Approaches for Improving the Sustainability of Conjugated Polymer Synthesis using Direct Arylation Polymerization (DArP)

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ARTICLE

Approaches for Improving the Sustainability of Conjugated Polymer Synthesis using Direct Arylation Polymerization (DArP)

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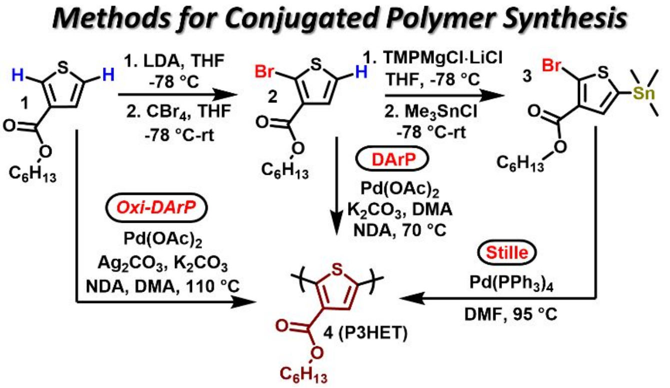
Direct arylation polymerization (DArP) provides a more sustainable alternative to conventional methods for conjugated polymer synthesis, such as Stille-Migita or Suzuki-Miyura polymerizations. DArP proceeds through a C-H activaiton pathway, allowing for a reduction in the synthetic steps needed to access the monomer, since the installation of a transmetallating reagent, such as an organostannane or organoboron, is not required. However, compared to small-molecule synthesis, the prevalent conditions employed for DArP still require hazardous or unsustainably sourced reaction components, such as the solvent and transition-metal catalyst. This mini-review highlights recent work on the implementation of sustainable solvents, transition metal catalysts, and overall polymerization methods for DArP. The extension of small-molecule direct arylation conditions towards polymer synthesis is also discussed, along with the associated challenges, mechanistic considerations, and outlook for future work.

Introduction

Direct Arylation Polymerization (DArP) has significantly expedited the synthesis of conjugated polymers through the use of C-H functionalization. This has eliminated the need for a transmetallating reagent, such as an alkylstannane used for Stille-Migita (Stille) polymerizations or a boronic acid or ester used for Suzuki-Miyaura (Suzuki) polymerizations. In doing so, conjugated polymers can be accessed without the need for toxic, hazardous reagents, thereby lowering the cost and improving the sustainable aspects of their preparation. An example of such synthetic simplification is depicted in Scheme 1, with the streamlined pathway for poly(3-hexylesterthiophene) (P3HET) provided through DArP and oxidative direct arylation polymerization (Oxi-DArP). From 1, accessing the monomer for Stille requires two separate steps that employ pyrophoric reagents and cryogenic conditions.[1] With DArP, the monomer can be prepared in a single step, and with Oxi-DArP P3HET can be prepared directly from 1.[2] Already, DArP has been used to prepare a wide-variety of conjugated polymers that have been used for optoelectronic applications, such as polymer solar cells, light-emitting diodes, thin-film transistors, and electrochromics.[3–8] Although still not as widely used as the aforementioned polymerization methods of Stille and Suzuki, the increasing employment and investigation of DArP is transforming this method into a reliable approach for conjugated polymer synthesis, rather than just a synthetic novelty.



Scheme 1. Comparison of the number of synthetic steps and polymerization conditions to prepare P3HET via Ox-DArP, DArP, and Stille polymerization.

Initial studies regarding DArP focused on transforming methodologies for the preparation of small-molecules via C-H activation into conditions suitable for polymerizations. For this, the contributions of Fagnou and Gorelsky provided critical mechanistic insight.[9–12] Additionally, the pioneering works of Ozawa, Kanbara, and Leclerc provided a starting point for DArP that could be further expanded upon and improved.[13–15] Within this initial period of development for DArP, our group contributed important work detailing conditions to improve the site selectivity of C-H activation, which eliminated the occurrence of branching (β) defects, and the correlation of structural defects with impact on polymer solar cell device performance.[16–18] These and other studies laid the groundwork needed to determine polymerization conditions that inhibit undesired couplings, such as homocoupling and branching defects, and allowed for the progression from simple homopolymers to donor-acceptor copolymers, semi-random, and semi-alternating copolymers.[19–21] Furthermore, state-of-art conditions have allowed for the ultra-low (ppm) loadings of Pd-catalysts for certain monomers, affording polymers with high molecular weights (M_n) and yields.[22,23] Many reviews have been

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published that detail various examples of the aforementioned polymer syntheses and mechanistic studies and so they will not be discussed here.[24–27]

The volume of work carried out on DArP would indicate that the field has matured and the methodology is well understood. However, this is not the case. DArP still does not possess the scope or generality demonstrated for other polymerization methods, which is largely due to the fact that the development of this field occurred within only the last decade. More importantly, there are still aspects of this methodology that can be considered unsustainable. For example, solvents used in many DArP protocols are toxic, hazardous, and require multi-step, energy intensive routes for their production, and are not sourced from sustainable or renewable sources (see Figure 1A). Another aspect, is the source of transition-metal catalyst. Up until now, DArP protocols almost exclusively rely on palladium, where first-row transition metals could provide a more sustainable alternative. Finally, underutilized polymerization methods, such as Oxi-DArP, could allow for further streamlined synthetic pathways for monomer preparation, since functionalization of the monomers with a halogen is not required. Regarding all of these aspects, significant work has been recently accomplished, providing starting points for more sustainable conditions to be realized. Within each of the aforementioned areas of study, our group has contributed to pioneering polymerization conditions that set a precedent for further enhancing the sustainable aspects of DArP.

In this mini-review, we detail the development of more sustainable conditions for conjugated polymer synthesis via DArP and provide perspective on major underlying issues that still need to be addressed. Given that many of the conditions used for DArP were preceded and inspired by small-molecule synthesis, we provide some background and discussion as to how small-molecule synthetic conditions led to the development of the corresponding polymer syntheses, and provide general mechanistic detail in an effort to stimulate the study and discovery of more sustainable conditions for DArP.

