Ni-catalysed dicarbofunctionalization for the synthesis of sequence-encoded cyclooctene monomers

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The properties of polymeric materials can be modulated by factors such as sequence-control or functional group modifications. However, the synthesis of new macromolecular scaffolds is limited by the accessibility of structurally diverse monomers. This work describes a one-step, nickel-catalysed synthesis of 5,6-diaryl cyclooctene monomers from the feedstock chemical 1,5-cyclooctadiene. The reaction proceeds in a modular, regio- and diastereo-selective fashion, granting access to both homo- and hetero-diaryl cyclooctene monomers that smoothly undergo ring-opening metathesis polymerization (ROMP). The resulting 1,2-diaryl-substituted polymers possess sequences with head-to-head styrene dyads that have not been previously explored, giving rise to unique and tunable properties. Density functional theory (DFT) calculations highlight mechanistic aspects of the nickel-catalysed diarylation reaction and the ruthenium-catalysed ROMP process, revealing a previously unappreciated role of the boronic ester in promoting migratory insertion which was leveraged to provide enantioinduction.

Sequence-controlled and stereo-defined polymers hold promise for fine-tuning material properties in applications ranging from microelectronics to catalysis yet remain challenging to synthesize[1–3]. Specifically, polystyrene and ethylene/styrene copolymers are attractive macromolecular scaffolds because of their favorable properties, including high melting point, high crystallinity, and low dielectric constant[4]. However, the synthesis of these polymers is limited by available synthetic techniques[5,6]. The aryl substituents are largely confined to unsubstituted phenyl rings with undefined relative stereochemistry, and the regiochemistry of polymerization is restricted to tail-to-tail dyads[7] (Figure 1A). As tacticity, spacing between substituents, and the appended functional groups all collectively influence the properties of the polymeric material, new methods that allow the construction of unexplored structures in a modular, selective, and sequence-controlled manner is of significant interest. Key to this endeavor is expanding synthetic access to novel monomers that can be unfolded to introduce complexity in polymeric structures.

Multicomponent conjunctive cross-couplings are a family of synthetic methods that hold great promise for assembling densely functionalized small-molecule products from abundant alkene starting materials in a modular, diastereo-, and regioselective manner[8-12] (Figure 1B). In many reports, Lewis-basic directing groups, such as amides[13], carboxylic acids[14], and sulfonamides[15,16], facilitate reactivity and selectivity of the catalyst. The possibility of extending alkene functionalization reactions towards the modification of macromolecules intrigued us (Figure 1C). Direct functionalization of alkenes within bulk polyenes, however, is complicated by several interrelated challenges including limited solubility of the starting materials and products, difficulty in achieving exhaustive functionalization, and lack of typical directing groups capable of promoting reactivity with internal olefins.

To circumvent these issues, we herein describe a two-step formal polyene 1,2-dicarbofunctionalization in which cyclic dienes, namely 1,5-cyclooctadiene (COD), are catalytically converted into functionalized cyclic olefins that then undergo ring-opening metathesis polymerization (ROMP)[17-22]. Pioneering work from Hillmyer and coworkers demonstrated that ROMP is a powerful means of accessing sequence-defined polymers from functionalized cyclooctenes (COEs)[23, 24]. However, multistep syntheses of these functionalized COE monomers restrict the modularity of the overall synthetic sequence. To date, 5,6-diarylated COE (DACOE) products, as well as the corresponding polymers, are unknown. Developing a formal dicarbofunctionalization of polyene macromolecules complements elegant work by Elacqua and Giri describing a Ni-catalysed difunctionalization reaction that assembles a polymer backbone through the reaction of 4-bromostyrene and an aryl coupling partner[25].

