Tandem Imine Formation and Alkyne Metathesis Enabled by Catalyst Choice

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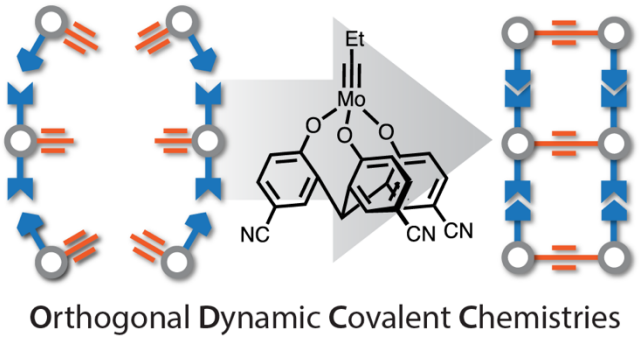
Supporting Information Placeholder



ABSTRACT: Three-rung molecular ladder **8** was prepared in one pot via tandem imine condensation and alkyne metathesis. Catalyst **VI** is demonstrated to successfully engender the metathesis of imine-bearing substrate **7** while catalyst **III** does not. The susceptibility of catalyst **VI** to deactivation by hydrolysis and ligand exchange is demonstrated. Assembly and disassembly of ladder **8** in one pot was demonstrated in the presence and absence of a Lewis acid catalyst.

INTRODUCTION

In the last three decades, dynamic covalent chemistry (DCC) has become a highly efficient tool for the synthesis of novel functional materials and complex molecular architectures such as cages,[1] macrocycles,[2] and frameworks.[3,4] Dynamic covalent synthesis is often a cyclooligomerization process that successfully produces a single, discrete product in high yield.[5] In part, success is achieved by virtue of dynamic covalent bonds that are reversible and therefore capable of thermodynamic error correction.[6] Typically, DCC syntheses rely on a single type of chemical transformation leading to highly symmetric architectures containing only one type of functionality. By contrast, orthogonal DCC (ODCC) offers great potential to construct molecular architectures with low symmetry and well-defined chemical functionalities.[7,8] However, explorations of ODCC have been hindered by the lack of functional group tolerance and chemical incompatibilities of multi-component dynamic exchange reactions.

Alkyne metathesis (AM) in particular, owing to the sensitivity of typical operative metal carbyne complexes to poisoning by air, water, and polar moieties, suffers from poor tolerance to even relatively mildly Lewis basic functional groups. Recently, the Fürstner,[9] Lee,[10] and Zhang[11–14] groups made considerable AM catalyst advances using tripodal ligand frameworks (Chart 1). Through the chelating effect, these scaffolds engender molybdenum carbyne species with improved robustness to hydrolysis and deleterious coordination to the metal center.[9,15] These studies have yielded a library of catalysts with impressive functional group tolerance and activity, which we posit will enable AM to operate in parallel with other dynamic covalent reactions. Recently, we reported the synthesis of a molecular cage *via* sequential imine condensation and AM using a canopy catalyst developed by Zhang *et al.* (Fig. 1).[16] However, the sensitivity of the metathesis catalyst to poisoning by unreacted amine groups mandated extensive purification between steps. Because one of the unique advantages of DCC is its operational simplicity, it is desirable to avoid such purifications whenever possible. The development of ODCC for AM would streamline procedures for synthetically challenging multifunctional architectures.

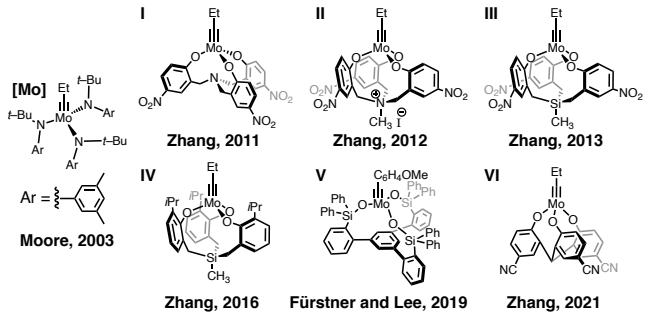


Chart 1. Representative alkyne metathesis catalysts generated from precursor **[Mo]** and tripodal ligand scaffolds.