Sustainable Solvents

Although the C-H activation pathway for DArP gives the appearance that it is inherently sustainable, there is still room for improvement. Specifically, the solvent and catalyst do not often meet this classification. Certainly, the acutely toxic hazards, such as alkylstannanes, which are produced in stoichiometric quantities during Stille polymerization, have been removed, but the solvent is still a major hazard for health and the environment. As with other methods for conjugated polymer synthesis, DArP primarily relies on a select variety of solvents that have been shown to be proficient in solubilizing a variety of conjugated polymers, such as tetrahydrofuran (THF), toluene, chlorobenzene (CB), and dimethylformamide (DMF), shown in Figure 1A. Given that the solvent is present in the highest quantity, in comparison to any other component present in the reaction, this presents the greatest hazard with respect to the reaction conditions. Of the aforementioned solvents, most can be classified as reproductive toxins, carcinogens, or specifically in the case of THF, organic peroxide formers.[28] Also, the preparation of these solvents can be highly energy intensive making them unsustainable overall.[29] Given these factors, it can be considered of utmost importance to identify solvents that do not require a large input of energy for their production, can be sourced from naturally occurring feedstocks, and do not present acute hazards to health.[30–34] Satisfying all of these parameters is challenging, although there is some precedent from small-molecule studies employing green and sustainable solvents, with examples shown in Figure 1B.[33,35–37]

Although small-molecule direct-arylation can provide insight into conditions that can be applied towards polymer synthesis, it is important to note that polymer synthesis often requires substantially different conditions than their small-molecule counterparts, which often use a stoichiometric excess of one reactant to ensure high-yields and also use high concentrations.[38] Other factors such as the solubility of the growing polymer chain, propensity for side-reactions to occur, potentially leading to structural defects or termination of a polymer chain-end, must be taken into account. Furthermore, polymer chains with embedded defects cannot be removed from the desired polymer product, in contrast to molecular purifications. Thus, it is not as easy as applying a reported small-molecule condition or substituting one solvent for another, e.g. replacing THF with 2-MeTHF. With such factors in mind, solvents such as GVL, DEC, and EtOAc are not generally viable solvents for conjugated polymer synthesis. GVL specifically can undergo side-reactions with the base, which facilitates ring-opening of the lactone.[39,40] Solvents such as DEC and EtOAc may inhibit polymer growth due to poor solubility of the growing polymer chain, and the boiling point of EtOAc (77 °C) is below that of many DArP protocols making this solvent only useful for high-pressure conditions. Solubility of the polymers could be modified through the diligent tailoring of the side-chains, to make DEC and EtOAc applicable to DArP. However, this still limits applicability of a green solvent in a general setting. Other considerations when selecting a solvent include solubility and stability of the catalyst and base, stability at high-temperatures, and propensity to stabilize the intermediates present in transition-metal cross-coupling reactions.[37]

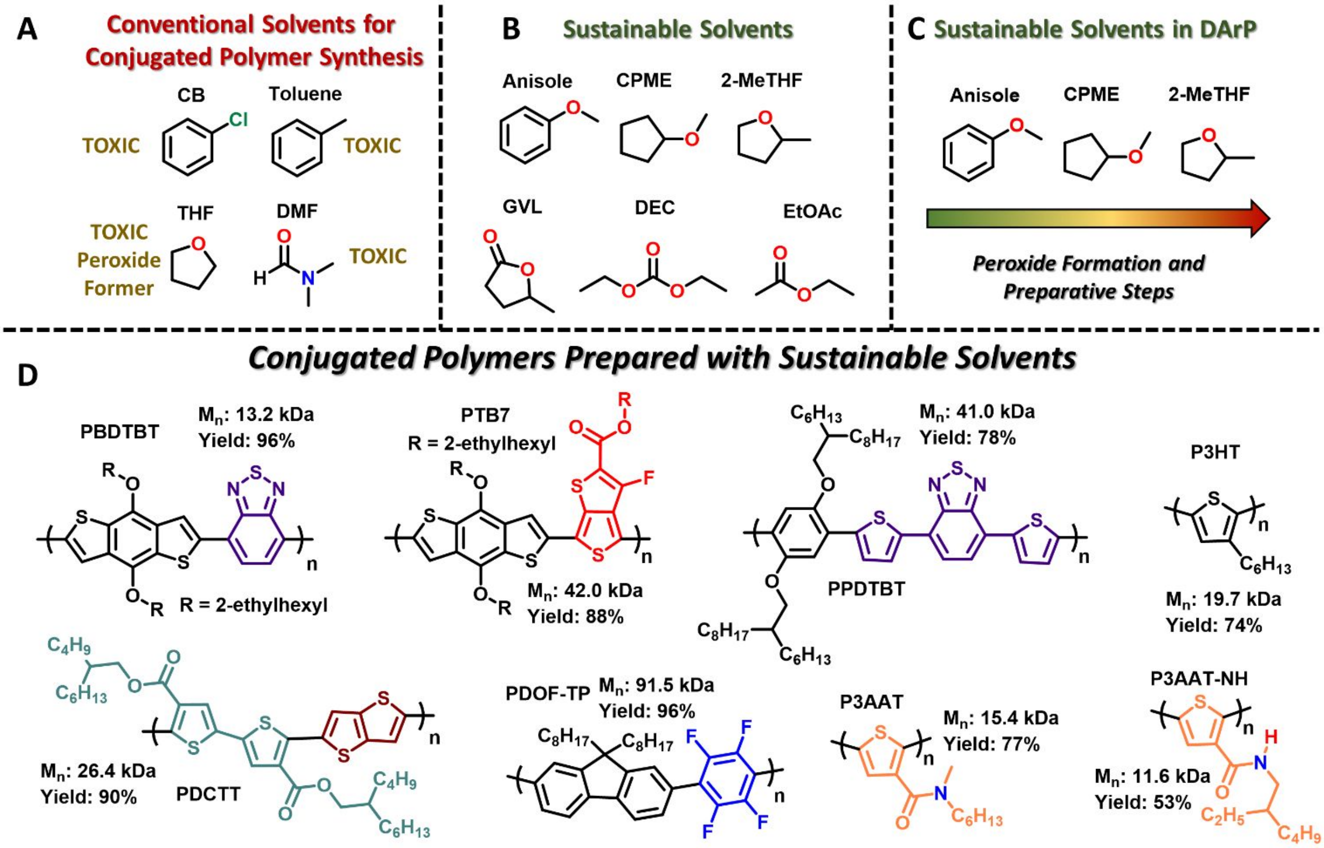

Figure 1. (A) Conventional solvents in conjugated polymer synthesis. (B) Examples of green or sustainable solvents. (C) Sustainable solvents used in DArP. (D) Examples of conjugated polymers prepared using DArP with sustainable solvents.

