, **8**, 3728-3732.
185. C. Gozzi, L. Lavenot, K. Ilg, V. Penalva and M. Lemaire, *Tetrahedron Lett.*, 1997, **38**, 8867-8870.
186. L. Lavenot, C. Gozzi, K. Ilg, I. Orlova, V. Penalva and M. Lemaire, *J. Organomet. Chem.*, 1998, **567**, 49-55.
187. M. Sévignon, J. Hassan, C. Gozzi, E. Schulz and M. Lemaire, *C. R. Acad. Sci., Ser. IIc: Chim.*, 2000, **3**, 569-572.
188. K. Matsumura, S. Yoshizaki, M. M. Maitani, Y. Wada, Y. Ogomi, S. Hayase, T. Kaiho, S. Fuse, H. Tanaka and T. Takahashi, *Chem. Eur. J.*, 2015, **21**, 9742-9747.
189. A. Osadnik and A. Lützen, *Arkivoc*, 2015, **2015**, 40-51.
190. S. Özenler, H. Kaya, N. Elmaci and U. H. Yildiz, *ChemistrySelect*, 2019, **4**, 8516-8521.
191. F. Grenier, K. Goudreau and M. Leclerc, *J. Am. Chem. Soc.*, 2017, **139**, 2816-2824.
192. N. S. Gobalasingham, S. Ekiz, R. M. Pankow, F. Livi, E. Bundgaard and B. C. Thompson, *Polym. Chem.*, 2017, **8**, 4393-4402.
193. M. Mainville, V. Tremblay, M. Z. Fenniri, A. Laventure, M. E. Farahat, R. Ambrose, G. C. Welch, I. G. Hill and M. Leclerc, *Asian J. Org. Chem.*, 2020, **9**, 1318-1325.
194. H. Ayalew, T.-l. Wang, T.-H. Wang, H.-F. Hsu and H.-h. Yu, *Synlett*, 2018, **29**, 2660-2668.
195. K. Tekin, N. Hao, S. Karagoz and A. J. Ragauskas, *ChemSusChem*, 2018, **11**, 3559-3575.
196. S. Bensaid, N. Laidaoui, D. El Abed, S. Kacimi and H. Doucet, *Tetrahedron Lett.*, 2011, **52**, 1383-1387.
197. S. K. Guchhait, M. Kashyap and S. Saraf, *Synthesis*, 2010, **2010**, 1166-1170.
198. Z.-J. Cai, C.-X. Liu, Q. Gu and S.-L. You, *Angew. Chem. Int. Ed.*, 2018, **57**, 1296-1299.
199. D. E. Ames and A. Opalko, *Tetrahedron*, 1984, **40**, 1919-1925.
200. D. Kalyani, K. B. McMurtrey, S. R. Neufeldt and M. S. Sanford, *J. Am. Chem. Soc.*, 2011, **133**, 18566-18569.
201. L. Liang, M.-S. Xie, H.-X. Wang, H.-Y. Niu, G.-R. Qu and H.-M. Guo, *J. Org. Chem.*, 2017, **82**, 5966-5973.
202. M. K. Sahoo, S. P. Midya, V. G. Landge and E. Balaraman, *Green Chem.*, 2017, **19**, 2111-2117.
203. T. S. Manikandan, R. Ramesh and D. Semeril, *Organometallics*, 2019, **38**, 319-328.
204. J.-H. Chu, H.-P. Huang, W.-T. Hsu, S.-T. Chen and M.-J. Wu, *Organometallics*, 2014, **33**, 1190-1204.
205. D. S. Lee, P. Y. Choy, C. M. So, J. Wang, C. P. Lau and F. Y. Kwong, *RSC Adv.*, 2012, **2**, 9179-9182.
206. E. T. Nadres, G. I. F. Santos, D. Shabashov and O. Daugulis, *J. Org. Chem.*, 2013, **78**, 9689-9714.
207. A. Tlahuext-Aca, S. Y. Lee, S. Sakamoto and J. F. Hartwig, *ACS Catal.*, 2021, **11**, 1430-1434.
208. L. Wang, Z. Li, X. Qu and W. Peng, *Chin. J. Chem .* 2015, **33**, 1015-1018.
209. S. Bensaid and H. Doucet, *C. R. Chimie*, 2014, **17**, 1184-1189.
210. L. Ackermann, A. Althammer and S. Fenner, *Angew. Chem. Int. Ed.*, 2009, **48**, 201-204.
211. K. Godula, B. Sezen and D. Sames, *J. Am. Chem. Soc.*, 2005, **127**, 3648-3649.
212. L. Ackermann and S. Fenner, *Chem. Commun.*, 2011, **47**, 430-432.
213. L. Wang, X. Qu, Z. Li and W.-M. Peng, *Tetrahedron Lett.*, 2015, **56**, 3754-3757.
214. R.-R. Liu, Y. Xu, R.-X. Liang, B. Xiang, H.-J. Xie, J.-R. Gao and Y.-X. Jia, *Org. Biomol. Chem.*, 2017, **15**, 2711-2715.