Another rarely explored advantage of ODCC is the ability to leverage differences in reaction rates, or orders of addition, to achieve preorganization in self-assembly. This general strategy is used in nature to direct protein folding: fast, dynamic

exchange processes (e.g. H-bond exchange) are often coupled with slower dynamic reactions (e.g. disulfide exchange) to lock proteins into their native tertiary structures.[17] Analogous reaction strategies have been used in the synthesis of structures like hydrogels[18] and nanowires,[19] as well as in the resolution of complex dynamic libraries,[20,21] but rarely have these strategies been explored in the dynamic covalent synthesis of discrete, well-controlled molecular architectures. AM, in particular, is well-suited for this strategy, as it is considerably slower than many common DCC reactions.[6] However, its kinetic sensitivity is underutilized in DCC syntheses.[22] Development of ODCC synthetic strategies involving AM might therefore also allow access to its underexplored kinetic manifold.

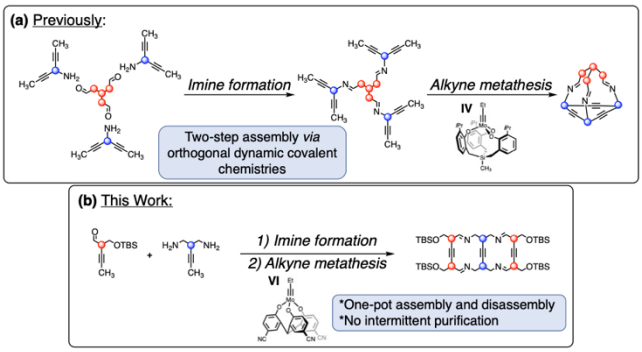


Figure 1. Developments in AM ODCC. (a) A molecular cage prepared *via* sequential orthogonal imine formation and alkyne metathesis. Reprinted from reference 16. Copyright 2019, Royal Society of Chemistry. (b) A molecular ladder prepared *via* one-pot ODCC without intermittent isolation and purification.

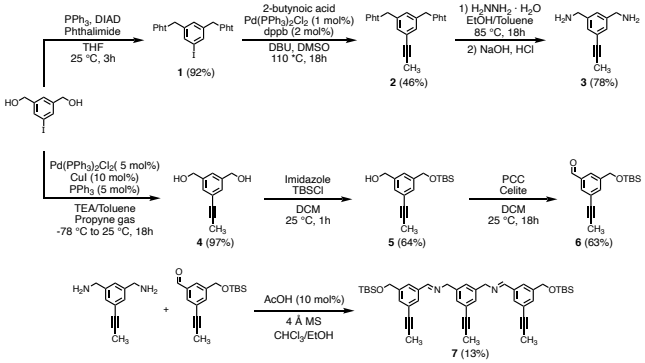
To these ends, we sought to investigate the cross-reactivity of AM and imine formation and to develop protocols for one-pot syntheses of molecular structures *via* AM ODCC. Herein, we report the first example of AM operating in the same pot as another dynamic covalent reaction applied to the synthesis of a three-rung molecular ladder.

RESULTS AND DISCUSSION

Imine formation was selected as the orthogonal complement to AM because it is relatively well established and amenable to a variety of functional groups and reaction conditions.[23] We reasoned that 5 Å molecular sieves, included in AM reactions for removal of the 2-butyne byproduct,[24,25] might also effectively remove condensate generated by imine formation. Furthermore, molecular sieves have been shown to catalyze imine formation via redistribution of adventitious acid in reaction media.[26] Thus, we anticipated that imine exchange would likely tolerate AM reaction conditions, while the sensitivity of AM catalysts might create challenges for one-pot ODCC. Specifically, we envisioned that imine or primary amine functionalities might poison the catalyst, as would hydrolyis by water generated from condensation reactions.