With these considerations, a list of solvents (anisole, CPME, and 2-MeTHF) that may facilitate more general application with DArP are shown in Figure 1C. These solvents have been used for the synthesis of conjugated polymers via DArP, with examples shown in Figure 1D and a discussion of their utility below. As general considerations for these solvents, it is important to note the number of synthetic steps for solvent production and the stability of the solvent or its shelf-life. For example, although capable of being derived from biomass, 2-MeTHF requires a greater number of synthetic steps, some of which are energy intensive, for its production, and it has been shown to be have increased organic peroxide formation with long-term storage compared to THF.[41] In contrast, anisole and CPME can each be produced from a single synthetic step, where anisole does not form any peroxides and it can be sourced from biomass, and CPME has been shown to be highly resistant to peroxide formation.[35,42,42,43]

Considering polymer examples prepared via DArP using these solvents, PBDTBT (Figure 1D) was prepared in high yield (96%) and good M_n (13.2 kDa) using anisole.[44]2-MeTHF has been extensively used, following an initial report by Sommer et al.[7] Examples of polymers prepared via DArP using this solvent include PTB7 (42.0 kDa and 88% yield) and P3HT (19.7 kDa and 74%), both of which are extensively used in organic electronics, particularly organic photovoltaic (OPV) applications.[3,5]

CPME has been shown to work for a variety of monomers, since its initial use in DArP by Ozawa et al.[45] In a recent study, we probed the application of CPME, 2-MeTHF, GVL, and DEC for the synthesis of PPDTBT (Figure 1D).[39] It was found that CPME provided the best M_n (41.0 kDa) and yield (78%). In subsequent studies, CPME was successfully applied towards the synthesis of the copolymer PDCTT (26.4 kDa and 90% yield), which contains two ester functionalities that can potentially function as directing-groups for distal protons.[46] Recent work from our group has also shown that amide functionalized polythiophenes can be synthesized using CPME, affording P3AAT (15.4 kDa and 77% yield) and P3AAT-NH (11.6 kDa and 63% yield).[47] With these examples we have shown that CPME is capable of being a suitable solvent in DArP for a wide-variety of conjugated polymers, allowing for high M_n and yield to be obtained.

Future work with sustainable solvents will require their implementation in a variety of protocols (some of which are discussed below), so as to show good tolerance for the conditions used in polymerizations and the structural variation of monomers. Specifically, many DArP reactions, like those described in the following sections, require highly-polar, coordinating solvents, such as dimethylacetamide (DMA). Identifying additional sustainable solvents that can satisfy this role and a general utility for the synthesis of a variety of conjugated polymers would be a significant advance. Since sustainable chemistry is a rapidly advancing field, monitoring the output and identification of new sustainable solvents that are applicable in aryl-aryl cross-coupling reactions should lead to the discovery of new solvents compatible with DArP.

Cu-Catalysed DArP

Aside from the solvent, another important area of interest is replacing the Pd-catalyst with a first-row transition metal, such as a Cu-catalyst. The concentration of copper present in the earth's crust is 60 g/ton (Table 1), which is orders of magnitude greater than that of Pd, which is at 0.015 g/ton (Table 1).[48] Based of the abundance of Cu in comparison to Pd alone, it becomes apparent that developing conditions that allow for the replacement of Pd with Cu in DArP are imperative. From a cost-analysis standpoint, there is again added benefit to using Cu. Shown in Table 1, the difference in cost per gram for CuI and $Pd(OAc)_2$, both of which are the most common metal sources for each, and the respective ligands (phenanthroline for Cu and P(*o*-anisyl)$_3$ for Pd) give Cu an obvious cost advantage. To facilitate this transition of metals, Cu-catalysed aryl-aryl cross-couplings have been studied, serving as a precursor to the development of conditions for DArP (Cu-DArP) to be realized.[48–50] As shown with the examples of Daugulis et al., Miura et al., and You et al. provided in Figure 2A, Cu-catalysed direct arylation conditions vary greatly from those of Pd.[51–53] Many protocols, such as those by Daugulis and You et al., employ an amine ligand, such as phenanthroline, rather than phosphine (Figure 2A).[51,52] Phosphine ligands still have utility, as shown with the work by Miura et al (Figure 2A), and each of the protocols provide the cross-coupled products in high-yields (75-96%), albeit with a stoichiometric excess of one reactant in all cases.[53] Another noticeable difference is that the conditions require generally higher temperatures (>120 °C) than Pd-catalysed protocols, owing to the lower reactivity of the Cu-catalysts. Additionally, carboxylic acid additives are not present with the Cu-catalyzed protocols, which are often used for Pd-catalyzed direct arylation, since these ligands can enable the disproportionation of Cu^I, leading to Cu^0 and Cu^{II}.[54]