215. C. M. So, C. P. Lau and F. Y. Kwong, *Chem. Eur. J.*, 2011, **17**, 761-765.
216. J. Zhang, J. Chen, X. Zhang and X. Lei, *J. Org. Chem.*, 2014, **79**, 10682-10688.

217. P. Y. Choy, K. C. Luk, Y. Wu, C. M. So, L.-l. Wang and F. Y. Kwong, *J. Org. Chem.*, 2015, **80**, 1457-1463.
218. S. Chikhi, S. Djebbar, J.-F. Soulé and H. Doucet, *Chem. Asian J.*, 2016, **11**, 2443-2452.
219. J.-H. Chu, C.-C. Wu, D.-H. Chang, Y.-M. Lee and M.-J. Wu, *Organometallics*, 2013, **32**, 272-282.
220. G. de Gonzalo, A. R. Alcántara and P. Domínguez de María, *ChemSusChem*, 2019, **12**, 2083-2097.
221. (a) G.-S. Zhang, M.-M. Zhu, Q. Zhang, Y.-M. Liu, H.-Y. He and Y. Cao, *Green Chem.*, 2016, **18**, 2155-2164; (b) N. Pino, G. Hincapié and D. López, *Energy Fuels*, 2018, **32**, 561-573.
222. K. Beydoun and H. Doucet, *ChemSusChem*, 2011, **4**, 526-534.
223. K. Beydoun, J. Boixel, V. Guerchais and H. Doucet, *Catal. Sci. Technol.*, 2012, **2**, 1242-1248.
224. Y. Bouazizi, K. Beydoun, A. Romdhane, H. Ben Jannet and H. Doucet, *Tetrahedron Lett.*, 2012, **53**, 6801-6805.
225. A. Hfaiedh, K. Yuan, H. Ben Ammar, B. Ben Hassine, J.-F. Soulé and H. Doucet, *ChemSusChem*, 2015, **8**, 1794-1804.
226. F. Belkessam, M. Aidene, J.-F. Soulé and H. Doucet, *ChemCatChem*, 2017, **9**, 2239-2249.
227. S. Yamada, K. N. Flesch, K. Murakami and K. Itami, *Org. Lett.*, 2020, **22**, 1547-1551.
228. H. Jiang, A. Bellomo, M. Zhang, P. J. Carroll, B. C. Manor, T. Jia and P. J. Walsh, *Org. Lett.*, 2018, **20**, 2522-2525.
229. M. Wakioka, Y. Kitano and F. Ozawa, *Macromolecules*, 2013, **46**, 370-374.
230. R. M. Pankow, L. Ye, N. S. Gobalasingham, N. Salami, S. Samal and B. C. Thompson, *Polym. Chem.*, 2018, **9**, 3885-3892.
231. R. M. Pankow, L. Ye and B. C. Thompson, *Polym. Chem.*, 2019, **10**, 4561-4572.
232. L. Ye, R. M. Pankow, M. Horikawa, E. L. Melenbrink, K. Liu and B. C. Thompson, *Macromolecules*, 2019, **52**, 9383-9388.
233. R. M. Pankow, L. Ye and B. C. Thompson, *Macromolecules*, 2020, **53**, 3315-3324.
234. D. Conelli, R. Grisorio and G. P. Suranna, *Macromol. Chem. Phys.*, 2020, **221**, 2000041.
235. (a) A.-A. G. Shaikh and S. Sivaram, *Chem. Rev.*, 1996, **96**, 951-976; (b) B. Schäffner, F. Schäffner, S. P. Verevkin and A. Börner, *Chem. Rev.*, 2010, **110**, 4554-4581.
236. T. Sakakura and K. Kohno, *Chem. Commun.*, 2009, 1312-1330.
237. C. Martín, G. Fiorani and A. W. Kleij, *ACS Catal.*, 2015, **5**, 1353-1370.
238. K. Shukla and V. C. Srivastava, *RSC Adv.*, 2016, **6**, 32624-32645.
239. P. Arockiam, V. Poirier, C. Fischmeister, C. Bruneau and P. H. Dixneuf, *Green Chem.*, 2009, **11**, 1871-1875.
240. M. K. Sahoo, J. Rana, M. Subaramanian and E. Balaraman, *ChemistrySelect*, 2017, **2**, 7565-7569.
241. J. Roger and J.-C. Hierso, *Eur. J. Org. Chem.*, 2018, **2018**, 4953-4958.
242. J. Roger, C. Verrier, R. Le Goff, C. Hoarau and H. Doucet, *ChemSusChem*, 2009, **2**, 951-956.
243. J. J. Dong, J. Roger, C. Verrier, T. Martin, R. Le Goff, C. Hoarau and H. Doucet, *Green Chem.*, 2010, **12**, 2053-2063.
244. I. Idris, F. Derridj, S. Djebbar, J.-F. Soulé and H. Doucet, *Tetrahedron*, 2015, **71**, 9617-9625.
245. V. Pace, P. Hoyos, L. Castoldi, P. Domínguez de María and A. R. Alcántara, *ChemSusChem*, 2012, **5**, 1369-1379.
246. D. F. Aycock, *Org. Process Res. Dev.*, 2007, **11**, 156-159.
247. R. Matsidik, A. Luzio, S. Hameury, H. Komber, C. R. McNeill, M. Caironi and M. Sommer, *J. Mater. Chem. C*, 2016, **4**, 10371-10380.