We began our study by investigating the efficacy of two different AM canopy catalysts in the assembly of an imine-bearing 3-rung molecular ladder. Precursor **7**, a single strand of ladder **8**, was synthesized from diamine **3** and aldehyde **6** (Scheme 1). Imine linkages form the strand segment with alkyne rungs as pendant groups. Ladder assembly was attempted using catalyst **III** or **VI**, generated from the corresponding ligand scaffold (**L-III** or **L-VI**) and molybdenum-trisamide alkylidyne precatalyst **[Mo]**. High (30 mol%) catalyst loadings were used to ensure thermodynamic error correction. The resulting mixture was heated at 40 °C for 18 h, then analyzed by MALDI-MS and size exclusion chromatography (SEC). The mass spectrum of the reaction mixture containing catalyst **III** showed only low molecular weight peaks, indicating that cyclooligomerization via AM likely did not occur (Fig. S1a[†]). By contrast, the mass spectrum of the reaction containing catalyst **VI** showed a single peak corresponding to the target molecular ladder **8** (Fig. 2 and S1b[†]). SEC analysis of the reaction mixture using catalyst **VI** also showed conversion to a higher molecular weight species, presumed to be ladder **8**. A high molecular weight tail is present in the metathesis reaction mixtures.

Scheme 1. Synthesis of ladder precursor **7** from diamine **3** and aldehyde **6**.



From these results, we concluded that the reportedly more active and robust catalyst **VI** can achieve AM of imine-bearing species, while the silyl analog **III** cannot. Independently, Zhang, Fürstner, and Lee have suggested that the differences in activity of these canopy catalysts may arise from ligand flexibility, though these effects are not yet completely understood.[12,27,28] It has been suggested that the inability of ancillary ligands to distort limits catalyst geometries that contribute to the formation off-pathway intermediates. It is possible that the flexibility of ligand **L-III** also negates some of the stabilizing effects imparted by its "canopy" design, such as tightly blocking active binding sites. This notion is supported by the ability of the more rigid analog **IV** to catalyze the metathesis of imine-bearing substrates,[16] although these ligands show drastically different sensitivities to steric and electronic effects and therefore defy direct comparison. This discrepancy will require a more nuanced follow-up study in the future.

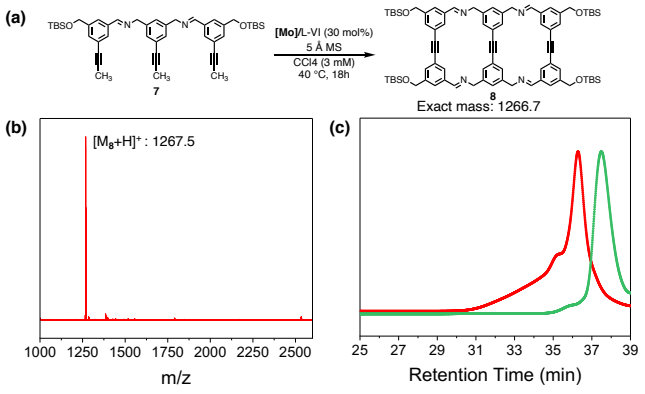


Figure 2. MALDI-TOF-MS and SEC results of the dimerization of strand **7** to ladder **8**. a) Reaction conditions. b) MALDI-MS mass spectrum of the reaction mixture. Expected exact mass $[M_8 + H]^+$

= 1267.7 g mol^{-1}. All MALDI-MS data were collected in reflectron positive ion mode using a DCTB matrix. c) SEC chromatograms comparing precursor **7** (green) and the metathesis reaction mixture (red).

To determine whether metathesis operates in parallel with imine formation, we next attempted the synthesis of **8** via simultaneous addition of all reaction components. Precursors **3** and **6**, in a molar ratio of 1:2.2 to avoid excess of primary amine, were combined with a solution of preactivated **VI** in CCl_4 and added to a slurry of 5 Å MS in CCl_4. MALDI-MS characterization revealed primarily low molecular weight species as well as a trace amount of **8** and some metathesis products (Fig. S2). The absence of high molecular weight species from the spectrum suggests incomplete AM cyclooligomerization, though the presence of the peak corresponding to **8** indicates some catalytic activity. We reasoned that the primary amine groups of **3** deactivated the catalyst, stifling metathesis activity. This explanation is consistent with previous reports of catalyst deactivation by basic amines.[29]

