

Circular Discovery in Small Molecule and Conjugated Polymer Synthetic Methodology

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ABSTRACT: Simple and efficient methods are a key consideration for small molecule and polymer syntheses. Direct arylation polymerization (DAP) is of increasing interest for preparing conjugated polymers as an effective approach compared to conventional cross-coupling polymerizations. As DAP sees broader utilization, advancements are needed to access materials with improved properties, different monomer structures, and to improve the scalability of conjugated polymer synthesis. Presented herein are considerations for developing new methods of conjugated polymer synthesis from small molecule transformations, exploring how DAP has successfully used this approach, and presenting how emerging polymerization methodologies are developing similarly. While it is common to adapt small molecule methods to polymerizations, we demonstrate the ways in which information gained from studying polymerizations can inform and inspire greater advancements in small molecule transformations. This circular approach to organic synthetic method development underlines the value of collaboration between small molecule and polymer-based synthetic research groups.

I. INTRODUCTION

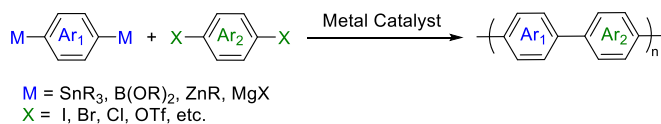
The advent and growth of organic electronics can be attributed to the breadth of synthetically accessible conjugated polymers, originating with polyacetylene,¹ and expanding to include recent examples of complex donor-acceptor copolymers.² In comparison to inorganic semiconducting materials, desired properties in conjugated polymers can be accessed by fine tuning the molecular structure. Although the development of high-performance conjugated materials has contributed immensely to advancements in the field of organic electronics in the last two decades,^{3–5} limited access to low-cost synthetic routes still represents a barrier for their large-scale production and commercial applications. Various synthetic methodologies have been developed to obtain high-performance conjugated polymers,^{6,7} including conventional cross-coupling polymerizations such as Stille and Suzuki polymerizations (**Scheme 1a**).^{8,9} These approaches are favored for their ability to generate materials with desired structural and electronic properties. The ability to access high molecular weight, low-defect materials arises from monomer prefunctionalization, which creates site-specific, highly reactive cross-coupling. At the same time, the requisite monomer prefunctionalization gives these conventional synthetic pathways poor atom and step economy. Most notably, the commonly used Stille polymerization generates stoichiometric amounts of toxic organostannane waste.

Developing an efficient, inexpensive, and green synthetic route is important for the large-scale industrial production of

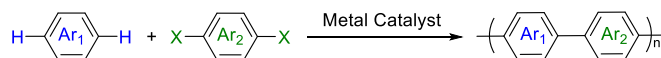
conjugated polymers. Recently, transition metal-catalyzed direct (hetero)arylation polymerization (DAP or DHAP) via C-H bond activation has emerged as a powerful and competent strategy for the synthesis of organic materials (**Scheme 1b**).^{10,11} The most appealing aspects of this approach are reduced organometallic waste and improved step economy as no organometallic prefunctionalization is required. DAP is distinguished as a sustainable and atom-economic approach for constructing C-C bonds over traditional coupling methods by features including generating benign by-products and only requiring functionalization of one component with routine and bench-stable halogens.

Scheme 1. Synthetic Approaches to Conjugated Polymers

(A) Classical Cross-Coupling Polymerization



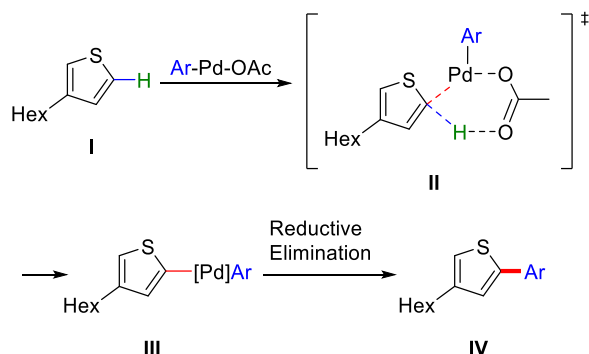
(B) Direct Arylation Polymerization (DAP)



Early DAP studies worked to adapt existing small molecule methodology to polymerizations.¹² Recent work has focused on controlling the C-H bond selectivity to minimize structural defects, and improving the sustainability of the method.¹³ Much of this work leverages fundamental mechanistic insight to make finely tuned modifications. While electrophilic

aromatic substitution (S_EAr) has been discussed,^{14,15} and some examples exist for Heck-type coupling,^{14,16,17} the concerted metalation-deprotonation (CMD) pathway has been indicated as the acting mechanism through which C-H bond activation in direct arylation occurs in the majority of cases (**Scheme 2, I-IV**).^{18–21} In these cases, the catalyst's metal center forms a C-M bond at the same time as a ligated carboxylate group assists in deprotonating the C-H bond undergoing functionalization (**Scheme 2, II**).

Scheme 2. CMD-Mediated Direct Arylation



The first breakthrough in utilizing C-H activation for polymer synthesis came from Lemaire and co-workers, synthesizing poly(3-alkylthiophene)s from 2-iodo-3-alkylthiophenes.²² However, the oligomers produced had low molecular weights of ~3 kg/mol, limiting broader interest in this strategy with only two articles published in the next 10 years.^{23,24} The seminal work of Ozawa and co-workers prepared poly(3-hexylthiophene) (P3HT) with high molecular weight ($M_n = 31$ kg/mol) and regioregularity ($rr > 98\%$) using Herrmann's catalyst and a phosphine ligand – results similar to those obtained using conventional polymerization methods.²⁵ Since then, significant progress has been realized, leading to a rapid increase in the study and utilization of DArP.

DArP as a relatively recent approach to conjugated polymer synthesis addresses significant needs in the broader commercial viability of conjugated polymers. DArP stands apart by making conjugated polymers easier to access, more affordable to prepare, and more synthetically sustainable. Significant progress has been made towards improving DArP methodology, including improving selectivity of C-H bonds, improving reaction yields, broadening substrate scope, and developing first-row transition metal catalysts. Greater improvements in accessing conjugated structures are still needed, both using direct arylation and by novel transformations. Current DArP methodology originates primarily from adapting seminal small molecule direct arylation reports. As such, continued advancements in synthetic methods for polymer synthesis should look to developments in the small molecule literature. At the same time, polymerization studies provide unique perspectives on a transformation, as even small deviations in selectivity and reactivity can have significant impact on a resultant polymer's properties. Polymerization studies can offer valuable considerations to improving the efficiencies of both future polymerizations and small molecule transformations.

A wealth of information on DArP can be found in the numerous review articles previously published.^{26–31} Topical review articles are also available, addressing topics such as defects in

DArP-produced polymers,^{32,33} and improving DArP's sustainability.^{34–36} To ameliorate the existing literature, this perspective article presents a strategy in developing new methodologies for conjugated polymer synthesis. DArP is focused on as a useful example, with guidance on how to adapt existing small molecule methodologies to develop novel polymerizations. Frequently, when this is done, resultant polymers have structural defects not predicted by the small molecule transformations. These defects provide valuable information on the nature of the polymerization and small molecule reaction. This perspective article discusses ways polymerizations' strict requirements can improve understanding of small molecule transformations. Examples of this strategy of method development are presented in both DArP and emerging polymerizations. We propose a synergistic, circular strategy to improved synthetic method development where in addition to the common use of small molecule reports to inspire new polymerizations, polymerization-based discovery is applied in the development of new small molecule methodologies.