Results and discussion

Method development and substrate scope

At the outset, we recognized several pitfalls that could hinder the initial dicarbofunctionalization, including competitive Suzuki–Miyaura two-component cross-coupling[26], Heck arylation[27], over-functionalization, and cyclization side reactions[28–31] (Figure 1D). Dicarbofunctionalization with conformationally flexible cyclic dienes, such as COD, increases the propensity of the catalyst to undergo β-hydride elimination, which would lead to Heck-type byproducts. Prior work on the catalytic dicarbofunctionalization of conformationally constrained systems, such as norbornadiene, has been reported[32,33], but these substrates do not map onto the ethylene/styrene copolymers targeted here. Nevertheless, the bidentate coordination of COD would provide an opportunity to facilitate and control the catalyst through transannular directivity, thereby also limiting the competing undirected over-functionalization of the diene[34]. While olefins have been used as directing groups for various catalytic transformations, transannular olefin directivity has rarely been explored[35–39]. Overall, this approach would achieve an iteroselective reaction in which only one of the two identical alkenes are functionalized.

To reduce this idea to practice, we investigated conditions for diarylation of COD. Under nickel catalysis, we found that using an aryl iodide electrophile, an aryl neopentyl boronic ester nucleophile, the moderately strong sodium methoxide base, and the electron-deficient olefin (EDO) ligand dimethyl fumarate (DMFU) formed the DACOE product (Figure 2A, entry 1). In transition metal catalysed cross-couplings EDO ligands have been shown to facilitate reductive elimination and suppress β-hydride elimination.[40] Both the base and the ligand are essential for desired reactivity (entries 2 & 3). Although a 1:1 ratio of DMFU to nickel catalyst

could be used (entry 4), we found that the reaction to be more reproducible across diverse substrates with 2:1 ligand-to-metal ratio. The method works well with $NiCl_2$(glyme) but also proceeds with $Ni(COD)_2$ (entry 6). However, the air-stable duroquinone (DQ) ligated Ni(0) complex, Ni(COD)(DQ),[41,42] was not active in this specific system (entry 7). Less reactive electrophiles, such as aryl chlorides or aryl bromides, gave low yields (entry 8), whereas changing the nucleophile to an aryl boronic acid only moderately lowered the yield of diarylated product (entry 9). Employing one equivalent of COD (entry 11) provided the desired product in a good yield, but because COD is inexpensive and easy to remove under vacuum, the more valuable aryl iodide was instead used as the limiting reagent. Notably, the reaction gives high yield with a 1:2 electrophile:nucleophile ratio and is low yielding in the inverse scenario (entry 12). Analysis of the product distribution and mass balance show that minor amounts of starting material are converted to the coupling product of either two electrophiles or two nucleophiles on COD. More details on the product distribution are discussed in the Supporting Information Scheme S1 and Table S9.

The scope of the nickel-catalysed 1,2-dicarbofunctionalization of COD was first investigated using structurally equivalent electrophiles and nucleophiles to afford 5,6-homodiaryl cyclooctene monomers (**2a**–**2f**, Figure 2B). Electron-neutral substitution at the *para*- or *meta*- positions of the coupling partners was well tolerated (**2b**, **2c**), but *ortho*-substituents generally hindered product formation (see SI Table S8). Naphthyl reagents gave 80% yield of the desired product (**2d**). When both coupling partners contained electron-withdrawing groups, the desired product was obtained in moderate yields (**2e**, **2f**), whereas coupling partners with strongly electron-donating groups did not provide the desired product. Next, the synthesis of 5,6-heterodiaryl cyclooctene monomers was investigated (**2g**–**2p**). Interestingly, a sterically demanding 1-napthyl electrophile could be appended when coupled in combination with a phenyl nucleophile (**2i**). The desired DACOEs could be obtained with electron-donating or -withdrawing substituents on the electrophilic (**2j**–**2m**) or nucleophilic (**2n**, **2o**) coupling partner. Diverse functional groups, such as nitrile (**2p**), ketone (**2q**), tertiary amide (**2r**), and methyl ester (**2s**), were all tolerated, and switching to $Ni(COD)_2$ as the nickel source gave access to a benzylic alcohol substituent (**2t**). A push–pull system was also successfully synthesized (**2u**). 1,2-Arylalkenylation of the diene was achieved in moderate yields (**2v**, **2x**) using alkenylboronic ester nucleophiles. Finally, when an additional substituent was added to one of the cyclic alkenes, diarylation selectively occurred at the less-hindered C=C bond (**2y**) and heterodiarylation of the same substrate gave a 1:1 ratio of regioisomers (**2z**). The reaction could be performed on larger scale (3.0 or 5.0 mmol), providing sufficient material to explore ROMP of five different monomers. On larger scale, maintaining vigorous mixing through high stir rate was found to be critical for obtaining high yield because the reaction is heterogeneous, and reaction kinetics appear to be mass-transfer limited under standard conditions (see SI for details). The relative stereochemistry of the diarylation was confirmed by the X-ray crystal structure of **2i** as syn (see SI, Figure S30).[43] Several chiral ligands with established utility in nickel catalysis were attempted, but they generally inhibited the reaction or yielded racemic product (see SI); preliminary results showed that stereoinduction could be achieved through use of a chiral boronic ester (vide infra).