To circumvent poisoning of the catalyst, a pre-stir strategy was employed. When diamine **3** and aldehyde **6** (1:2.2 ratio in CCl_4) were allowed to react overnight prior to addition of preactivated catalyst **VI**, the product distribution shifted to favor the target ladder **8**, as indicated by MALDI-MS (Fig. 3). In contrast to the simultaneous addition experiment, metathesis appears to proceed smoothly when all amine groups are first converted to the corresponding imine. This result supports the notion that AM operates orthogonally to imine formation in one pot and further validates our hypothesis that self-assembly *via* parallel AM and imine formation is stymied by residual amine. The apparent abundance of the in-register molecular ladder (the putative the thermodynamic product) in the product distribution also suggests that AM is under thermodynamic control under the reaction conditions.[30]

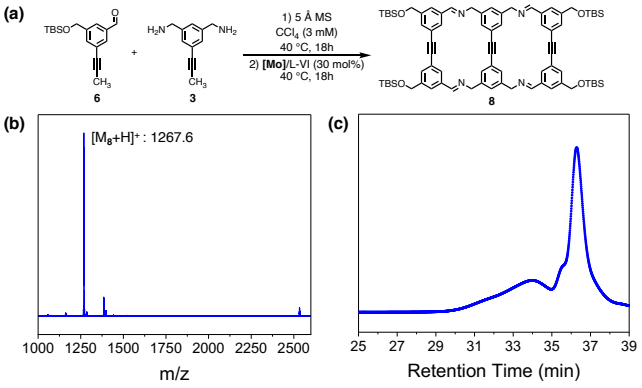


Figure 3. Characterization of the reaction mixture from the pre-stir experiment. a) Reaction conditions. b) MALDI-MS mass spectrum of the reaction mixture. c) SEC chromatogram of the reaction mixture. We reason that the broad, high molecular weight shoulder is from longer, out of register oligomers of **7**.

With a synthetic route to **8** established, we next investigated the necessity of molecular sieves in the reaction. Given the robustness of canopy-type catalysts to hydrolysis,[9] we reasoned that catalyst **VI** might tolerate water produced as a result of imine formation. The activity of catalyst **VI** in the absence of molecular sieves was previously demonstrated by Zhang and coworkers, albeit only over short timescales and in solvents highly immiscible with water.[13] We feared that in a molar excess of water, and on the timescales required for cyclooligomerization, hydrolytic decomposition of the catalyst would impede error correction. As predicted, metathesis of both strand **7** and pre-stirred **3** and **6** under open air conditions failed. SEC traces of both reaction mixtures revealed only strand **7**, indicating that metathesis did not occur (Fig. 4). To investigate whether the catalytic inactivity could have been the result of poisoning by adventitious water, reactions were also run in an inert atmosphere under dynamic vacuum to remove 2-butyne. Conversion to ladder **8** was achieved for strand **7** but not for a pre-stirred mixture of **3** and **6**, suggesting that molecular sieves act not only as efficient scavengers of 2-butyne, but also of moisture produced during the reaction. These results also demonstrate that, despite improved stability of canopy catalysts, even robust species such as **VI** are susceptible to hydrolysis.

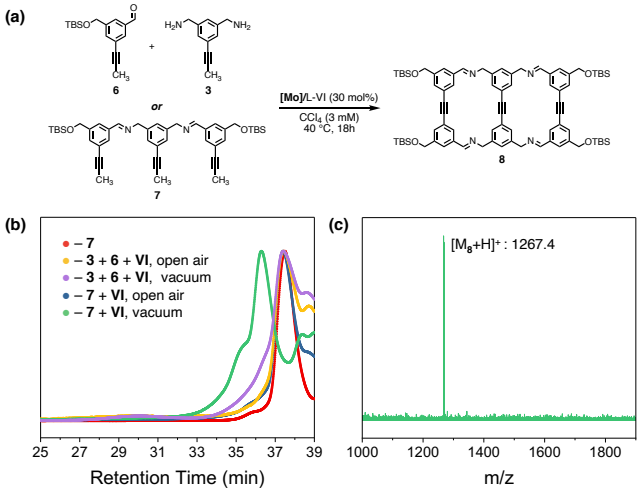


Figure 4. Metathesis of strand **7** or precursors **3** and **6** in the absence of molecular sieves. When **7** is subjected to metathesis under dynamic vacuum conditions, ladder **8** is generated. By contrast, when **7** is generated *in situ* by reaction of **3** and **6**, or when the reaction takes place in open air, metathesis products are not observed. These results suggest that the catalyst is susceptible to deactivation by water. (a) SEC traces of reaction mixtures run under open air or dynamic vacuum conditions. The trace of strand **7** is included for reference. (b) MALDI mass spectrum of the metathesis reaction mixture of strand **7** under dynamic vacuum conditions.