II. DArP METHOD DEVELOPMENT

For electronic applications, the π -conjugated backbone of a material is an essential consideration, influencing the material's optical and electronic performance. Sufficiently high molecular weight is a key consideration for many applications of conjugated polymers. Molecular weight affects the polymer's solid-state structure, directly influencing charge transport properties.³⁷ In addition to molecular weight, there are many parameters affecting the electronic performance of a material, including dispersity and defects. A critical goal of polymer synthesis is having precise structural control with highly reproducible syntheses. Achieving this goal enables accessing the desired structure for a given application, and provides researchers with insight into which structural modifications led to which performance outcomes. There are two main ways well defined, reproducible materials can be realized in DArP. Firstly, homocoupling and branching defects should be limited or absent. Secondly, resultant polymers should have sufficiently high molecular weight to achieve the desired electronic properties.

Cross-coupling polymerizations are governed by a polycondensation mechanism. While different polymerization mechanisms (e.g. chain polymerization) are not readily predictable from small molecule reactions, adapting small molecule methods is an appropriate strategy for developing novel polycondensation reactions. Adapting a small molecule reaction to a polymerization has several considerations, summarized in **Table 1**. It should be noted that these are general guidelines when new small molecule conditions are considered for polymerization studies. Due to the dynamic nature of a growing polymer chain, meeting these conditions is not guaranteed to provide excellent polymers nor does not meeting these requirements preclude the possibility of successful polymerizations. Nonetheless, they provide helpful guidance.

Table 1. Relationship between Polymerization and Small Molecule Reactions

Polymerization Requirements	Small Molecule Indication	Outcome
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High conversion	High yield	High molecular weight
Stoichiometric monomer loading	Proceeds with stoichiometric substrate loading	High molecular weight
Linear chains	Complete regioselectivity	Fewer branching defects
Alternating copolymers	Complete chemoselectivity	Fewer homocoupling defects
Growing chain stays reactive	Disubstituted substrates react	Polymerization possible

Firstly, molecular weight will be considered. One way to think about polycondensation reactions is that every n-mer displays the same effective reactivity as the monomer, in contrast to chain polymerization where the growing polymer chain reacts preferentially to monomers (**Figure 1a**).³⁸ In polycondensation reactions, the same coupling is repeated extensively until long chains are produced. This has been described mathematically by the Carothers equation, indicating that exceptionally high conversion is needed for achieving high molecular weights (**Equation 1, Figure 1b**).³⁹

$$DP = \frac{1 + r}{1 + r - 2rp} \quad (1)$$

Here, the degree of polymerization (DP) is related to the stoichiometric ratio of monomer coupling partners (r), and the conversion of monomer functional groups (p). The Carothers equation is a simple relationship governed by a few assumptions which are not always realized in polycondensation reactions.⁴⁰ Firstly, all reactive groups are assumed to be equally reactive, meaning that a monomer will react with either a monomer or growing polymer chain without preference. Additionally, this model assumes an equilibrium polymerization with complete solubility of monomers and polymers.³⁹ Since polymerizations are dynamic as the reactant changes from monomer to oligomer, features observed in the small molecule transformation do not always translate to the subsequent polymerization.

In addition to very high conversion, equimolar monomer loading is required to achieve high molecular weight polymers. This is demonstrated in the table in **Figure 1b**: as the monomer molar ratio deviates from one, the DP accessible at 99% conversion decreases rapidly. This has two practical implications. Firstly, monomer purity is essential - one reason DARp is appealing over harder to purify organostannane monomers. Secondly, this is a challenging requirement not typically explored in the small molecule literature, where one coupling partner is often used in excess to drive the reaction forward while avoiding homocoupling. In sum, small molecule reactions demonstrating high yields (~99%) with close to 1:1 stoichiometric ratio of coupling partners are suitable for adaptation to polymerization.

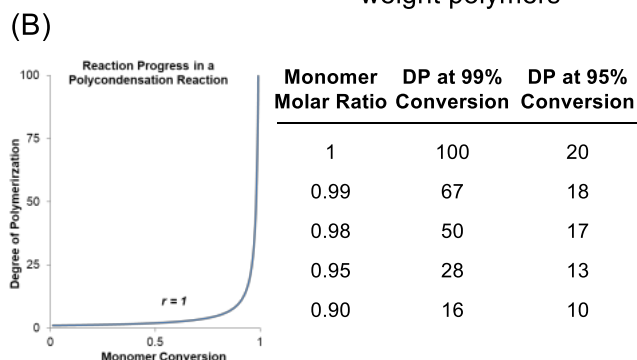
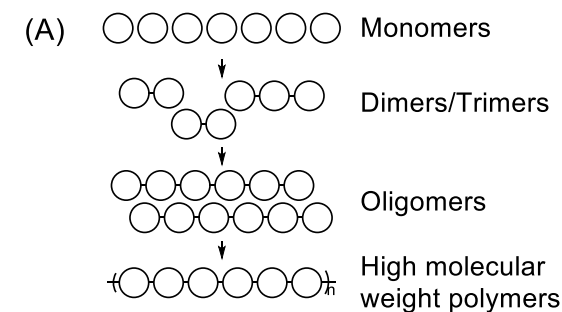


Figure 1. Qualitative and Quantitative Representation of Polycondensation Reactions

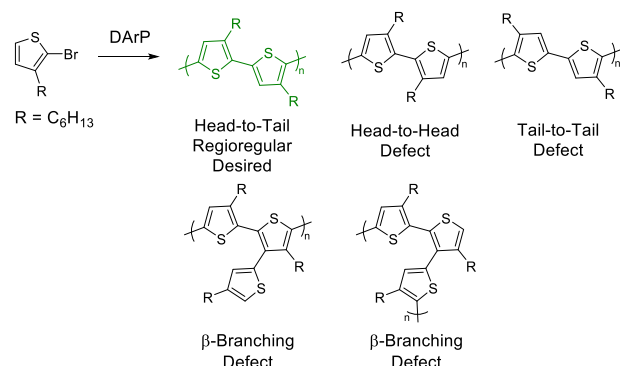
III. EXAMPLES IN C-H ARYLATION

Having reviewed important factors for developing new methods of polymer synthesis, this section presents examples of the types of insights polymerizations can offer. Even when the Small Molecule Indications outlined in **Table 1** are present, there can still be problems with resultant polymers (i.e., low molecular weight, high defect concentration). This discrepancy between what was anticipated from a small molecule reaction and the results of a new polymerization provides insight into mechanistic factors governing regioselectivity, chemoselectivity, and reactivity. Rather than a comprehensive overview, we will primarily focus our discussion on ways that results in polymerization studies can differ from what would be expected from the corresponding small molecule transformations. In addition to presenting some of these challenges, we highlight ways these deviations can serve as opportunities to inform the broader synthetic community about the nature of a given transformation.

a. DEFECT-DRIVEN DARp STUDIES

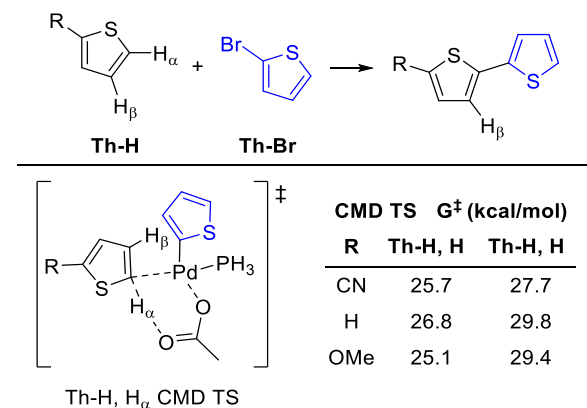
Selectivity in C-H functionalization reactions can be problematic in substrates with multiple, similar C-H bonds. For example, the C-H bonds on unsubstituted thiophene, a prevalent motif in conjugated polymers, demonstrate reactivity under the same reaction conditions. Unlike in small molecule reactions where undesired regioisomers can be removed using purification techniques, regiodefects in polymers are permanently incorporated into the chain. For optoelectronic applications, these defects are typically detrimental to the electronic performance of a material.⁴¹ Commonly encountered defects in DARp are outlined in **Scheme 3** using P3HT as a model system; included are branching defects, head-to-head, and tail-to-tail coupling defects.