Mechanistic studies

The importance of DMFU ligand and the high selectivity for 5,6-diarylation prompted us to investigate the mechanism via density functional theory (DFT) calculations (Figure 3A). The

initial oxidative addition of the aryl iodide is promoted by a DMFU-supported Ni(0) complex (via **TS1**), followed by 1,2-migratory insertion (**TS3**) into one of the equivalent alkenes in COD. Transmetalation with the aryl boronate nucleophile (**TS5**), followed by DMFU-assisted reductive elimination (**TS6**) releases the desired product and regenerates the Ni(0) catalyst. Interestingly, neither coordination of the second COD alkene nor the DMFU ligand is necessary in the 1,2-migratory insertion step, in which the square-planar aryl Ni(II) complex is bound to a κ^2-coordinated boronate anion (**TS3**). Coordination of the strong π-acceptor DMFU during reductive elimination significantly lowers the transition state energy of this step (**TS6**) compared to other reductive elimination pathways[13,44] (*e.g.*, **TS7** and **TS8**). The calculations indicated that the 1,2-migratory insertion releases the COD ring strain[45], making the step exergonic. The low kinetic barriers to the subsequent transmetalation and reductive elimination steps indicate that 1,2-migratory insertion is also irreversible. Therefore, the 1,2-migratory insertion would be enantioselectivity-determining in an asymmetric transformation. The finding that 1,2-migratory insertion is promoted by coordination to the nucleophilic boronate coupling partner (**TS3**), rather than the DMFU ligand or an iodide ligand (**TS4**), is corroborated experimentally by the finding that boronic ester nucleophiles derived from chiral diols provide slight yet significant enantioinduction[11] (Figure 3B; see SI for details). Generally, the six-membered boronic esters provided higher *ee* than five-membered boronic esters. Across the investigated chiral nucleophiles, boronic ester **13a** provided the highest yield and *ee* for the reaction. Control experiments with the corresponding free chiral diols as additives led to low yield or no reaction (see SI, Table S11). The role of transannular directivity for achieving an iteroselective reaction was probed by subjecting COE, which lacks the second olefin, to the reaction conditions. The low yield of the corresponding diarylated product, demonstrate the importance of coordination to the otherwise spectator alkene in the catalytic cycle (Figure 3C). Additional control experiments using either (1*Z*, 3*Z*)-cyclooctadiene (1,3-COD) or DACOE **2a** as substrates yielded trace or no product.