248. A. S. Dudnik, T. J. Aldrich, N. D. Eastham, R. P. H. Chang, A. Facchetti and T. J. Marks, *J. Am. Chem. Soc.*, 2016, **138**, 15699-15709.
249. T. J. Aldrich, A. S. Dudnik, N. D. Eastham, E. F. Manley, L. X. Chen, R. P. H. Chang, F. S. Melkonyan, A. Facchetti and T. J. Marks, *Macromolecules*, 2018, **51**, 9140-9155.
250. N. S. Gobalasingham, R. M. Pankow, S. Ekiz and B. C. Thompson, *J. Mater. Chem. A*, 2017, **5**, 14101-14113.
251. T. M. Pappenfus, F. Almyahi, N. A. Cooling, E. W. Culver, S. C. Rasmussen and P. C. Dastoor, *Macromol. Chem. Phys.*, 2018, **219**, 1800272.
252. M. Wakioka, N. Yamashita, H. Mori, Y. Nishihara and F. Ozawa, *Molecules*, 2018, **23**, 981.
253. D. M. Alonso, S. G. Wettstein and J. A. Dumesic, *Green Chem.*, 2013, **15**, 584-595.
254. I. T. Horváth, H. Mehdi, V. Fábos, L. Boda and L. T. Mika, *Green Chem.*, 2008, **10**, 238-242.
255. D. Fegyverneki, L. Orha, G. Láng and I. T. Horváth, *Tetrahedron*, 2010, **66**, 1078-1081.
256. Q. Bu, E. Gońka, K. Kuciński and L. Ackermann, *Chem. Eur. J.*, 2019, **25**, 2213-2216.
257. I. Anastasiou, N. Van Velthoven, E. Tomarelli, A. Lombi, D. Lanari, P. Liu, S. Bals, D. E. De Vos and L. Vaccaro, *ChemSusChem*, 2020, **13**, 2786-2791.
258. S. Tabasso, E. Calcio Gaudino, L. Rinaldi, A. Ledoux, P. Larini and G. Cravotto, *New J. Chem.*, 2017, **41**, 9210-9215.
259. (a) A. Wang and T. Zhang, *Acc. Chem. Res.*, 2013, **46**, 1377-1386; (b) J. Xi, D. Ding, Y. Shao, X. Liu, G. Lu and Y. Wang, *ACS Sustain. Chem. Eng.*, 2014, **2**, 2355-2362.
260. (a) J. Chen, S. K. Spear, J. G. Huddleston and R. D. Rogers, *Green Chem.*, 2005, **7**, 64-82; (b) M. Vafaeezadeh and M. M. Hashemi, *J. Mol. Liq.*, 2015, **207**, 73-79.
261. L. Ackermann and R. Vicente, *Org. Lett.*, 2009, **11**, 4922-4925.
262. L. Jian, H.-Y. He, J. Huang, Q.-H. Wu, M.-L. Yuan, H.-Y. Fu, X.-L. Zheng, H. Chen and R.-X. Li, *RSC Adv.*, 2017, **7**, 23515-23522.
263. N. Barbero, R. SanMartin and E. Domínguez, *Tetrahedron Lett.*, 2009, **50**, 2129-2131.
264. M.-A. Hiebel, Y. Fall, M.-C. Scherrmann and S. Berteina-Raboin, *Eur. J. Org. Chem.*, 2014, **2014**, 4643-4650.
265. (a) T. Welton, *Chem. Rev.*, 1999, **99**, 2071-2084; (b) J. P. Hallett and T. Welton, *Chem. Rev.*, 2011, **111**, 3508-3576.
266. (a) M. J. Earle and K. R. Seddon, *Pure Appl. Chem.*, 2000, **72**, 1391-1398; (b) T. L. Greaves and C. J. Drummond, *Chem. Rev.*, 2008, **108**, 206-237.
267. (a) T. P. Thuy Pham, C.-W. Cho and Y.-S. Yun, *Water Res.*, 2010, **44**, 352-372; (b) M. Amde, J.-F. Liu and L. Pang, *Environ. Sci. Technol.*, 2015, **49**, 12611-12627.
268. O. Vakuliuk and D. T. Gryko, *Eur. J. Org. Chem.*, 2011, **2011**, 2854-2859.
269. M. C. Ortiz Villamizar, F. I. Zubkov, C. E. Puerto Galvis, L. Y. Vargas Méndez and V. V. Kouznetsov, *Org. Chem. Front.*, 2017, **4**, 1736-1744.
270. T. Fukuyama, M. T. Rahman, H. Mashima, H. Takahashi and I. Ryu, *Org. Chem. Front.*, 2017, **4**, 1863-1866.
271. (a) E. L. Smith, A. P. Abbott and K. S. Ryder, *Chem. Rev.*, 2014, **114**, 11060-11082; (b) D. V. Wagle, H. Zhao and G. A. Baker, *Acc. Chem. Res.*, 2014, **47**, 2299-2308.