Scheme 3. Defects in DArP P3HT Synthesis



One problem that arises when adapting a small molecule reaction to a polymerization is the changing reactivity of various C-H bonds throughout the growing polymer chain. The activation free energies of both the α -position and the β -position on a substrate change with changing substitution (**Scheme 4**).^{42,43} In the case of a growing polymer chain the α and β protons' reactivity may differ on the monomer compared to the dimer, and for the terminal repeat units compared to H β on interior repeat units. These variations will be even more pronounced in donor-acceptor copolymers with changing electronic character of the alternating repeat units. When developing new DArP protocols, it is important to investigate regioselectivity beyond the initial cross-coupling event, as the second and third C-C couplings will have inherently different electronic character that may be detrimental to previously observed regioselectivity.

Scheme 4. Activation Free Energies for CMD of Substituted Thiophenes^a



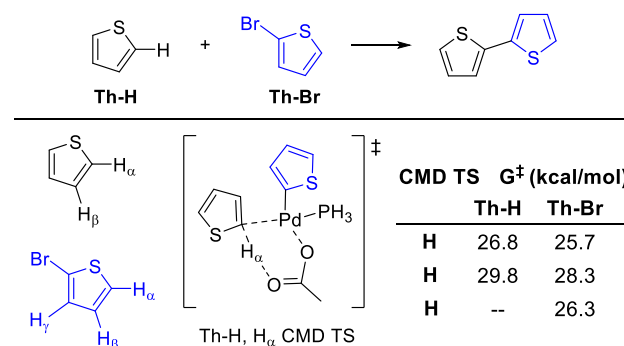
^aAdapted from ref. 43.

Polymerization studies lend themselves to exploring factors influencing regioselectivity. As a polymerization proceeds on a thiophene monomer, the free C-H bonds at the desired α -position become scarce, whilst undesired β -position C-H bonds are still abundant for cross-coupling. In light of the need for very high monomer conversion to observe high molecular weights, polymerizations are often allowed to react longer than analogous small molecule transformations. In small molecule systems, after the initial desired cross-coupling occurs in good-to-excellent yield, the reaction can be stopped prior to undesired cross-coupling events – an approach not possible in

the polymerization context. Highlighted below are select studies investigating controlling regioselectivity in DArP.

For thiophene direct arylation by a CMD process, C-2 selectivity is favored, although β -branching is a known problem in polymerizations (**Scheme 3**). Leclerc et al. have reported on the cause of β -defects in polymers involving thiophene C-H arylation.⁴³ Parameters impacting regioselectivity for substituted thiophenes were evaluated, accounting for both steric and electronic influences on C α -H and C β -H bond functionalization by CMD (**Scheme 4**). Focusing on thiophene, this work characterizes the increased reactivity of all C-H sites on the halogenated coupling partner, compared to a halogen-free thiophene (**Scheme 5**, Th-Br, H γ vs. Th-H, H α). When halogenated, H γ on Th-Br becomes much more accessible for CMD (26.3 kcal/mol). This demonstrates that poor selectivity for C α -H over C β -H can frequently be attributed to the activating effect bromination has. While addressing a materials-specific problem regarding defect formation in DArP, this report provides analysis on the nature of reactivity at competing C-H bonds useful for small molecule applications as well. To achieve highly selective couplings where a bromothiophene unit is involved, ensuring the C-H coupling partner is electron-rich or electron-poor will make the desired α -position C-H functionalization more competitive to CMD than the C-H adjacent to the C-Br bond on the coupling partner.

Scheme 5. Activation Free Energies for CMD of Thiophene^a



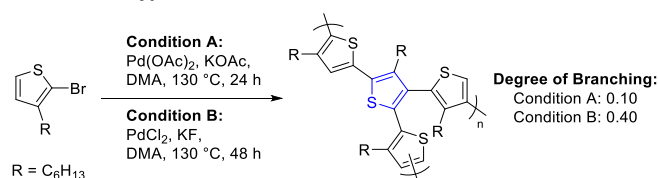
^aAdapted from ref. 43.

Undesired branching has also been investigated to access novel hyperbranched materials. Our group studied thiophene's β -branching to prepare hyperbranched P3HT, leading to greater understanding of conditions favoring α/β selectivity (**Scheme 6**).⁴⁴ In this case, β -branching was a feature of the polymerization and was never evidenced in the corresponding small molecule reaction. This highlights the regioselectivity issue of a changing substrate from monomers to oligomers in the early stages of polycondensation reactions (**Scheme 4**). The authors examined how reaction conditions could be used as a tool to tailor degree of branching in thiophene-based polymers, using NMR spectroscopy to quantify the number of α to β couplings in these systems.

Within Condition A, variation in branching could be reduced by adding ligands. Compared with the ligand-free system, phosphine ligands PPh₃, XPhos, and dppe provided high molecular weight polymers but with a decrease in the degree of branching. Polymers prepared with nitrogen-based ligands, bpy and TMEDA, had no dendritic units. More extensive

branching was observed with Condition B. Notably, a carboxylate is absent from these reaction conditions, minimizing the likelihood that this process occurs by CMD, which features a carboxylate-assisted deprotonation. This likely difference in mechanism between Conditions A and B contributes to the loss in regioselectivity over the course of the polymerization. Should the mechanism be S_EAr or oxidative polymerization where cations are generated on the polymer backbone, regiodefects are to be expected. This hypothesis is further supported by the fact that when a carboxylate is introduced into Condition B by using $Pd(OAc)_2$ in place of $PdCl_2$, branching is reduced. This is a trend that will be returned to in this article, where for C-H functionalization polymerizations, there is significant opportunity for non-CMD-mediated polymerizations to offer inherent improvements over transformations governed by CMD, including lower energy requirements, broader substrate tolerance, and greener reaction conditions. At the same time, the mechanistic shift typically results in a loss of regioselectivity creating polymers with intolerable defect concentrations. This is an opportunity in the larger synthetic community to develop greater understanding of the mechanisms for different C-H bond arylations, and of the factors influencing regioselectivity under these different mechanisms.

Scheme 6. Hyperbranched P3HT^{a,b,c}

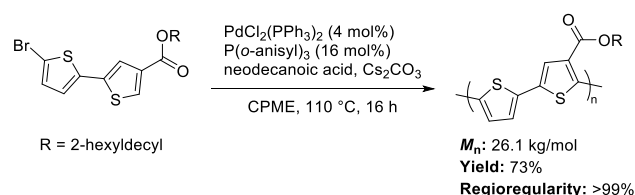


^aAdapted from ref. 44. ^bDendritic unit shown in blue ^cCondition A: $Pd(OAc)_2$ (1 mol%), KOAc (2 equiv.), Condition B: $PdCl_2$ (3 mol%), KF (4 equiv.)