Polymer synthesis

Next, we turned our attention to polymerization of the DACOE monomers. In addition to DACOEs being unexplored in ROMP for generating sequenced materials, the *cis*-arrangement of the substituents was expected to increase the monomer ring strain through torsional interactions. To investigate this hypothesis, ROMP was attempted on 5,6-diphenylcycloocetene **2a** using the 1st generation (**G1**) or 3rd generation (**G3**) Grubbs initiator with a 100:1 ratio of monomer to initiator[46] (M/I). Interestingly, **G1** was unable to initiate the polymerization of **2a**, while **G3** reached 82% conversion after 30 min at room temperature (See SI, Table S12). This is in stark contrast to the parent COE monomer which readily polymerizes with **G1** and reach full conversion within seconds when initiated with **G3**. Optimal reaction conditions for the polymerization were identified by increasing the concentration to 1 M and extending the reaction time to 1 h, which prevented oligomeric byproducts and raised the conversion to 97% (Figure 4A, entry 1).

Control of target molecular weight in cyclooctene systems has traditionally been realized by chain-transfer agents due to the facile chain-transfer and backbiting reactions[17]. In contrast, the polymerization of **2a** yielded targetable molecular weights when the M/I ratios of 200 and 500 were performed (Figure 4B; Table S12, entries 12 & 13). While molecular weight distributions were moderate ($Đ$ = 1.7-1.9) due to chain transfer reactions occurring alongside propagation, this represents an increased level of polymerization control compared to traditional *cis*-cyclooctene derivatives reported in the literature to date.

To test the impact of the steric and electronic properties of the aryl groups on polymerization rates and thermal properties of the resulting materials, four representative DACOE monomers were tested under optimized ROMP conditions, including a monomer with an electron-withdrawing trifluoromethyl group (**2e**), a push-pull system (**2u**), and sterically hindered naphthyl-substituted monomers (**2d** and **2i**) (Figure 4A). All achieved high conversions with targetable molecular weights and moderate dispersities ($Đ$ > 1.6). Interestingly, the rates of polymerization relative to the parent **2a** monomer were slowed by approximately 50%, which suggests that the substituents impact polymerization, despite their remote location on the monomer framework (Figure 4C and 4D). Notably, unsubstituted COE displays much faster polymerization under the same reaction conditions, with full conversion achieved in seconds (Figure 4C). In addition, monomers containing functional groups that could hinder ROMP were explored to understand the limitations of the polymerization reaction. These monomers included **2k**, which bears a thioether group, as well as monomer **2t**, which features a benzyl alcohol. Both monomers showed full conversion by ^{1}H NMR under the standard reaction conditions. However, **P2k** displayed reduced polymerization control (M_n: 26.7 kg/mol, $Đ$: 4.88) due to the coordination of the thioether to the ruthenium center during propagation (Figure S13). Additionally, accurate molecular weight characterization by SEC of alcohol-containing **P2t** was hindered by poor solubility in chloroform after concentration, likely due to extensive interpolymer hydrogen bonding (Figure S14).

To understand the origin of the distinct polymerization rates of COE and DACOE monomers, DFT studies were performed. The calculations indicate that although DACOE (**2a**) is indeed more strained than COE by 3.3 kcal/mol, meaning the former has a greater thermodynamic driving force for ROMP, **2a** requires higher kinetic barriers in both initiation and propagation compared to COE (see SI for details). In the rate-determining retro-[2+2] cycloaddition transition state in propagation (**TS9** and **TS10**), the DACOE moiety adopts a boat-chair conformation. This boat-chair conformer is the most stable for unsubstituted COE while this conformation is destabilized in DACOE (**2a**) because of 1,3-diaxial-type interactions with a pseudoaxial Ph group (see Figure S30 for crystal structure of **2i**). As a result, the boat–chair conformer of **2a** is 3.5 kcal/mol less stable than the half-chair–boat conformer, which is catalytically inactive in ROMP because its C=C bond is shielded[47,48]. Therefore, attenuated reactivity of DACOE compared to COE is attributed to the steric effects of the Ph substituents that destabilize the catalytically active boat–chair conformer of the eight-membered ring.