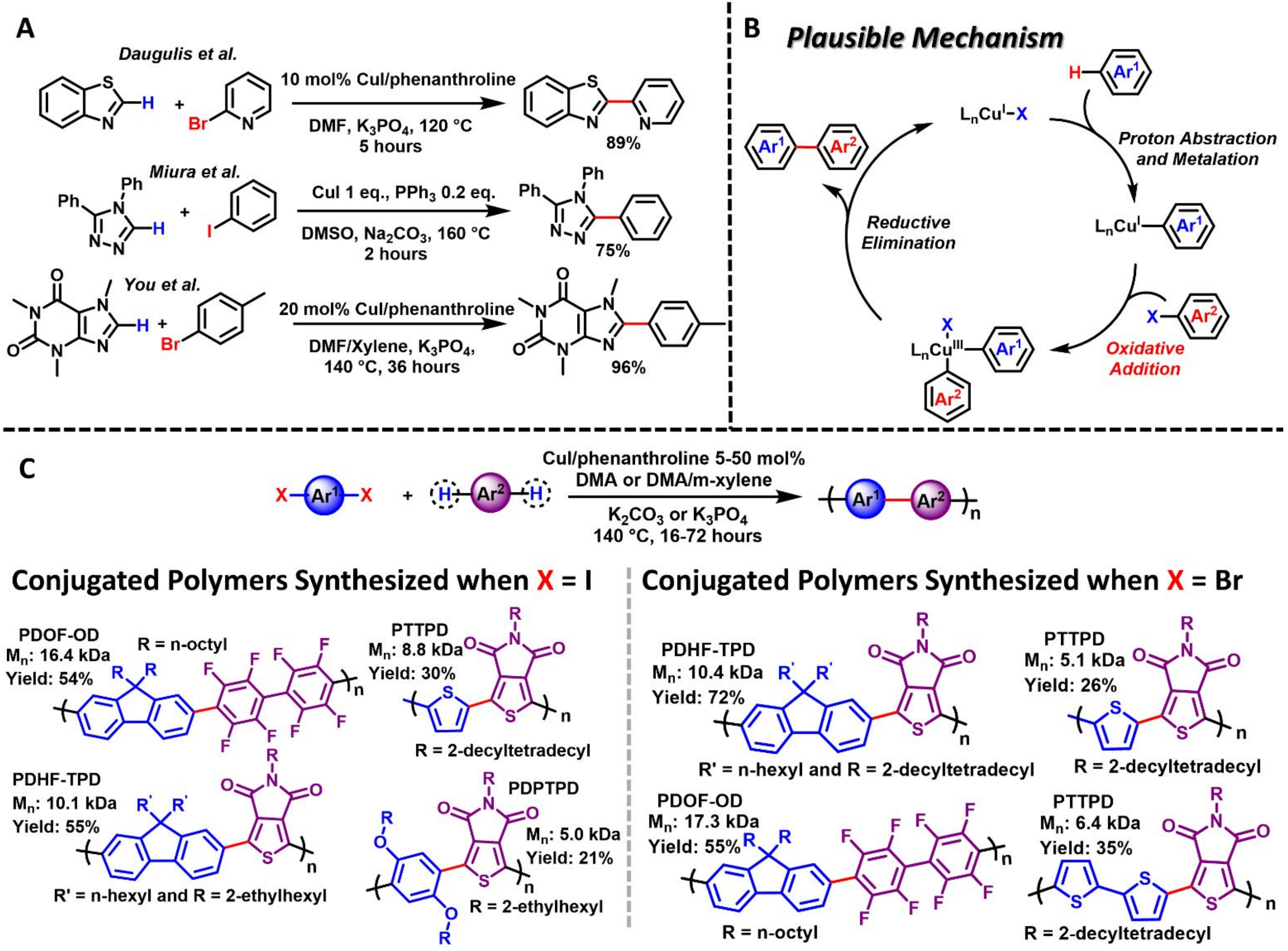

Figure 2. (A) Examples of small-molecules synthesized via Cu-catalysed direct arylation. (B) A plausible mechanism for Cu-catalysed direct arylation. (C) Examples of conjugated polymers prepared using Cu-DArP.

Entry	Abundance[a]	Purity[b]	Cost per gram[b]
Pd	0.015 g/ton	99.98%	($Pd(OAc)_2$) $146
Cu	60 g/ton	99.999%	(CuI) $9
Phenanthroline	-	>99%	$7
P(*o*-anisyl)$_3$	-	>96%	$43

Table 1. Comparison of Pd and Cu with regards to abundance and cost of a typical catalyst, including their respective ligands (phenanthroline for Cu and P(*o*-anisyl)$_3$ for Pd).[a]Concentrations obtained from reference 46.[b]Obtained from MilliporeSigma; Catalog#: 215554 for CuI, 131377 for phenanthroline, 379875 for $Pd(OAc)_2$, and 710563 for P(*o*-anisyl)$_3$.

With regards to a potential catalytic cycle (Figure 2B), it is proposed that the Cu-catalyst proceeds through Cu^{I} to Cu^{III} oxidation states, which is based on the work by Daugulis and mechanistic studies by Lin.[51,55] It should be noted copper has access to a wide range of oxidation states (Cu^{0}-Cu^{I}-Cu^{II}-Cu^{III}), and these may be present depending on the copper source, additives, and substrates or monomers used.[56] Concerning the mechanism depicted in Figure 2B, it is believed that the oxidative addition step is rate-limiting given the relative instability of Cu^{III}.[57] Aside from the disproportionation of Cu^{I}, which was mentioned above, another side-reaction that can occur is hydrodehalogentation.[58,59] This side-reaction also occurs with Pd-catalysed methodologies, leading to the termination of chain ends, and eliminating sources of adventitious water may help to avoid this.[58]

Despite the aforementioned challenges with adapting Cu-catalyzed direct arylation conditions to DArP, we have recently reported pioneering studies detailing the synthesis of a variety of conjugated polymers using conditions derived from those developed by Daugulis et al. and You et al (shown in Figure 2C).[60,61] These seminal reports provide another example of how small-molecule conditions can be meticulously transformed to allow for conjugated polymer synthesis. Initially, we found after extensive optimization of the solvent, concentration, and base that thieno[3,4-c]pyrrole-4,6-dione (TPD) can be copolymerized with a variety of aryl-iodide donors using a mild base (K_2CO_3) and amide solvent (DMA), shown in Figure 2C. For example PDHF-TPD was afforded in 10.1 kda and 55% yield, and the heterocycle thiophene was incorporated into the copolymer PTTPD in 8.8 kDa and 30% yield (Figure 2C). These conditions were reliant on 50 mol% of the Cu-phenanthroline catalyst, where lower loadings did not afford optimal M_n and yield. Through ^{1}H-NMR experiments, we found hydrodehalogenation as the dominant side-reaction, terminating the chain ends. We attributed the required high loadings of catalyst and frequency of dehalogenation to a lower reactivity of the C-H bond in TPD. Although the use of a more reactive aryl iodide was required, even for Pd-catalysed DArP, certain condition sets have required the use of an aryl-iodide to afford satisfactory M_n and yield when using TPD based monomers.[62] Another point of concern was that TPD contains a directing-group, which may be an essential functionality of the monomer to allow for C-H activation. We were therefore interested in applying these polymerization conditions to a monomer without a directing group, in order to ensure that this methodology is not limited in scope.

As such, we focused on a class of monomers that has been used frequently to test the efficacy of various DArP condition sets, which are the polyflourinated arenes, such as tetrafluorbenzene and octofluorobiphenyl.[8,45,63] These monomers are commercially available, can be incorporated into conjugated polymers with high M_n and yields, and provide access to a highly-reactive C-H bond without any directing groups. Because of the high-temperatures required for Cu-DArP, we chose octafluorobiphenyl as the ideal monomer for study. We found that with optimization of the polymerization conditions (increasing concentration and changing the base from K_2CO_3 to K_3PO_4) for PDOF-OD (Figure 2C), we could lower the loading of the CuI-phenanthroline catalyst from 50 to 5 mol%, yielding a polymer of 16.4 kDa in 54% yield. This result shows the utility of Cu-DArP towards the replacement of conventional Pd-catalysts, since a C-H bond was functionalized without the use of a directing-group.

A lingering issue from these initial studies is the employment of aryl-iodides, which require aggressive reaction conditions for their synthesis and exhibit lower stability.[61,64–66] Since aryl-bromides have allowed for the cross-coupled product via Cu-catalysed small-molecule direct arylation (Figure 2A), we envisioned that these conditions could be optimized to facilitate polymer synthesis. Indeed, by using a mixed solvent system with DMA/*m*-xylene we were able to obtain the desired conjugated polymers using aryl-bromides.[67] Examples, shown in Figure 2C, include PDHF-TPD (10.4 kDa and 72% yield), PDOF-OD (17.3 kDa and 54% yield), and PTTPD (6.4 kDa and 65% yield). In the case of PDHF-TPD and PDOF-OD, the M_n and yields are similar to those prepared using aryl iodides. To explain the dependence of the solvent, e.g. a mixture of DMA and m-xylene, computational studies by Lin indicate two potential, distinct mechanistic pathways for Cu-catalysed arylations, where one pathway is categorized as anionic and one is characterized as neutral. For the neutral pathway, a non-polar solvent, such as m-xylene, is preferred, and so it is likely that the Cu-catalysed polymerization with aryl bromides proceeds via the neutral pathway.[55] This study by our group provides a missing critical piece in identifying Cu-DArP conditions that provide an equivalent outcome to Pd-DArP.