Regioselectivity is often ameliorated in small molecule reactions by directing groups; this approach is not commonly used in DArP. The installation of directing groups have typically been viewed as negatively influencing the molecular design of the desired material, where commonly used ester or amide directing groups have not frequently been considered valuable structural features. This view is becoming outdated with growing interest in the inclusion of heteroatoms in the sidechains of thiophene-based monomers, arising from the recent attention towards mixed ionic-electronic conductors.⁴⁵ Alongside this, some early studies indicate the beneficial impact introducing side chains that can participate in H-bonding has on improving charge mobility through intermolecular H-bonds of nearby side chains.⁴⁶ Esters in particular have been evidenced for their ordering morphological effect with demonstrably shorter π - π stacking distance in polymers with ester-containing side chains.^{47,48} The improvements in regioselectivity, and application-specific properties (e.g. ion conductivity, charge mobility) afforded by using pendant directing groups present an opportunity for innovation. Here, creative design of directing groups could be utilized to facilitate improvements in regioselectivity without deleterious effects on polymer properties. With proper design, it may be possible that directing groups could add to the final properties of a material.

The influence directing groups may have on the properties of a polymer is one consideration. A secondary concern arises from the presence of directing groups on repeat units already installed on the polymer chain during synthesis. These mid-chain directing groups can lead to undesired branching and/or cross-linking in polymers when the active catalyst interacts with a mid-chain directing group rather than the desired chain-end site. This problem arises when a secondary suitable C_{aryl} -H bond is present in the monomer structure, as in thiophenes' β and γ positions.⁴⁹ Thompson et al. report DArP conditions for a thiophene monomer with an ester directing group at C_β (Scheme 7).⁵⁰ They successfully used the ester directing group to prepare regioregular polymers, showing the promise using the small molecule directing group strategy has for new polymerizations. In order to avoid mid-chain cross-linking/branching couplings, they selected branched alkyl side chains. These sterically bulky side chains prevented undesired reactions along the polymer backbone by improving separation between discrete polymer chains. These rationally designed monomers were utilized to avoid defect formation. Thoughtfully designed monomers containing directing groups should be considered for cases where the end use application of a polymer would benefit from introducing heteroatom-containing functionalities. This may be a path forward to reliably regioregular DArP and Oxi-DArP prepared polymers. Continued work in both the small molecule and polymer communities provides opportunities to make an impact on thoughtfully defined directing groups and directing-group containing polymers.

Scheme 7. Ester Directed DArP for Regioregular P3HT^a



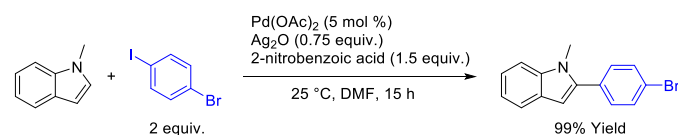
^aAdapted from ref. 50.

The stringent requirements for successful polycondensation can drive greater understanding of the underlying mechanism. In part, this is due to the very high number of cross-coupling events required for high molecular weight, allowing for deviations in reactivity at the final stages of the reaction to become observable. Moreover, small changes in the steric and electronic properties of the growing polymer chain and the subsequent activation or suppression of desired reactivity can indicate greater details about the nature of catalysis.

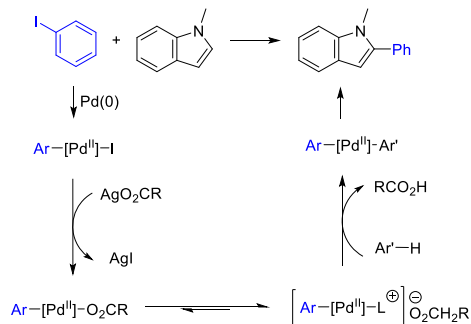
One such example investigated preparing polyindole,⁵¹ drawing inspiration from a small molecule method. Here, indole underwent C-H arylation with iodoarene coupling partners (Scheme 8a).⁵² This small molecule report seemed to be a notable precursor for polymerization as it demonstrated complete regioselectivity without the use of a directing group. Secondly, excellent yields were reported even at room temperature. Lastly, this transformation utilized only two equivalents of the aryl iodide, indicating

Scheme 8. Indole C-H Arylation by Iodoarenes at Room Temperature^a

(A) Small Molecule Method



(B) Mechanistic Proposal with Small Molecule Work

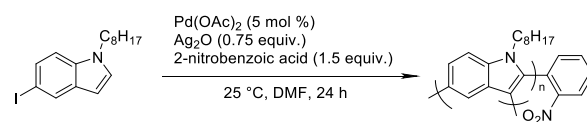


^aAdapted from ref. 52 (left), 51 (right).

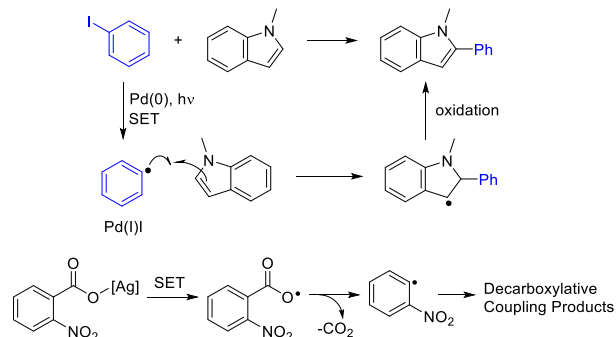
a stoichiometric ratio may be tolerated. The authors proposed the room temperature reactivity could be owed to Ag-mediated halide scavenging, exchanging the iodide ligand after oxidative addition with 2-nitrobenzoate. This carboxylate could dissociate from the metal center, affording a highly electrophilic metal catalyst (**Scheme 8b**).

When this was adapted to an iodoindole monomer for polymerization studies, surprising incorporation of the benzoate was observed in the resultant polymer chain, alongside β -branching (**Scheme 8c**). Neither structural feature was observed in the small molecule reaction. This observation catalyzed mechanistic studies of the polymerization and corresponding small molecule reaction, revealing a novel photosensitivity atypical of CMD direct arylation without an exogenous photosensitizer. Rather, this light-mediated, room temperature process was likely accessible by a different mechanism (**Scheme 8d**). Here, a proposed light-mediated single electron transfer (SET) event occurred between the Pd catalyst and the aryl iodide.⁵³ The subsequent phenyl radical can be trapped by indole, eventually affording the observed product. The origins of nitrophenyl incorporation were unclear. Commonly, metal benzoates lose CO₂ thermally, providing organometallic arenes for cross-coupling reactions.⁵⁴ In the absence of elevated temperatures, metal benzoates can be transformed into aryl radicals through single electron activation.^{54,55} While the precise source of an unpaired activating electron has yet to be elucidated, this is likely the process responsible for nitroarene incorporation in the polymer chain. Since the reaction required palladium, a radical chain reaction initiated by the silver carboxylate decomposition is unlikely as the primary mechanism for polymerization. The mechanistic studies were replicated in both small molecule and polymer trials, achieving the same results. This indicates the decarboxylative coupling is not indicative of a polymerization-specific mechanism. The photosensitivity is likely responsible for the ability of this reaction to proceed at room temperature, where most CMD-mediated processes require elevated temperatures.