The thermal properties of the materials synthesized were found to be affected by the encoded aryl substituents. Glass transition temperatures ranged from 58 ºC for diphenyl **P2a** up to 108 ºC for bis-2-naphthyl **P2d**. Given the overall composition of these polymers as sequenced butadiene–styrene–styrene copolymers, this range agrees with the weighted averages of the respective homopolymer glass transition temperatures. Hydrogenation of **P2a** with diimide yielded fully saturated **P2a-H$_2$**, which represents a sequenced copolymer of ethylene and styrene with head-to-head linkages. Despite the lack of long-range stereoregularity, this material was found to be semicrystalline with a melting temperature of 189 ºC (Figure 4A, entry 6). This is significantly higher than alternating ethylene–styrene copolymers prepared through coordination-insertion polymerization with the same composition (T_m = 128 ºC), highlighting the impact of monomer sequence and orientation on polymer properties[49]. These

observations underscore the future potential of fine-tuning this polymer architecture to achieve high-performance materials.

Conclusion

In conclusion we have developed a transannular directed 1,2-dicarbofunctionalization of COD to obtain structurally complex DACOE monomers. ROMP of these monomers generates previously unexplored stereo- and sequence-controlled polymer architectures. Key mechanistic considerations for both catalytic processes were elucidated using DFT calculations and kinetic studies. The presented strategy establishes the utility of modular multi-component reactions to prepare unexplored monomer structures within polymer chemistry and demonstrates how this approach can be leveraged to tune material properties.

Methods

To a 1-dram (4-mL) reaction vial equipped with a magnetic stir bar was added arylboronic neopentylglycol ester (0.4 mmol). The vial and its contents were brought into a glovebox maintained under inert argon or nitrogen atmosphere. To the vial was added NaOMe (14 mg, 0.26 mmol), dimethyl fumarate (8.6 mg, 0.06 mmol), $NiCl_2$(glyme) (6.6 mg, 0.03 mmol) or $Ni(COD)_2$ (8.2 mg, 0.03 mmol), *tert*-butanol (1 mL), 1,5-cyclooctadiene (74 µL, 0.6 mmol), and aryl iodide (0.2 mmol). The vial was sealed with a septum cap, removed from the glovebox, and allowed to stir vigorously (1400–1500 rpm) at room temperature for 24-36 h. The reaction was quenched with 2M HCl (aq.), and the mixture extracted with 50% ether/50% pentanes (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered, concentrated, and purified by preparative thin layer chromatography to afford **2**.

Data Availability

The data that support the findings of this study are available within the paper and its supplementary information files. Experimental procedures, characterization data for all new compounds, and details for DFT calculations can be found in the Supporting Information. Crystallographic data for the structure reported in this Article have been deposited at the Cambridge Crystallographic Data Centre, under deposition numbers CCDC 2294340 (**2i**), copies of the data can be obtained free of charge via https://www.ccdc.cam.ac.uk/structures/.

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Author Contributions Statement

V.T.T., A.K.R., and C.Z.R. performed optimization and evaluated the scope of the nickel-catalyzed 1,2-dicarbofunctionalization reaction. M.X. and E.M.W. carried out polymerization experiments. Y.F. and P.L. carried out computation work. S.R.W. performed kinetic experiments on the nickel-catalysed 1,2-dicarbofunctionalization reaction. V.T.T., P.L., W.R.G., and K.M.E. conceived the project. A.K.R., P.L., W.R.G, and K.M.E. wrote the manuscript with input from all authors. Corresponding Authors: * willgute@gatech.edu, pengliu@pitt.edu, keary@scripps.edu

Competing Interests Statement

The authors declare no competing interests.