It should be noted that aryl-chlorides have been used in DArP with Cu-catalysts, although these required a Pd-catalyst as well.[68] In the report by Kanbara et al., the Cu-catalyst is proposed to operate as a binary catalytic system with Pd, assisting with the deprotonation and transmetallation of the C-H functionalized monomer.

The amount of future work and potential for Cu-DArP is vast, given that this methodology is not as developed as Pd-DArP, and optimization of the polymerization conditions is critical for further expansion of this methodology. Major areas of focus should be on using more sustainable solvents, and optimizing Cu-catalysts via ligand design or through the use of additives to help facilitate C-H activation and stabilize Cu^{III}-species after oxidative addition.

Oxi-DArP

Oxidative direct arylation, also referred to as dehydrogenative direct arylation, is a straightforward and efficient method for the synthesis of biaryl compounds. It is distinct from conventional direct arylation in that the substrates or monomers used do not require any functionalization, such as the installation of a halogen required for C-H/C-X cross coupling reactions, since the reaction proceeds through an oxidative C-H/C-H coupling pathway.[69–71] This simplifies the synthesis of monomers even more, allowing for rapid access and shorter synthetic pathways, thereby enhancing the overall sustainability.

The development of this methodology towards the preparation of conjugated polymers is again reliant on the precedent of small-molecule studies, depicted in Figure 3A. The seminal work by Mori et al. (Figure 3A) described the homocoupling of thiophenes functionalized with a bromine, affording the desired bithiophene product in 77% yield.[72] The conditions included $PdCl_2(PhCN)_2$ as a catalyst and AgF as the terminal oxidant. Comparing to other direct arylation methodologies, this one is intriguing because it is done at room temperature and the C-H/C-H coupling is selective over the C-H/C-Br coupling, the latter of which occurs with most direct arylation protocols. This initial condition set was improved upon by the works Zhang and Shi.[73,74] Each describe the use of a $Pd(OAc)_2$ catalyst, Ag_2CO_3 as the terminal oxidant, and acetic acid as an additive. The conditions of Shi et al. differ mainly in the choice of solvent, where they chose benzene and were required to use diisopropyl sulphide in order to avoid the precipitation of Pd-black.[74]

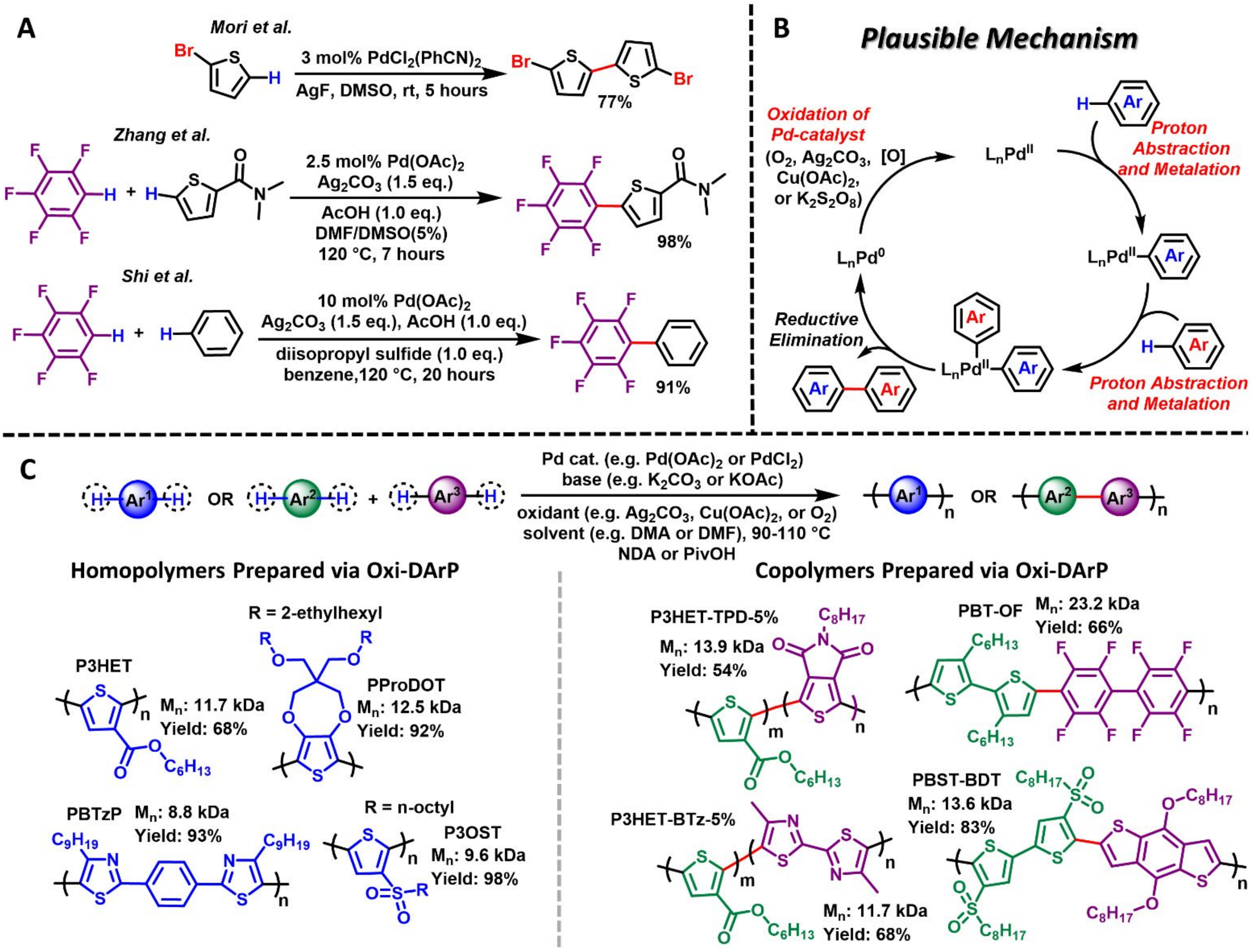

Figure 3. (A) Examples of small-molecules synthesized via oxidative direct arylation. (B) A plausible mechanism for oxidative direct arylation. (C) Examples of conjugated polymers prepared using Oxi-DArP.