272. B. Kudłak, K. Owczarek and J. Namieśnik, *Environ. Sci. Pollut. Res.*, 2015, **22**, 11975-11992.
273. A. Punzi, D. I. Coppi, S. Matera, M. A. M. Capozzi, A. Operamolla, R. Ragni, F. Babudri and G. M. Farinola, *Org. Lett.*, 2017, **19**, 4754-4757.
274. (a) G. W. V. Cave, C. L. Raston and J. L. Scott, *Chem. Commun.*, 2001, 2159-2169; (b) Z. Sainath and P. Pravinkumar, *Curr. Org. Chem.*, 2019, **23**, 2295-2318.

275. K. Tanaka and F. Toda, *Chem. Rev.*, 2000, **100**, 1025-1074.
276. R. B. Bedford, C. J. Mitchell and R. L. Webster, *Chem. Commun.*, 2010, **46**, 3095-3097.
277. C. Arroniz, J. G. Denis, A. Ironmonger, G. Rassias and I. Larrosa, *Chem. Sci.*, 2014, **5**, 3509-3514.
278. S. Castro, J. J. Fernández, R. Vicente, F. J. Fañanás and F. Rodríguez, *Chem. Commun.*, 2012, **48**, 9089-9091.
279. S. Bensaid and H. Doucet, *ChemSusChem*, 2012, **5**, 1559-1567.
280. D. K. Pandey, A. B. Shabade and B. Punji, *Adv. Synth. Catal.*, 2020, **362**, 2534-2540.
281. A. Punzi, M. A. M. Capozzi, S. Di Noja, R. Ragni, N. Zappimbulso and G. M. Farinola, *J. Org. Chem.*, 2018, **83**, 9312-9321.
282. G. Albano, G. Decandia, M. A. M. Capozzi, N. Zappimbulso, A. Punzi and G. M. Farinola, *ChemSusChem*, 2021, **14**, 3391-3401.
283. R. B. N. Baig and R. S. Varma, *Chem. Soc. Rev.*, 2012, **41**, 1559-1584.
284. (a) G. Ciamician, *Science*, 1912, **36**, 385-394; (b) H. D. Roth, *Angew. Chem. Int. Ed.*, 1989, **28**, 1193-1207.
285. N. Hoffmann, *Chem. Rev.*, 2008, **108**, 1052-1103.
286. T. P. Yoon, M. A. Ischay and J. Du, *Nat. Chem.*, 2010, **2**, 527-532.
287. (a) B. König, *Eur. J. Org. Chem.*, 2017, **2017**, 1979-1981; (b) J. Liu, L. Lu, D. Wood and S. Lin, *ACS Cent. Sci.*, 2020, **6**, 1317-1340.
288. (a) A. Albini, M. Fagnoni and M. Mella, *Pure Appl. Chem.*, 2000, **72**, 1321-1326; (b) C. G. Bochet, *CHIMIA*, 2019, **73**, 720-723.
289. Y. Cheng, X. Gu and P. Li, *Org. Lett.*, 2013, **15**, 2664-2667.
290. F. Gomes, V. Narbonne, F. Blanchard, G. Maestri and M. Malacria, *Org. Chem. Front.*, 2015, **2**, 464-469.
291. L. Candish, M. Freitag, T. Gensch and F. Glorius, *Chem. Sci.*, 2017, **8**, 3618-3622.
292. X. Zheng, L. Yang, W. Du, A. Ding and H. Guo, *Chem. Asian J.*, 2014, **9**, 439-442.
293. Z. Xu, L. Gao, L. Wang, M. Gong, W. Wang and R. Yuan, *ACS Catal.*, 2015, **5**, 45-50.
294. J. Kan, S. Huang, H. Zhao, J. Lin and W. Su, *Sci. China Chem.*, 2015, **58**, 1329-1333.
295. A. U. Meyer, T. Slanina, C.-J. Yao and B. König, *ACS Catal.*, 2016, **6**, 369-375.
296. Y.-S. Feng, X.-S. Bu, B. Huang, C. Rong, J.-J. Dai, J. Xu and H.-J. Xu, *Tetrahedron Lett.*, 2017, **58**, 1939-1942.
297. S. Zhang, Z. Tang, W. Bao, J. Li, B. Guo, S. Huang, Y. Zhang and Y. Rao, *Org. Biomol. Chem.*, 2019, **17**, 4364-4369.
298. X. Zuo, W. Wu and W. Su, *Acta Chim. Sinica*, 2015, **73**, 1298-1301.
299. A. Arora and J. D. Weaver, *Org. Lett.*, 2016, **18**, 3996-3999.
300. B. Michelet, C. Deldaele, S. Kajouj, C. Moucheron and G. Evano, *Org. Lett.*, 2017, **19**, 3576-3579.
301. R. Kapoor, R. Chawla and L. D. S. Yadav, *Tetrahedron Lett.*, 2019, **60**, 805-809.
302. Y.-X. Liu, D. Xue, J.-D. Wang, C.-J. Zhao, Q.-Z. Zou, C. Wang and J. Xiao, *Synlett*, 2013, **24**, 507-513.
303. P. Natarajan, A. Bala, S. K. Mehta and K. K. Bhasin, *Tetrahedron*, 2016, **72**, 2521-2526.
304. I. Ghosh, R. S. Shaikh and B. König, *Angew. Chem. Int. Ed.*, 2017, **56**, 8544-8549.
305. M. Tobisu, T. Furukawa and N. Chatani, *Chem. Lett.*, 2013, **42**, 1203-1205.
306. H. Baguia, C. Deldaele, B. Michelet, J. Beaudelot, C. Theunissen, C. Moucheron and G. Evano, *J. Vis. Exp.*, 2019, **147**, e59739.