Figure Legends/Captions

Fig. 1 | Overview and concept. a, Traditional route: ethylene/styrene copolymerization[5-7]. Common catalysts are Ti^{IV}, Zr^{IV}, or Hf^{IV}. **b**, Emerging small-molecule methodology: Catalytic 1,2-diarylation of alkenes[8-12]. Common catalysts are Pd^{n}, Ni^{n}, or Cu^{n}. **c,** Hypothetical macromolecule methodology: Catalytic 1,2-diarylation of a polyene. **d,** Strategy developed herein to access 1,2-diarylated polymeric structures in a sequence-, regio-, and stereo-defined manner.

Fig. 2 | Reaction optimization and scope for the 5,6-diarylation of COD. a Optimization of diarylation reaction. **b,** Scope and scale-up of diarylation reaction. [a] Reaction conditions using PhI (0.1 mmol), 0.2 M *t*-BuOH. [b] Percentages represent ^{1}H NMR spectroscopic yields using CH_2Br_2 as internal standard. n.d. = not detected. [c] Parentheses represent isolated yield. [d] Reactions performed on 0.2 mmol scale unless stated otherwise and percentages represent isolated yields (see SI for details). The products are formed as a single diastereomer. [e] Reactions performed using $Ni(COD)_2$ instead of $NiCl_2$(glyme). [f] Reaction performed using (1*Z*,5*Z*)-1-methylcycloocta-1,5-diene **1b** instead of **1a**. DMFU, dimethylfumarate; Ar, aryl; Ph, phenyl; *t*-Bu, *tert*-butyl; Me, methyl; COD, 1,5-cyclooctadiene; r.t., room temperature; DQ, duroquinone; r.r., regioisomeric ratio.

Fig. 3 | Mechanistic studies of the Ni-catalysed diarylation of 1,5-cyclooctadiene. a, Reaction energy profile of the Ni-catalysed 1,5-cyclooctadiene diarylation. **b**, Enantioinduction by use of chiral boronic esters. **c**, Control experiments using standard conditions: ~~defined in Fig. 2a~~ aryl iodide (1 equiv), arylboronic neopentylglycol ester (2 equiv), $NiCl_2$(glyme) (15 mol%), dimethyl fumarate (30 mol%), NaOMe (1.3 equiv), *tert*-butanol (0.1 M), alkene or diene (3 equiv). [a] Reactions performed on 0.1 mmol scale. Percentages represent yields determined by ^{1}H NMR spectroscopy using CH_2Br_2 as internal standard. [b] The e.e. is determined by chiral 2D supercritical fluid chromatography, SFC, of the crude reaction mixture. [c] Mixture of regioisomers. DACOE, diarylated cyclooctene; DMFU, dimethyl fumarate; *t*-Bu, *tert*-butyl; Me, methyl; Ph, phenyl; COD, 1,5-cyclooctadiene; r.t., room temperature; n.d., not detected; e.e., enantiomeric excess.

Fig. 4 | Ring-opening metathesis polymerization of diarylcyclooctene. a, Scope of diaryl cyclooctene (DACOE) monomers in ring-opening metathesis polymerization (ROMP). **b**, Overlaid experimental SEC data of **P2a** with varying degree of polymerization ~~Targeted molecular weights of **P2a**~~. **c**, Kinetic data for the conversion of monomers **2a**, **2d**, **2e**, **2i**, **2u**, or cyclooctene (COE) vs time. **d**, Rate constants for the polymerizations. **e**, Density functional theory (DFT) studies for propagation in ROMP comparing COE with DACOE. [a]Relative stereochemistry is shown that does not imply long range tacticity. [b] Number-average molecular weights (M_n) and dispersities ($Đ$) of purified polymer products determined by size exclusion chromatography (SEC) using polystyrene standards. [c] Temperature at 5% mass loss. [d] **P2a-H$_2$** was obtained from backbone reduction of **P2a** (See SI Figure S16 for details). [e] Melting temperature. EVE, ethyl vinylether; DCM, dichloromethane; Ar, aryl; py, pyridine; SIMes, 1,3-Bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene.

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