As depicted in the works of Zhang and Shi, shown in Figure 3A, achieving a high-level of selectivity for the cross-coupled product, through the activation of only C-H bonds, is reliant on the selectivity of distinct C-H bonds at the two different points of proton abstraction and metalation during the plausible catalytic cycle, shown in Figure 3B.[70] Specifically, after metalation of the first aryl substrate, the corresponding complex must react with the second substrate selectively. It should be noted that the catalytic cycle for this reaction is subject to the conditions employed, namely the choice of oxidant, catalyst, and monomer, given that Pd^{II}-Pd^{IV} catalytic cycles are possible in place of the Pd^0-Pd^{II} cycle presented.[71] In such a cycle, the Pd-catalyst is oxidized before the C-H activation step, rather than after reductive elimination, differing from what is shown in Figure 3B. It is likely that selection of electronically distinct cross-coupling partners, such as those selected by Zhang and Shi et al., help to ensure a high selectivity of the cross-coupled rather than homocoupled product. It should be noted that conditions with Ag-based terminal oxidants are shown simply because they were employed in the initial reports, but many oxidants can be used, such as molecular oxygen, $K_2S_2O_8$, oxone, and $Cu(OAc)_2$ (Figure 3B).[69,70]

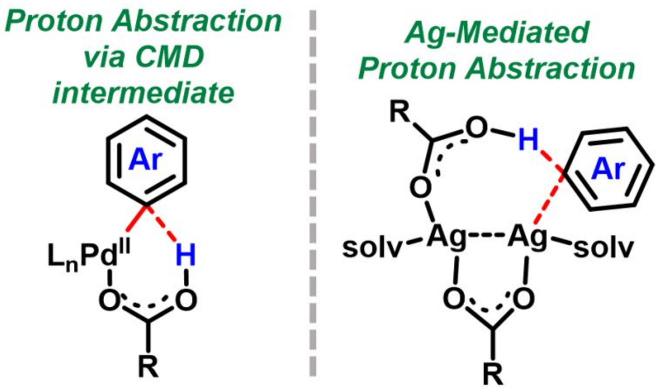

Figure 4. Depiction of different transition states for C-H functionalization for the CMD intermediate found in DArP (left) and the Ag-mediated proton abstraction found in Oxi-DArP (right).

However, in the case of Ag-based oxidants, a study by Sanford et al. has described a more intimate role of the Ag-oxidant rather than serving as simply a terminal oxidant for the Pd-catalyst.[75] Specifically, the Ag-cation may be participating in the C-H activation step facilitating metalation of the monomer to the Pd-catalyst. Such reactivity is found to occur most prevalently with Ag-carboxylates, which can in principle be generated *in situ* with the addition of a carboxylic acid additive, or the silver-carboxylates can be easily prepared and isolated. This difference in mechanistic pathway is depicted in Figure 4, with the conventional CMD pathway on the left and the intermediate for the Ag-mediated pathway on the right. In addition, evidence for a bimetallic pathway (C-H activation at two separate Pd^{II} centers followed by transmetallation) has been shown by Stahl et al., in contrast to the monometallic mechanism shown (Figure 3B).[76]

Concerning the polymerization, oxidative direct arylation polymerization (Oxi-DArP) has been gaining interest with numerous studies using conditions derived from the initial small-molecule studies of Mori, Shi, and Zhang, which employ a Pd-catalyst with Ag-oxidant. Early work focused on the development of conditions that could afford homopolymers so as to provide a proof-of-concept that the small-molecule conditions can be applied to a polymerization, but were very limited in scope.[77,78] Additionally, the potential for this methodology to simplify conjugated polymer synthesis had not yet been realized since the monomers studied required very specific structural functionalities adding additional steps to the syntheses. To overcome this limitation, we developed conditions that allow for the polymerization of an unsymmetrical monomer (1) (Scheme 1). In comparison, preparation of the monomer for Stille-P3HET requires an extended synthesis containing multiple steps that used hazardous reagents and cryogenic conditions, depicted in Scheme 1.[1,2] From our initial report, we were able to optimize conditions to afford P3HET in 11.7 kDa and 68% yield with a regioregularity (rr) of 89% (Figure 3C).[79] In a subsequent study, Chen et al. applied similar conditions toward the synthesis of P3OST (9.6 kDa and 98% yield) with a reported rr of 99% (Figure 3C).[2,80] This validates Oxi-DArP as a method that with further development could rival conventional DArP.[80] The underlying mechanism influencing rr is the ability of the carbonyl (in the case of P3HET) or the sulfone (in the case of P3OST) to function as a directing group, allowing for the site-selective activation of the neighbouring C-H bond.[24] The preparation of PProDOT, described by Reynolds et al., is particularly interesting because it shows that Oxi-DArP methodologies can be tuned to allow for the activation of electron-rich monomers without any directing-groups, which can be found with the carboxylate of P3HET or the sulfone of P3OST (Figure 3C).[81] Sommer et al. has also achieved homopolymerizations of an electron rich indacenodithiophene monomer, showing utility for Oxi-DArP with different electron-rich monomers commonly used for organic electronic applications.[82] $Cu(OAc)_2$ can also be employed as an oxidant with Pd-catalysed Oxi-DArP, which was reported in the aforementioned study by Sommer et al. and for PBTzP (8.8 kDa and 93% yield) by You et al., depicted in Figure 3C.[83] It should be noted that many of these protocols are reliant on an excess of oxidant, which, in the case of Ag-based oxidants specifically, diminishes the overall sustainability of the polymerization conditions.

The utility of this method for copolymer synthesis is shown in Figure 3C. We reported the synthesis of the random copolymers P3HET-TPD-5% (13.9 kDa and 54% yield) and P3HET-BTz-5% (11.7 kDa and 68% yield).[79] Perfectly alternating donor-acceptor copolymers have also been prepared, such as PBT-OF (23.2 kDa and 66%) by Kanbara et al. and PBST-BDT (13.6 kDa and 83% yield) by Chen et al.[63,80] The synthesis of PBT-OF by Kanbara is of particular interest because they were able to use a sub-stoichiometric amount of Ag-oxidant (0.5 equivalents).