(C) Polymerization Studies



(D) Mechanistic Proposal from Polymerization



b. DEFECT-DRIVEN OXI-DARP STUDIES

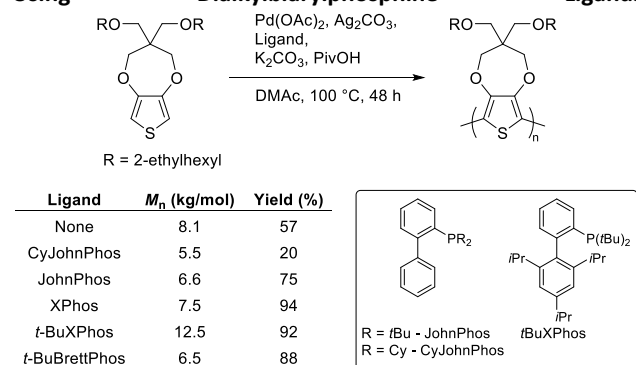
Mechanistic insight arising from polymerization studies can also occur in oxidative DARp (Oxi-DARp), also referred to as cross dehydrogenative coupling (CDC) polymerization. This is similar to direct arylation, however involves the direct coupling between two aryl C-H/C-H bonds instead of coupling between C-H/C-X bonds as in direct arylation. Some of the original methods of conjugated polymer synthesis, electrochemical and chemical oxidation methods, utilize unfunctionalized monomers.^{56,57} These historical methods achieve materials with significant defects, which Oxi-DARp is able to improve upon by using transition metal catalysis. Since Oxi-DARp is still a polycondensation, it shows the same interplay between small molecule couplings and polymerizations as DARp. For donor-acceptor copolymers, it is desired that orthogonal reactivity controls are available to aid in cross-coupling during dual C-H bond activation.

Dialkylbiarylphosphine ligands are widely used in cross-coupling reactions, with extensive examples of their ability to tune reactivity of a given transformation.^{58,59} This category of ligands, often referred to as Buchwald ligands, has undergone screening studies in small molecule direct arylation.^{60,61} Minimal efforts to employ this type of catalyst have been seen in the polymerization literature, despite the possibilities to leverage these ligands for improved reactivity and selectivity. One report has systematically screened a selection of Buchwald ligands by using Oxi-DARp on 3,4-propylenedioxythiophene (ProDOT) as a model study (**Scheme 9**).⁶² By selecting ProDOT monomers, the authors demonstrate a viable strategy for synthesizing regioregular polymers, where potentially problematic C-H bonds are blocked with substituents. Depending on the application of the target material, this can be a simple approach to regioselectivity issues commonly encountered with C-H arylation polymerizations, although is not generalizable.

From the above study, it was clear that ligand selection significantly impacted the polymerization results. Particularly, bulkier ligands with *t*Bu substituted phosphines, and adding bulky *i*Pr groups to the lower ring improved both yield and *M_n*

(**Scheme 9**). The impact of the ligand on catalysis in small molecule Pd-mediated cross-couplings has been extensively studied.^{59,63,64} These studies demonstrate that bulky, electron-donating biarylphosphine ligands effectively stabilize the key catalytic species, monoligated palladium (L₁Pd).^{59,63} By affording L₁Pd in place of bisligated palladium (L₂Pd), these bulky ligands enhance oxidative addition by allowing the substrate and catalyst to interact. Bulky ligands favoring L₁Pd have also been shown to increase the rate of reductive elimination compared to the comparable L₂Pd species with less strain.^{65–67} In Oxi-DArP, the CMD step is analogous to oxidative addition in a traditional cross-coupling reaction, where bulky ligands which favor formation of L₁Pd improve reactivity. Using bulky *t*Bu phosphine substituents and introducing *ortho*, *ortho'* substitution with a bulky *i*Pr on the lower ring favors L₁Pd formation by increasing the ligand's size, explaining why *t*-BuXPhos performed the best in the Oxi-DArP report.⁵⁹ Thus, oxidative direct arylation shows a similar relationship between ligand selection and catalytic efficiency as C-M/C-X cross-couplings. By studying these ligands for Oxi-DArP, information on the ligand's impact on C-H activation and reductive elimination is provided for future small molecule and polymer systems.

Scheme 9. PolyProDOT Prepared via Oxi-DArP Polymerization Using

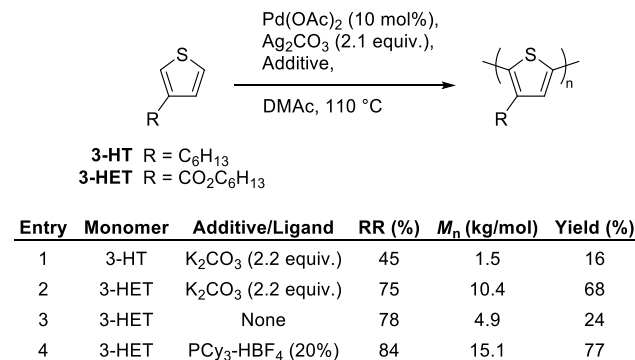


^aAdapted from ref. 62.

Ligand impact on Oxi-DArP performance has also been evaluated in tandem with directing group effect. Thompson et al. evaluated Oxi-DArP for preparing ester-functionalized thiophenes.⁶⁸ The authors systematically optimized reaction conditions, comparing the effect of variables including oxidant, additive, and ligand on the resultant polymer's properties (**Scheme 10**). By choosing 3-hexylesterthiophene (3-HET) as a model substrate which has three inequivalent but reactive aromatic C-H bonds, this report presents a valuable insight into regioselectivity in oxidative direct arylation. Notably, the authors compared 3-HET to 3-hexylthiophene (3-HT), showing the dramatic improvement in regioselectivity offered by the ester directing group (45% for 3-HT vs. 75% for 3-HET, **Scheme 10**, entry 1, 2, 3). From there, improvements in regioselectivity were achieved using a phosphine ligand (PCy₃-HBF₄) to achieve polymers around 85% regioselective (**Scheme 10**, entry 4). Molecular weight showed similar trends, where the best results used a phosphine ligand. This work highlights the important role directing groups are able to play in achieving regioselective

polymers using dual C-H activation. Moreover, the insights gained on regioregularity and molecular weight for monomers provides guidance on achieving regioselective, high yielding small molecule transformations. In particular these trends are valuable for challenging small molecule C-H/C-H coupling reactions with multiple inequivalent C-H bonds, showcasing the value of ester directing groups and phosphine ligands.

Scheme 10. Conditions Optimization for Oxi-DArP of 3-Substituted Thiophenes^a



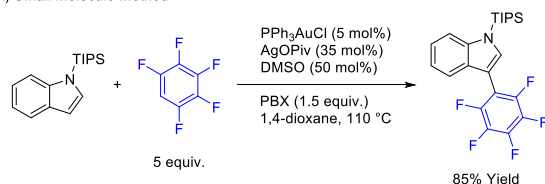
^aAdapted from ref. 68.

In another example of Oxi-DArP, a promising small molecule reaction was investigated as a polymerization.^{69,70} The small molecule report demonstrated orthogonal reactivity between electron-rich and electron-poor coupling partners (**Scheme 11a**). This methodology was demonstrated on heteroaromatic electron-rich species including indole, thiophene, and pyrrole undergoing C-C bond forming events with fluorinated benzenes. These are suitable monomers for a conjugated donor-acceptor copolymer. Moreover, this report was able to achieve cross-coupling selectivity without extreme excess of one of the coupling partners, making it more likely that stoichiometric monomer loadings could be tolerated. Here, the high cross-coupling selectivity came from an infrequently used gold catalyst. In this strategy, it was hypothesized that different oxidation states could be used to change selectivity, rather than in Pd-mediated cross-couplings where only small changes in the ligands must sufficiently turn on and off reactivity for the electron-rich and electron-poor arenes. The authors propose the Au(I) species selectively activates the electron-deficient arene while a Au(III) species in the catalytic cycle selectively activates the electron-rich arene (**Scheme 11b**).