307. D. P. Hari, P. Schroll and B. König, *J. Am. Chem. Soc.*, 2012, **134**, 2958-2961.
308. F. Yang, J. Koeller and L. Ackermann, *Angew. Chem. Int. Ed.*, 2016, **55**, 4759-4762.
309. R. K. Yadav, A. Kumar, N.-J. Park, D. Yadav, J. Y. Kim and J.-O. Baeg, *Sustain. Energy Fuels*, 2019, **3**, 3324-3328.
310. Y.-P. Zhang, X.-L. Feng, Y.-S. Yang and B.-X. Cao, *Tetrahedron Lett.*, 2016, **57**, 2298-2302.
311. S. Vidyacharan, B. T. Ramanjaneyulu, S. Jang and D.-P. Kim, *ChemSusChem*, 2019, **12**, 2581-2586.
312. S. Jang, S. Vidyacharan, B. T. Ramanjaneyulu, K.-W. Gyak and D.-P. Kim, *React. Chem. Eng.*, 2019, **4**, 1466-1471.
313. K. Rybicka-Jasińska, B. König and D. Gryko, *Eur. J. Org. Chem.*, 2017, **2017**, 2104-2107.
314. V. Dichiarante, M. Fagnoni and A. Albini, *Angew. Chem. Int. Ed.*, 2007, **46**, 6495-6498.
315. C. Raviola, V. Canevari, S. Protti, A. Albini and M. Fagnoni, *Green Chem.*, 2013, **15**, 2704-2708.
316. M. E. Budén, J. F. Guastavino and R. A. Rossi, *Org. Lett.*, 2013, **15**, 1174-1177.
317. S. A. Rodríguez, M. A. Nazareno and M. T. Baumgartner, *Aust. J. Chem.*, 2013, **66**, 1334-1341.
318. D. Saporito, S. A. Rodriguez and M. T. Baumgartner, *Aust. J. Chem.*, 2019, **72**, 978-982.
319. L. Marzo, S. Wang and B. König, *Org. Lett.*, 2017, **19**, 5976-5979.
320. K. Skonieczny and D. T. Gryko, *J. Org. Chem.*, 2015, **80**, 5753-5763.
321. K. Skonieczny and D. T. Gryko, *Chem. Asian J.*, 2016, **11**, 2513-2517.
322. K. Skonieczny, J. Yoo, J. M. Larsen, E. M. Espinoza, M. Barbasiewicz, V. I. Vullev, C.-H. Lee and D. T. Gryko, *Chem. Eur. J.*, 2016, **22**, 7485-7496.
323. D. Wang, C. Cheng, Q. Wu, J. Wang, Z. Kang, X. Guo, H. Wu, E. Hao and L. Jiao, *Org. Lett.*, 2019, **21**, 5121-5125.
324. K. C. C. Aganda, J. Kim and A. Lee, *Org. Biomol. Chem.*, 2019, **17**, 9698-9702.
325. (a) C. O. Kappe, *Angew. Chem. Int. Ed.*, 2004, **43**, 6250-6284; (b) C. Oliver Kappe, *Chem. Soc. Rev.*, 2008, **37**, 1127-1139.
326. S. Yanagisawa, T. Sudo, R. Noyori and K. Itami, *J. Am. Chem. Soc.*, 2006, **128**, 11748-11749.
327. B. Pieber, D. Cantillo and C. O. Kappe, *Chem. Eur. J.*, 2012, **18**, 5047-5055.
328. C. N. Scott and M. D. Bisen, *Polymer*, 2019, **170**, 204-210.
329. B. Mariampillai, J. Alliot, M. Li and M. Lautens, *J. Am. Chem. Soc.*, 2007, **129**, 15372-15379.
330. A. Voutchkova, A. Coplin, N. E. Leadbeater and R. H. Crabtree, *Chem. Commun.*, 2008, 6312-6314.
331. S. Oi, R. Funayama, T. Hattori and Y. Inoue, *Tetrahedron*, 2008, **64**, 6051-6059.
332. R. B. Bedford, R. L. Webster and C. J. Mitchell, *Org. Biomol. Chem.*, 2009, **7**, 4853-4857.
333. R. B. Bedford and M. Betham, *J. Org. Chem.*, 2006, **71**, 9403-9410.
334. R. B. Bedford, M. Betham, J. P. H. Charmant and A. L. Weeks, *Tetrahedron*, 2008, **64**, 6038-6050.
335. P. Franck, S. Hostyn, B. Dajka-Halász, Á. Polonka-Bálint, K. Monsieurs, P. Mátyus and B. U. W. Maes, *Tetrahedron*, 2008, **64**, 6030-6037.