Significant progress has been achieved for Oxi-DArP, with polymerization conditions affording homopolymers prepared from an unsymmetrical monomer with high-levels of regioregularity and copolymers with minimized homocoupling defects. The aforementioned work validates this method as a tool for simplifying the synthesis of conjugated polymers, and it promotes sustainability by reducing the number of synthetic steps and the associated waste for monomer preparation. Given all this, there are still areas where Oxi-DArP can be improved. Namely, the monomer scope remains rather limited, since clear correlations between the monomer structure, catalyst, and oxidant are not known. Additionally, it is challenging to determine if an oxidant and catalyst will provide any polymer product *a priori*, where with DArP many condition sets have been shown to work with a broad scope of monomers. Also, more importantly with regards to sustainability, many Oxi-DArP protocols require using stoichiometric amounts of silver-oxidants, often Ag_2CO_3. Thus, identifying more sustainable oxidants or finding more general conditions for known oxidants, such as molecular oxygen and $Cu(OAc)_2$, is important. In a more practical sense, the use of this methodology to synthesize functional materials with proven utility in organic electronic applications equivalent to that of conventional polymerization methods has not been realized. This may remain a major challenge however, since the performance conjugated polymers is often sensitive to oxidants, such as molecular oxygen, which can lead to defects in the structure and therefore compromise performance for a given application.[84]

Cu-Catalysed Oxi-DArP

A methodology combining the sustainable aspects of Oxi-DArP and Cu-DArP is Cu-catalysed Oxi-DArP, which is depicted in Figure 5. This synthetic method proceeds through dehydrogenative or oxidative direct arylation, where a C-H/C-H cross coupling occurs, using a copper catalyst.[69,70,85] The monomers do not require functionalization, and so the number of synthetic steps and associated workup and purification becomes simplified. As with Cu-DArP, the use of a copper catalyst provides another aspect of sustainability and low-cost to this synthetic method.

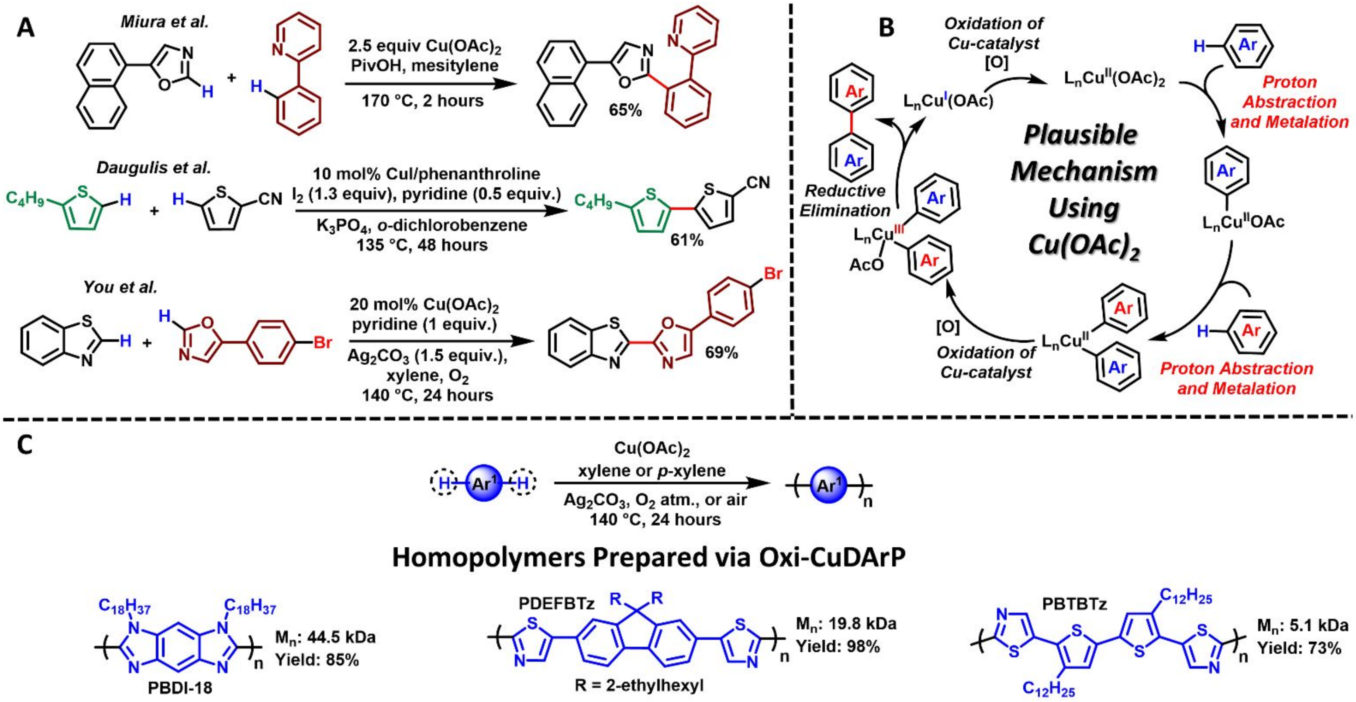

Figure 5. (A) Examples of small-molecules synthesized via Cu-catalysed oxidative direct arylation. (B) A plausible mechanism for Oxi-CuDArP. (C) Examples of conjugated polymers prepared using Oxi-CuDArP.

Shown in Figure 5A, the pioneering work of Miura et al. paved the way for Cu-catalysed Oxi-DArP.[86] The conditions described used an excess of $Cu(OAc)_2$ with a carboxylic acid additive (PivOH) to afford the cross-coupled products of various 2-arylazines and azoles. Although the amount of $Cu(OAc)_2$ needed seems excessive (2.5 eq.), it should be noted that $Cu(OAc)_2$ is functioning as a single-source for a catalyst and oxidant. No other oxidants are employed, and in comparison typical procedures for Pd-catalysed Oxi-DArP require a Pd-catalyst and an oxidant, such as Ag_2CO_3 or $Cu(OAc)_2$, in similar quantities.

Following up on the initial findings of Miura et al., Daugulis et al. reported a dehydrogenative cross-coupling using a CuI/phenanthroline catalysed system with molecular iodine as the oxidant (Figure 5A).[51] They concluded that the iodine iodinates one of the substrates, presumably the electron-rich one, which then undergoes Cu-catalysed cross-coupling as described in Figure 2B. Given that one of the monomers becomes iodinated *in situ*, the cross-coupling likely proceeds through the mechanistic pathway described in Figure 2B rather than that of Figure 5B. However, it provides useful conditions for achieving dehydrogenative cross-coupling using a Cu^{I}-catalyst, and their study showed a comprehensive scope for the methodology, affording cross-coupled products in good yields and with high regioselectivity.

In the report by You et al., dehydrogenative cross-coupling was shown to occur with good chemoselectivity, affording the bromine-functionalized azole in good yield (69%), which is shown in Figure (Figure 5A).[87] The conditions required only a sub-stoichiometric amount (0.5 eq.) of Ag_2CO_3 as an additional terminal oxidant, since molecular oxygen was also employed, showing that such a synthetic transformation can occur with the simplest and most sustainable of oxidants.