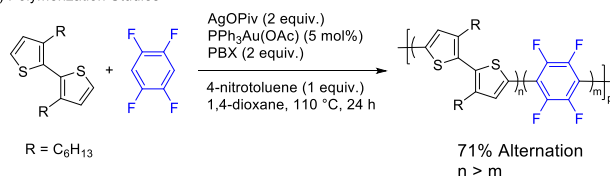
This small molecule oxidative direct arylation report presented an inspiring strategy for donor acceptor copolymers – using a Au(I)/Au(III) catalytic cycle to mediate orthogonal cross-coupling. This could provide an efficient approach to achieving perfectly alternating copolymers. This selective activation approach was subsequently adapted to the polymerization of a thiophene/tetrafluorobenzene copolymer. Unexpectedly, in contrast to the small molecule report, cross-coupling selectivity was lost when polymerization trials were performed (**Scheme 11c**). While the fluoroarene did not undergo homo-coupling, the thiophene units did. Subsequently, the

Scheme 11. Au-Mediated Arene Oxidative Direct Arylation^a

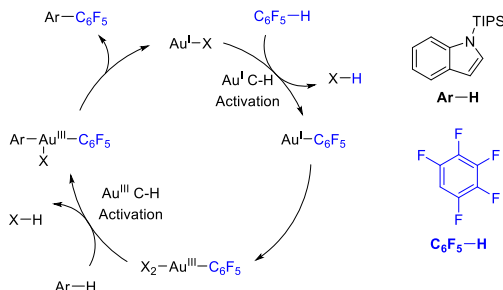
(A) Small Molecule Method



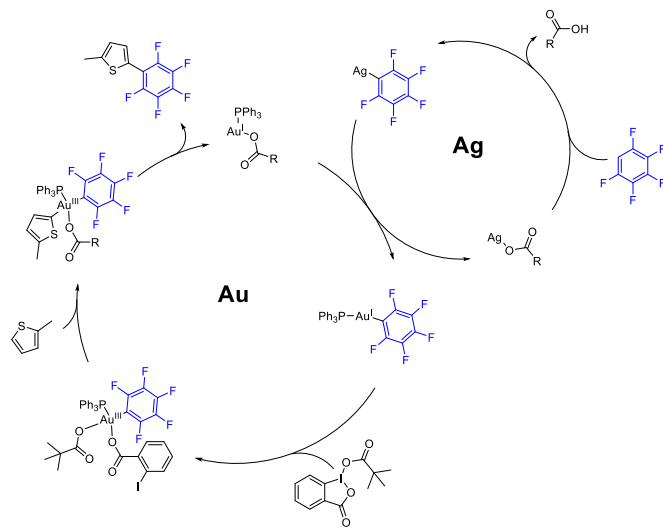
(C) Polymerization Studies



(B) Mechanistic Proposal with Small Molecule Work



(D) Mechanistic Proposal with Polymerization



^aAdapted from ref. 70 (left), 69 (right).

resultant polymer had a high degree of homocoupling, with 71% alternation between the electron-rich and electron-poor repeat units.

In order to investigate this change from small molecule to polymer conditions, mechanistic studies were performed. Rather than a Au(I)/Au(III) catalytic cycle as proposed in the small molecule work, mechanistic work reported in the polymerization study revealed different mechanistic features. Namely, a dual catalytic cycle enables cross-coupling, where Au and Ag selectively activate electron rich and electron poor substrates, respectively (**Scheme 11d**). This cooperative catalysis was later supported by two additional studies.^{71,72} In the polymerization, the initial installation of fluorinated benzene on thiophene made the free C-H bond on thiophene meaningfully more reactive to Ag during the second coupling event. This causes Ag to be able to activate C-H bonds on both the electron-poor tetrafluorobenzene monomer, and on the biaryl tetrafluorophenylthiophene. This phenomenon arises from the electron-withdrawing effect of the fluorinated benzene. In the small molecule setting, the biaryl product's reactivity did not need to be considered. However, the biaryl species' reactivity is of fundamental importance for preparing the polymer. The loss of cross-coupling selectivity in the polymerization reveals that the C-H activation selectivity is not driven by the gold catalyst's oxidation state.

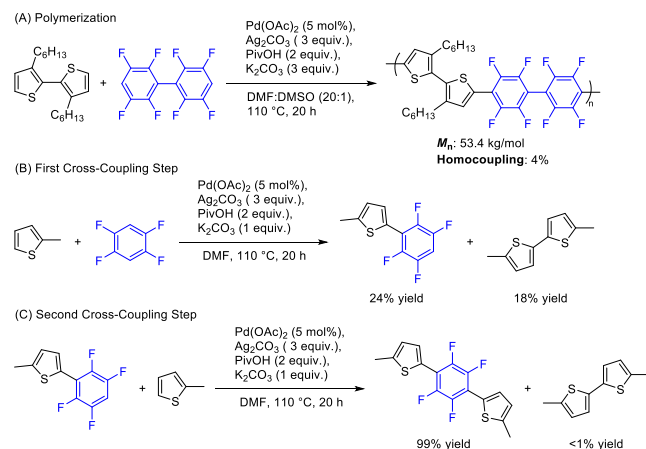
This polymerization work discovered in depth information about the catalytic cycle, including the nature of Au/Ag selectivity. Since these reports of Au/Ag dual catalysis, new methods have been reported drawing insight from the Au/Ag transmetalation step initially discovered in this polymerization study. One such example uses stoichiometric Ag in a method

of decarboxylative coupling.^{73,74} Here, a Ag carboxylate is delivered to the Au metal center using Ag(I) to Au(III) transmetalation. Another report, inspired by a Au/Ag dual catalytic system sought to discover a Pd/Ag system with catalytic amounts of both metals for direct arylation.⁷⁵ In this case, silver's demonstrated ability to activate C-H bonds in electron-deficient arenes was utilized jointly with a Pd-mediated oxidative addition of aryl bromides. Both of these reports apply findings originating from mechanistic studies on a polymerization, showing cooperative discovery between small molecule and polymerization transformations.

In addition to work highlighting mechanistic shifts and factors influencing regioselectivity, reactivity has also been assessed.⁴⁰ Kanbara et al. reported a Pd/Ag Oxi-DARF system with high molecular weights and low homocoupling that used the same substrates as the Au/Ag system outlined in **Scheme 11c**.⁷⁶ While high homocoupling was observed in the Au/Ag system, the Pd/Ag report showed excellent cross-coupling selectivity (**Scheme 12a**). Luscombe et al. investigated this deviation, observing the Pd/Ag polymerization result was in contrast to small molecule model studies, where the equivalent small molecule cross-coupling showed poor yield and poor selectivity (**Scheme 12b**). Considering the Carothers equation (**Figure 1**), **Scheme 12b** does not forecast the successful polymerization achieved by Kanbara. Luscombe et al. investigated the origins of the discrepancy, and found that the second cross-coupling event occurs much more readily than the first (**Scheme 12b** vs. **12c**), approximately 10 times faster. Through kinetic and computational experiments, they demonstrated the activating effect the thienyl substituent has on the fluoro-aryl coupling partner. This activating effect fundamentally

changes the reactivity of the monomer with growing polymer chains, subverting the Carothers equation's assumptions. The change in reactivity from the first cross-coupling step to the second demonstrates the limitations of studying small molecules as precursors to polymerizations, indicating that studying the second cross-coupling step may be more accurate. Moreover, this work also may inform oxidative direct arylation on small molecule substrates, particularly in late-stage functionalization settings. In cases where addition of thiophene to electron-deficient scaffolds is desired or tolerable, it may provide more efficient access to target cross-coupled products.