336. J. M. Quimby and L. T. Scott, *Adv. Synth. Catal.*, 2009, **351**, 1009-1013.
337. A. B. Dounay, P. G. Humphreys, L. E. Overman and A. D. Wrobleski, *J. Am. Chem. Soc.*, 2008, **130**, 5368-5377.
338. S. Ponnala and W. W. Harding, *Eur. J. Org. Chem.*, 2013, **2013**, 1107-1115.
339. D. S. Roman, Y. Takahashi and A. B. Charette, *Org. Lett.*, 2011, **13**, 3242-3245.
340. J. V. Suárez-Meneses, A. Oukhrib, M. Gouygou, M. Urrutigoïty, J. C. Daran, A. Cordero-Vargas, M. C. Ortega-Alfaro and J. G. López-Cortés, *Dalton Trans.*, 2016, **45**, 9621-9630.
341. J. Wu, L. Nie, J. Luo and W.-M. Dai, *Synlett*, 2007, **2007**, 2728-2732.
342. Z. Sipos and K. Kónya, *Synthesis*, 2018, **50**, 1610-1620.

343. M. Tsukao, Y. Hashikawa, N. Toyama, M. Muraoka, M. Murata, T. Sasamori, A. Wakamiya and Y. Murata, *Inorganics*, 2019, **7**, 109.
344. S. Chaudhary, S. Pecic, O. LeGendre and W. W. Harding, *Tetrahedron Lett.*, 2009, **50**, 2437-2439.
345. S. Chaudhary and W. W. Harding, *Tetrahedron*, 2011, **67**, 569-575.
346. K. Takagi, Y. Hirano, K. Mikami, S. Kikkawa and I. Azumaya, *Eur. J. Org. Chem.*, 2019, **2019**, 2071-2080.
347. E. M. Beccalli, G. Broggini, M. Martinelli, G. Paladino and C. Zoni, *Eur. J. Org. Chem.*, 2005, **2005**, 2091-2096.
348. J. C. Lewis, A. M. Berman, R. G. Bergman and J. A. Ellman, *J. Am. Chem. Soc.*, 2008, **130**, 2493-2500.
349. M. Iwasaki, H. Yorimitsu and K. Oshima, *Chem. Asian J.*, 2007, **2**, 1430-1435.
350. W. Liu, Y. Li, R. Wang, Y. Jiang and C. Kuang, *Tetrahedron Lett.*, 2020, **61**, 151390.
351. J. C. Lewis, J. Y. Wu, R. G. Bergman and J. A. Ellman, *Angew. Chem. Int. Ed.*, 2006, **45**, 1589-1591.
352. P. V. Kumar, W.-S. Lin, J.-S. Shen, D. Nandi and H. M. Lee, *Organometallics*, 2011, **30**, 5160-5169.
353. M. Baghbanzadeh, C. Pilger and C. O. Kappe, *J. Org. Chem.*, 2011, **76**, 8138-8142.
354. A. Mahindra, N. Bagra and R. Jain, *J. Org. Chem.*, 2013, **78**, 10954-10959.
355. K. Takagi, T. Miwa and H. Masu, *Macromolecules*, 2016, **49**, 8879-8887.
356. F. Besselièvre, F. Mahuteau-Betzer, D. S. Grierson and S. Piguel, *J. Org. Chem.*, 2008, **73**, 3278-3280.
357. S. K. Kim, J.-H. Kim, Y. C. Park, J. W. Kim and E. K. Yum, *Tetrahedron*, 2013, **69**, 10990-10995.
358. S. Li, P. Wan, J. Ai, R. Sheng, Y. Hu and Y. Hu, *Adv. Synth. Catal.*, 2017, **359**, 772-778.
359. S. Fuse, M. Inaba, S. Sato, M. Joshi and H. Nakamura, *Synthesis*, 2018, **50**, 1493-1498.
360. S. Yanagisawa, K. Ueda, T. Taniguchi and K. Itami, *Org. Lett.*, 2008, **10**, 4673-4676.
361. V. Abet, A. Nuñez, F. Mendicuti, C. Burgos and J. Alvarez-Builla, *J. Org. Chem.*, 2008, **73**, 8800-8807.
362. L. Basolo, E. M. Beccalli, E. Borsini and G. Broggini, *Tetrahedron*, 2009, **65**, 3486-3491.
363. J. T. Myers and J. M. Hanna, *Tetrahedron Lett.*, 2012, **53**, 612-615.
364. S. Hostyn, B. U. W. Maes, G. Van Baelen, A. Gulevskaya, C. Meyers and K. Smits, *Tetrahedron*, 2006, **62**, 4676-4684.
365. G. Van Baelen, C. Meyers, G. L. F. Lemière, S. Hostyn, R. Dommisse, L. Maes, K. Augustyns, A. Haemers, L. Pieters and B. U. W. Maes, *Tetrahedron*, 2008, **64**, 11802-11809.