Given that the identity of transition-metal catalyst has changed when compared to Oxi-DArP, there are major differences and considerations to be made with regards to the mechanism of Cu-catalysed dehydrogenative cross coupling (Figure 5B), which can have profound effects when selecting monomers to employ for this methodology. The proposed cycle proceeds through a Cu^{II}-Cu^{III}-Cu^{I} cycle containing two separate oxidations, one before reductive elimination and one after, of the Cu-catalyst (Figure 5B).[70,85] This differs greatly from Pd-catlyzed Oxi-DArP, where oxidation of the catalyst is proposed as occurring after reductive elimination (Figure 3B). Also, aza-heterocycles, e.g. imidazole, thiazole, and oxazole, are often used because of the coordinative ability of the nitrogen in the heterocycle to a metal-center, such as copper, to further enhance the acidity and reactivity of the adjacent C-H bond, thereby lowering the energy needed for proton abstraction and functionalization.[88] This structural feature can also be seen with the representative polymers in Figure 5C.

Compared to the other methodologies described, the number of polymers prepared via Cu-catalysed Oxi-DArP is limited, which is due to the fact that this is a more emergent methodology for conjugated polymer synthesis. Shown in Figure 5C, You et al. reported the synthesis of a variety of biimidazole functionalized homopolymers, such as PBDI-18 (44.5 kDa and 85% yield), using 20 mol% $Cu(OAc)_2$, sub-stoichiometric quantities of Ag_2CO_3 (0.5 equiv), and with molecular oxygen as an additional oxidant.[89] Kanbara et al. prepared the polymers PDEFBTz (19.8 kDa and 98% yield) and PBTBTz (5.1 kDa and 73% yield) using 10 mol% $Cu(OAc)_2$ and under air (where molecular oxygen serves as the oxidant).[90] The polymers synthesized in Kanbara's study were also evaluated for practical applications through the fabrication of OFET and OLED devices, demonstrating the effectiveness of this methodology for the preparation of functional polymers.

Given the relative infancy of this Cu-catalysed Oxi-DArP, there is much work to be done related to the optimization of conditions and improvement of sustainability. Discovering new Cu-catalysts, ligands, and additives may help improve the polymerization outcome. Additionally, finding sustainable solvents that can achieve the high-temperatures required for the dehydrogenative coupling to occur without inducing side-reactions is critical for enhancing the sustainable aspects of this method. Since this method for polymerization has been primarily used for aza-heterocylces, discovering conditions that tolerate monomers more frequently employed for organic electronic applications, such as thiophenes, is imperative.

Conclusions and Outlook

Strategies for improving the sustainability of DArP have been presented, including using sustainable solvents, Cu-DArP, Oxi-DArP, and Cu-catalysed Oxi-DArP. As discussed in this mini-review, DArP can be considered inherently sustainable when compared to other polymerizations, e.g. Stille or Suzuki, but by changing the solvent, catalyst, or method of polymerization to more sustainable alternatives, the sustainability of DArP can be further improved. With numerous small-molecule studies performed that address these points, the greatest challenge becomes applying and optimizing these conditions towards conjugated polymer synthesis.

A central theme or strategy for improving sustainability for any polymerization method is by employing a solvent sourced from a renewable resource or one that can be produced with relative simplicity and without presenting hazards to health and the environment. The sustainable solvents anisole, CPME, and 2-MeTHF have been used for the synthesis of a variety of polymers via DArP, and their application for future study should be considered. Our group has developed and optimized conditions for CPME, and this solvent offers great appeal as a general solvent for DArP.

Also, the source of the transition-metal, which is typically Pd, for the DArP catalyst must be considered, and developing catalysts that incorporate first-row transition metals, such as copper, is imperative. While Cu-DArP does not have as broad of scope as its Pd-catalysed counterpart, it is important to note that the extent of study and availability of pre-catalysts are far from complete. Towards this end, we have contributed multiple studies showing that Cu can be used in catalytic quantities (5 mol% loading) targeting a variety of conjugated polymer architectures. Fine-tuning the conditions through optimization of the pre-catalyst, ligand, solvent, and base (as has been done with Pd-catalyzed DArP over the last decade) will facilitate the discovery of more general conditions.

Additionally, developing conditions that allow for a broader monomer scope for Oxi-DArP, both Pd and Cu-catalysed, will enhance the utility of each of these synthetic methods. The potential for Oxi-DArP to become the most sustainable method for conjugated polymer synthesis is apparent. However, it currently suffers from requiring unsustainable solvents, such as DMA, and precious metal oxidants, such as Ag_2CO_3, which are often present in stoichiometric or excess quantities. The development of conditions that address all of these points will be challenging, but given the broad application of conjugated polymers the appeal of such an enabling advancement is significant.

Conflicts of interest

There are no conflicts to declare.

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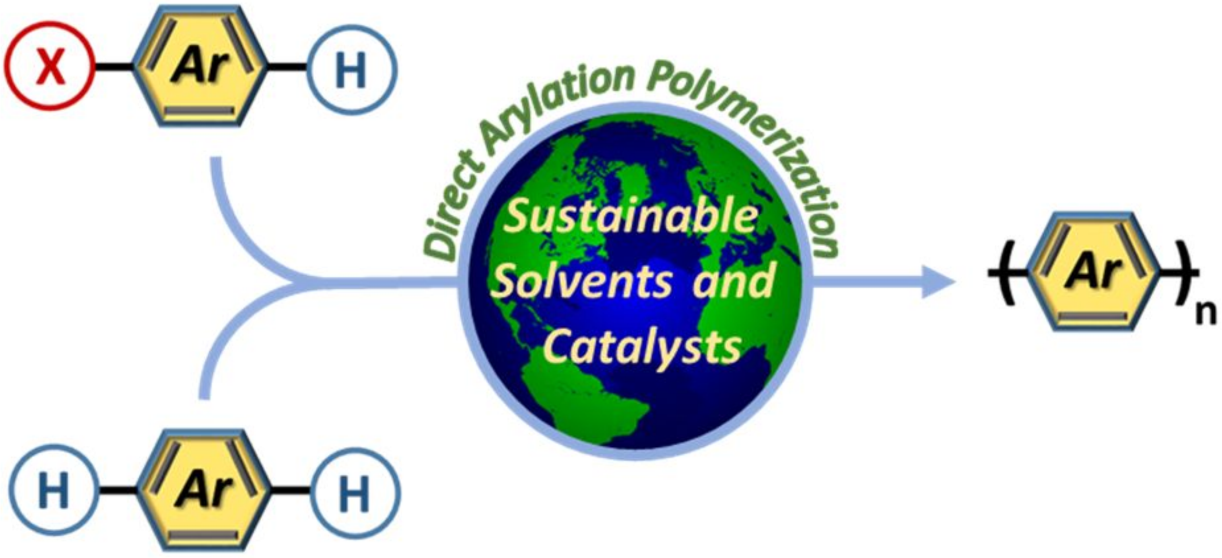

Emerging strategies to enhance the sustainability of Direct Arylation Polymerization (DArP) are discussed, illustrating the great potential of this method.