Scheme 12. First and Second Cross-Coupling Steps, Compared to Oxi-DArP Study^a



^aAdapted from ref. 76 (Scheme A). Adapted from ref. 40 (Scheme B and C).

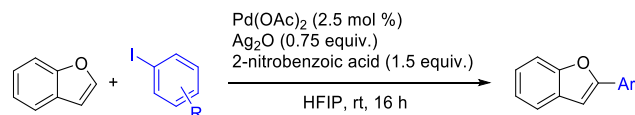
c. IMPROVEMENTS TO SMALL MOLECULE METHODOLOGIES INSPIRED BY POLYMERIZATIONS

Examples have been presented of new methods of polymer synthesis inspired from efficient small molecule reactions. This is a common and useful approach, especially as new and significantly improved transformations are developed in the small molecule literature. Of particular value are those transformations that offer a significant improvement in atom economy, environmental and economic impact of the conditions (e.g. solvents, catalysts), as well as those that offer access to novel polymeric architectures. A few of these polymerization-based discoveries have subsequently led to new innovations for small molecule transformations and targets. This strategy could be more broadly utilized for developing novel and improved transformations in the small molecule literature.

An example of this small molecule $\rightarrow$ polymer $\rightarrow$ small molecule innovation pipeline is from the study on room temperature arylation of indole (**Scheme 8**). As discussed in Section IIIa, the original small molecule work for indole direct arylation with iodoarenes was adapted to polymerization.^{51,52} In the course of these polymerization studies, new mechanistic insights on the room temperature transformation were discovered. Namely, photosensitivity was observed and proposed to be the driving force enabling this transformation to proceed at room temperature. Curious about the generality of this process, exploratory work was performed, eventually leading to improved conditions for benzofuran C-H arylation (**Scheme 13**).¹⁷ This small molecule report was inspired directly from our

studies on adjacent polymerizations. While it is common for new polymerization methods to be informed by small molecule work, it is worth considering in what ways new polymerizations can inform new small molecule synthetic methods as well. The indole/polyindole/benzofuran progression is one example of this circular pathway to developing greater insight into a type of transformation.

Scheme 13. Benzofuran Direct Arylation by Aryl Iodides^a



^aAdapted from ref. 17.

The benzofuran small molecule C-H arylation method offers significant improvement over existing methodologies, with improved functional group tolerance, mild conditions, and commercially available aryl iodides. This method shows a number of similarities in conditions to those for indole room temperature arylation (**Scheme 8a**), with the only meaningful difference arising from a change in solvent from DMF to HFIP. Interestingly, despite these similarities a significantly different mechanism was evidenced using dark conditions screenings, deuterium exchange and kinetic isotope effect experiments. Rather than a photosensitive transformation as with indole, the benzofuran report appears to be governed by a Heck-type process, similar to a method for β -arylation of benzothio-*phene*.¹⁶ Notably, neither the indole nor the benzofuran room temperature direct arylation systems can be described by a more conventional CMD mechanism. It is likely these mechanistic changes are what enable such mild reaction conditions compared to elevated temperatures typically found in direct arylation conditions. While still accessible from small molecule studies, polymerizations served as a valuable driving force to gain increased fundamental insight into the processes underlying these room temperature transformations. This serves as an example of how considering polymerization studies in small molecule methodology is a useful strategy for gaining new insights and inspiration for small molecule methods.

IV. EMERGING POLYMERIZATION METHODOLOGIES BEYOND DArP

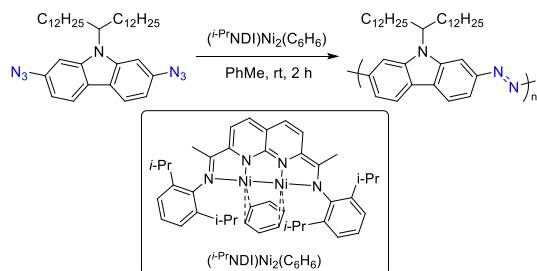
Examples presented thus far have focused on ways in which DArP has grown out of existing small molecule methodologies. Mechanistic insights driving the properties of a given method, including regioselectivity have also been discussed. Some examples have also been presented on ways in which DArP studies can inform future small molecule work on a given transformation. Beyond DArP methodology, there are emerging methods of polymerization, both for fully conjugated and nonconjugated optoelectronic materials that have been informed by the small molecule literature.

A preliminary example of a novel approach to new polymer structures is based off of a small molecule report detailing the utility of a dinuclear nickel catalyst in preparing aryl azides.⁷⁷ A wide range of aromatic groups are tolerated, including heteroarenes. This work included a preliminary polymerization example, highlighting the efficiency of the reaction. Later, a full

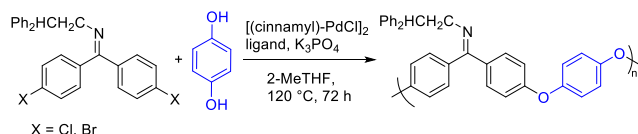
report was published on the preparation of azopolymers using several different heteroaromatic monomers (**Scheme 14a**).⁷⁸ Azopolymers have not been thoroughly explored in conjugated polymers; this methodology opens up an efficient synthetic route to their greater study.

Scheme 14. Representative Polymers Prepared from Aryl Azides and by C-O Cross-Coupling^a

(A) Poly(Azocarbazole)



(B) Model Compound for Poly(Arylene Ethers)



^aAdapted from ref. 78 (Scheme A). Adapted from ref. 79 (Scheme B).

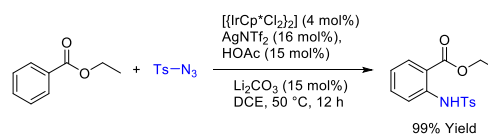
A secondary example of adopting established small molecule methods to polymerization utilizes C-O cross-coupling. While C-H bond arylation has been discussed earlier in this article, polycondensation using C-O and C-N bond forming events is a developing strategy to access different polymeric structures. A number of synthetic strategies exist for preparing diaryl ethers from C-O cross-couplings.^{80,81} Recently, the small molecule understanding of Pd-catalyzed C-O cross-coupling was applied to synthesize a unique class of poly(arylene ethers) not previously accessible by the more conventional S_NAr approach (**Scheme 14b**).⁷⁹ Here, cross-coupling occurs between aryl halides and hydroquinone's hydroxyl groups. This specific report focuses on space-promoting repeat units for porous organic polymers, but the approach should be generalizable to prepare other poly(arylene ethers). Similar to the previously discussed Oxi-DARp study exploring Buchwald ligands (**Scheme 9**), this report provides useful information into the efficiencies of different pairings of ligands with aryl halides. This information is certainly useful for further advancements in the polymerization context but could also inform conditions screening for similar small molecule reactions.