366. J.-W. Yuan, L.-R. Yang, P. Mao and L.-B. Qu, *Org. Chem. Front.*, 2017, **4**, 545-554.
367. D. R. Stuart and K. Fagnou, *Science*, 2007, **316**, 1172-1175.
368. H. Dong, C. Limberakis, S. Liras, D. Price and K. James, *Chem. Commun.*, 2012, **48**, 11644-11646.
369. T. Miao, P. Li, G.-W. Wang and L. Wang, *Chem. Asian J.*, 2013, **8**, 3185-3190.
370. E. L. Watson, A. Ball, S. A. Raw and S. P. Marsden, *Synlett*, 2016, **27**, 146-150.
371. (a) G. Albano, M. Morelli and L. A. Aronica, *Eur. J. Org. Chem.*, 2017, **2017**, 3473-3480; (b) G. Albano, M. Morelli, M. Lissia and L. A. Aronica, *ChemistrySelect*, 2019, **4**, 2505-2511.
372. J. Koubachi, S. El Kazzouli, S. Berteina-Raboin, A. Mouaddib and G. Guillaumet, *Synlett*, 2006, **2006**, 3237-3242.
373. A. El Abbouchi, J. Koubachi, N. El Brahmi and S. El Kazzouli, *Mediterr. J. Chem.*, 2019, **9**, 347-354.
374. D. S. Ermolat'ev, V. N. Giménez, E. V. Babaev and E. Van der Eycken, *J. Comb. Chem.*, 2006, **8**, 659-663.
375. A. El Akkaoui, S. Berteina-Raboin, A. Mouaddib and G. Guillaumet, *Eur. J. Org. Chem.*, 2010, **2010**, 862-871.
376. S. Grosse, C. Pillard, S. Massip, J. M. Léger, C. Jarry, S. Bourg, P. Bernard and G. Guillaumet, *Chem. Eur. J.*, 2012, **18**, 14943-14947.
377. S. Grosse, C. Pillard, P. Bernard and G. Guillaumet, *Synlett*, 2013, **24**, 2095-2101.
378. S. Fuse, T. Ohuchi, Y. Asawa, S. Sato and H. Nakamura, *Bioorg. Med. Chem. Lett.*, 2016, **26**, 5887-5890.
379. A. Gigante, E.-M. Priego, P. Sánchez-Carrasco, L. M. Ruiz-Pérez, J. Vande Voorde, M.-J. Camarasa, J. Balzarini, D. González-Pacanowska and M.-J. Pérez-Pérez, *Eur. J. Med. Chem.*, 2014, **82**, 459-465.
380. N. I. Abdo, A. A. El-Shehawy, A. A. El-Barbary and J.-S. Lee, *Eur. J. Org. Chem.*, 2012, **2012**, 5540-5551.
381. D. Kumar, M. Pilania, V. Arun and S. Pooniya, *Org. Biomol. Chem.*, 2014, **12**, 6340-6344.
382. S.-H. Wang, W.-J. Liu, H.-Y. Zhan, H. Zhang, Y. Liang and Y. Tian, *RSC Adv.*, 2013, **3**, 23972-23975.
383. Y.-S. Zhu, B. Shi, R. Fang, X. Wang and H. Jing, *Org. Biomol. Chem.*, 2014, **12**, 5773-5780.
384. C. Copin, N. Henry, F. Buron and S. Routier, *Synlett*, 2016, **27**, 1091-1095.
385. S. Yanagisawa, T. Sudo, R. Noyori and K. Itami, *Tetrahedron*, 2008, **64**, 6073-6081.
386. A. Luzio, D. Fazzi, F. Nübling, R. Matsidik, A. Straub, H. Komber, E. Giussani, S. E. Watkins, M. Barbatti, W. Thiel, E. Gann, L. Thomsen, C. R. McNeill, M. Caironi and M. Sommer, *Chem. Mater.*, 2014, **26**, 6233-6240.
387. M. Durso, M. Zambianchi, A. Zanelli, M. G. LoBello, F. De Angelis, S. Toffanin, S. Cavallini, D. Gentili, F. Tinti, M. Cavallini, N. Camaioni and M. Melucci, *Tetrahedron*, 2014, **70**, 6222-6228.
388. A. D. Hendsbee, C. M. Macaulay and G. C. Welch, *Dyes Pigm.*, 2014, **102**, 204-209.
389. A. D. Hendsbee, J.-P. Sun, L. R. Rutledge, I. G. Hill and G. C. Welch, *J. Mater. Chem. A*, 2014, **2**, 4198-4207.
390. J. Kudrjasova, J. Kesters, P. Verstappen, J. Brebels, T. Vangerven, I. Cardinaletti, J. Drijkoningen, H. Penxten, J. Manca, L. Lutsen, D. Vanderzande and W. Maes, *J. Mater. Chem. A*, 2016, **4**, 791-795.
391. J. Kudrjasova, M. Van Landeghem, T. Vangerven, J. Kesters, G. H. L. Heintges, I. Cardinaletti, R. Lenaerts, H. Penxten, P. Adriaensens, L. Lutsen, D. Vanderzande, J. Manca, E. Goovaerts and W. Maes, *ChemistrySelect*, 2017, **2**, 1253-1261.
392. N. I. Abdo, J. Ku, A. A. El-Shehawy, H.-S. Shim, J.-K. Min, A. A. El-Barbary, Y. H. Jang and J.-S. Lee, *J. Mater. Chem. A*, 2013, **1**, 10306-10317.