The C-O cross-coupling polymerization demonstrates some interplay between insights from new polymerization strategies and applications in small molecule methodologies, primarily for guiding conditions screenings. There are other examples of this in recent polymerization approaches. Focusing on a different transformation utilizing C-H bond functionalization, C-H amidation has been extensively studied in the small molecule literature.^{82–85} One such study reported by Chang et al. detailed an iridium-catalyzed C-H amidation of substrates with weakly coordinating directing groups (esters and ketones) (**Scheme 15a**).⁸² This method's ability to form C-N bonds under mild conditions and with excellent yields later inspired a novel method of polymerization, direct C-H amidation polymerization (DCAP)

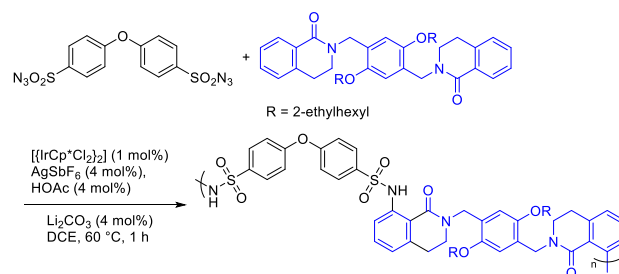
(**Scheme 15b**). A suite of unique, fluorogenic polysulfonamides were produced, all with high yields and good molecular weights.⁸⁶ During characterization of these materials, it was observed that these polysulfonamides were blue-light emitters with high quantum yields, arising from hydrogen bonds between the sulfonamide and adjacent carbonyl. Notably, these polymerization conditions were later applied to a new set of small molecule substrates, focusing on C-H amidation of aryl amides by tosyl azide.⁸⁷ Using the insights from the polymer synthesis, the materials prepared contained various substitution patterns to provide a collection of multicolor fluorophores. These three methods, starting from a small molecule method, then a novel polymerization, and lastly a new small molecule approach, demonstrate the synergistic discovery accessible between small molecule methodology and new methods of polycondensation.

Scheme 15. Iridium-Catalyzed C-H Amidation^a

(A) Small Molecule C-H Amidation by Chang, 2014



(B) Polymer Direct C-H Amidation Polymerization by Choi, 2017



^aAdapted from ref. 82 (Scheme A). Adapted from ref. 86 (Scheme B).

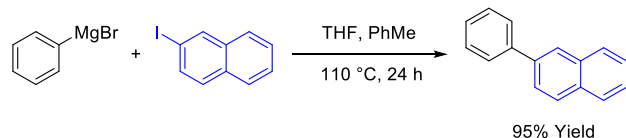
A similar pathway to new conditions has emerged with a type of $S_{RN}1$ reactions, where aryl Grignard coupling partners are used as anionic nucleophiles with an aryl halide. This strategy was first reported by Hayashi et al., providing a transition metal-free approach to biaryls from aryl Grignards and haloarenes (**Scheme 16a**).⁸⁸ This method is able to achieve transition metal-free cross-coupling by a thermally initiated SET event between the aryl Grignard and the aryl halide, successfully activating the aryl halide. Later, Studer et al. developed an analogous TEMPO-initiated cross-coupling polymerization between aryl Grignards and aryl halides (**Scheme 16b**).⁸⁹ This report hypothesizes this is a chain polymerization. Building off of both of these contributions, Kalow et al. later reported a method of photocontrolled synthesis of a range of conjugated polymers (**Scheme 16c**).⁹⁰

The photocontrolled polymerization was demonstrated to have the properties of chain polymerization. Later, extensive mechanistic work was reported on this transformation investigating the role of light.⁹¹ The initial stages of the polymerization proceed readily without photoexcitation, but as the chain grows, the Grignard has problematic preferential interactions with internal repeat units; interaction at the chain ends is required for continued propagation. Light excites the growing chain, causing a shift in electron density away from internal

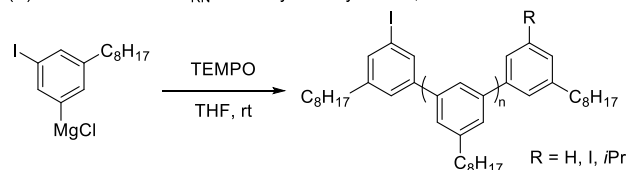
repeat units and towards the chain ends. This causes the Grignard monomer to move from internal repeat units to the chain end, leading to chain propagation. The dynamic changes in electron density make polymer chains accessible, whereas without the use of light only oligomeric materials with around four repeat units are observed. This work indicates that there could be a small molecule method accessible for heteroaryl Grignard cross-couplings with aryl halides without photoexcitation, and without the high temperatures used in the previous report, which required a heating to 110 °C for sufficient cross-coupling.

Scheme 16. $S_{RN}1$ -Mediated Cross-Coupling between Aryl Grignards and Aryl Halides^a

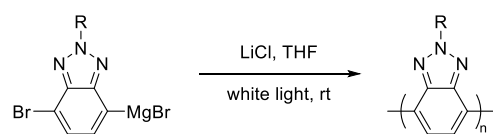
(A) Thermally Initiated $S_{RN}1$ Cross-Coupling by Hayashi, 2012



(B) TEMPO Initiated $S_{RN}1$ for Polymers by Studer, 2012



(C) Photocontrolled $S_{RN}1$ for Polymers by Kalow, 2020



R = 2-octyldodecyl

^aAdapted from ref. 88 (Scheme A). Adapted from ref. 89 (Scheme B). Adapted from ref. 90 (Scheme C).

V. OUTLOOK

In this perspective, we summarize important advances in conjugated polymer synthesis, highlighting the circular discoveries in small molecule and polymer C-H arylation methodologies. Direct arylation has become an important synthetic approach to conjugated molecules due to its improved simplicity and efficiency over conventional methods of cross-coupling. As with many polymerization strategies, DArP was inspired by small molecule reports. As improvements are continually made in the small molecule C-H arylation literature, superior polymerization protocols will be developed. The stringent reactivity and selectivity requirements of preparing high quality polymers require efficient synthetic methods, and can provide insight into small deviations in selectivity not readily observable in all small molecule studies. This is valuable for not just future polymerizations, but also addresses needs in industrial scale-up of small molecules in pharmaceutical settings. In these cases, improved yield and regioselectivity are important for scalable synthetic routes, arising from the practicalities of purifying the target product. As improved methods in the small molecule and polymerization fields are discovered, new approaches for C-H arylation transformations are being utilized. These present challenges to achieving the high yields and

selectivity needed for both polymerization and practical scale-up of pharmaceutical compounds. At the same time, they also hold significant promise for developing the next generation of C-H arylation conditions that can allow for novel disconnections, controlled polymerization, and sustainable syntheses.

A number of examples have been discussed within this article for areas most promising for continued innovation. Amongst these, ligand design, greater inclusion and exploration of directing groups, improved understanding of new mechanisms for direct arylation for greater regioselectivity are important themes. Within DArP specifically, creating methods with improved control over molecular weight is a key advancement needed that could arise from polymerization-specific studies as has been developed in the controlled Grignard metathesis method of polymer synthesis.

In the future, we anticipate new, emerging reactions will continue to improve upon the simplicity and efficiency of conjugated polymer synthesis, while allowing study of more diverse polymer structures. As has occurred with DArP, these methods can be inspired by continued innovation in small molecule transformations. Greater advancements will be achieved if the results of these polymerization trials are also accounted for in developing new small molecule reactions. A circular path of methodology development and understanding where new small molecule and polymerization discoveries inform the other is a useful strategy to new synthetic method discovery. This approach showcases the utility of collaborative research efforts between synthetic research groups working on small molecules and those working on materials as an improved strategy for synthetic method development.

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