393. S. J. Choi, J. Kuwabara and T. Kanbara, *ACS Sustain. Chem. Eng.*, 2013, **1**, 878-882.
394. J. Kuwabara, T. Yasuda, S. J. Choi, W. Lu, K. Yamazaki, S. Kagaya, L. Han and T. Kanbara, *Adv. Funct. Mater.*, 2014, **24**, 3226-3233.
395. J. Kuwabara, T. Yasuda, N. Takase and T. Kanbara, *ACS Appl. Mater. Interfaces*, 2016, **8**, 1752-1758.
396. J. Kuwabara, N. Takase, T. Yasuda and T. Kanbara, *J. Polym. Sci., Part A: Polym. Chem.*, 2016, **54**, 2337-2345.
397. W. Li and T. Michinobu, *Polym. Chem.*, 2016, **7**, 3165-3171.
398. S. Chen, K. C. Lee, Z.-G. Zhang, D. S. Kim, Y. Li and C. Yang, *Macromolecules*, 2016, **49**, 527-536.
399. W. Li, T. Mori and T. Michinobu, *MRS Commun.*, 2018, **8**, 1244-1253.

400. F. V. Drozdov, N. M. Surin, S. M. Peregudova, V. A. Trukhanov, P. V. Dmitryakov, S. N. Chvalun, D. Y. Parashchuk and S. A. Ponomarenko, *Polym. Sci. B*, 2019, **61**, 56-76.
401. (a) J. B. Sperry and D. L. Wright, *Chem. Soc. Rev.*, 2006, **35**, 605-621; (b) J.-i. Yoshida, K. Kataoka, R. Horcajada and A. Nagaki, *Chem. Rev.*, 2008, **108**, 2265-2299; (c) B. A. Frontana-Uribe, R. D. Little, J. G. Ibanez, A. Palma and R. Vasquez-Medrano, *Green Chem.*, 2010, **12**, 2099-2119.
402. (a) M. Yan, Y. Kawamata and P. S. Baran, *Chem. Rev.*, 2017, **117**, 13230-13319; (b) T. H. Meyer, I. Choi, C. Tian and L. Ackermann, *Chem*, 2020, **6**, 2484-2496.
403. G. Sun, S. Ren, X. Zhu, M. Huang and Y. Wan, *Org. Lett.*, 2016, **18**, 544-547.
404. O. N. Chupakhin, A. V. Shchepochkin and V. N. Charushin, *Green Chem.*, 2017, **19**, 2931-2935.
405. D. Hata, M. Tobisu and T. Amaya, *Bull. Chem. Soc. Jpn.*, 2018, **91**, 1749-1751.
406. (a) W. Bonrath and R. A. P. Schmidt, *Adv. Org. Synth.*, 2005, **1**, 81-117; (b) L. Ji-Tai, W. Shu-Xiang, C. Guo-Feng and L. Tong-Shuang, *Curr. Org. Synth.*, 2005, **2**, 415-436.
407. (a) P. R. Gogate, A. M. Wilhelm and A. B. Pandit, *Ultrason. Sonochem.*, 2003, **10**, 325-330; (b) M. Ashokkumar, J. Lee, S. Kentish and F. Grieser, *Ultrason. Sonochem.*, 2007, **14**, 470-475.
408. S. Puri, B. Kaur, A. Parmar and H. Kumar, *Curr. Org. Chem.*, 2013, **17**, 1790-1828.
409. L. Zhang, M. Geng, P. Teng, D. Zhao, X. Lu and J.-X. Li, *Ultrason. Sonochem.*, 2012, **19**, 250-256.
410. S. L. James, C. J. Adams, C. Bolm, D. Braga, P. Collier, T. Friščić, F. Grepioni, K. D. M. Harris, G. Hyett, W. Jones, A. Krebs, J. Mack, L. Maini, A. G. Orpen, I. P. Parkin, W. C. Shearouse, J. W. Steed and D. C. Waddell, *Chem. Soc. Rev.*, 2012, **41**, 413-447.
411. A. Stolle, T. Szuppa, S. E. S. Leonhardt and B. Ondruschka, *Chem. Soc. Rev.*, 2011, **40**, 2317-2329.
412. L. Takacs, *Chem. Soc. Rev.*, 2013, **42**, 7649-7659.
413. D. Das, Z. T. Bhutia, A. Chatterjee and M. Banerjee, *J. Org. Chem.*, 2019, **84**, 10764-10774.
414. J. Yu, X. Yang, C. Wu and W. Su, *J. Org. Chem.*, 2020, **85**, 1009-1021.
415. S. A. Aboud, A. B. Altemimi, A. R. S. Al-HiIphy, L. Yi-Chen and F. Cacciola, *Molecules*, 2019, **24**, 4125.
416. (a) R. Escobedo, R. Miranda and J. Martínez, *Int. J. Mol. Sci.*, 2016, **17**, 453; (b) N. Zappimbulso, M. A. M. Capozzi, A. Porcheddu, G. M. Farinola and A. Punzi, *ChemSusChem*, 2021, **14**, 1363-1369.