Given the success of these preliminary experiments, we next explored the effects of a Lewis acid catalyst on cross-reactivity. Many applications of imine exchange DCC rely on a Lewis acid catalyst such as $Sc(OTf)_3$ not only for acceleration of transimination, but also for *in-situ* deprotection of acetals.[31] Ideally, AM would tolerate these conditions, though ligand exchange between the Lewis acidic Sc(III) and Mo(VI) metal centers could threaten metathesis activity. Metathesis of **7** with 40 mol% $Sc(OTf)_3$ yielded a multitude of products, as indicated by a broad SEC trace. Multiple peaks were observed by MALDI-MS with masses corresponding to out-of-register oligomers of **7** (Fig. 6b and c). This misregistration of ladder precursors is indicative of an inability of the metathesis system to "error correct," since products containing fewer constituent building blocks are favored over larger oligomers.[30,32,33] Moreover, many of the out-of-register species bear propyne functional groups, suggesting catalyst deactivation occurs on a competitive timescale with cyclooligomerization. When the reaction mixture was resubjected to metathesis in the absence of $Sc(OTf)_3$, only ladder **8** was observed by MALDI-MS and SEC (Fig. 5). The apparent error-correction of out-of-register species to **8** further

supports our assignment of the in-register ladder as the thermodynamic product of metathesis, as well as our hypothesis that $Sc(OTf)_3$ inhibits metathesis.

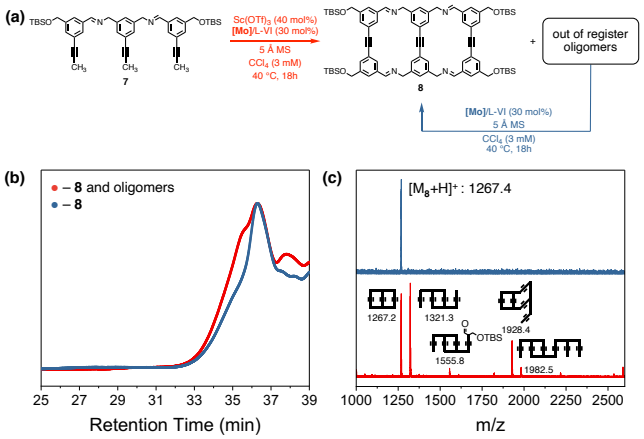


Figure 5. Metathesis of ladder precursor **7** in the presence of $Sc(OTf)_3$. (a) Reaction conditions. When **7** is subjected to metathesis in the presence of $Sc(OTf)_3$, high molecular weight oligomers are observed. When the reaction mixture is then resubjected to metathesis, only ladder **8** is observed. (b) SEC chromatograms of the reaction mixture before (red) and after (blue) error-correction. (c) MALDI mass spectra of the assembly reaction mixtures before (red) and after (blue) resubjecting to metathesis. Schematic representations of ladder **8** and out-of-register oligomers generated from metathesis in the presence of $Sc(OTf)_3$ are shown next to the corresponding mass peaks.

To further explore the possible antagonistic effects of Sc(III) on metathesis, we next attempted a one-pot synthesis of **8** from its constituent aldehyde and amine building blocks. Intriguingly, sequential reaction of **3** and **6** *via* $Sc(OTf)_3$-mediated imine formation followed by AM yielded a different product distribution than previous self-assembly trials. In addition to ladder **8**, MALDI-MS revealed a high molecular weight species tentatively assigned to structure **10**, identified as the cyclic tetramer of ladder precursor **7** (Fig. 6a and b). SEC analysis further confirmed the shift in product distribution, as well as the presence of low molecular weight species potentially indicative of incomplete assembly of precursor **7**. Generally, under acidic conditions, the rate of imine formation and hydrolysis is fast and favors the hydrolyzed amine and aldehyde products.[34] Thus, it is possible that in the presence of the Sc(III) catalyst, transimination occurs in parallel with AM, leading to partial deactivation of the metathesis catalyst by the primary amine as well as $Sc(OTf)_3$.

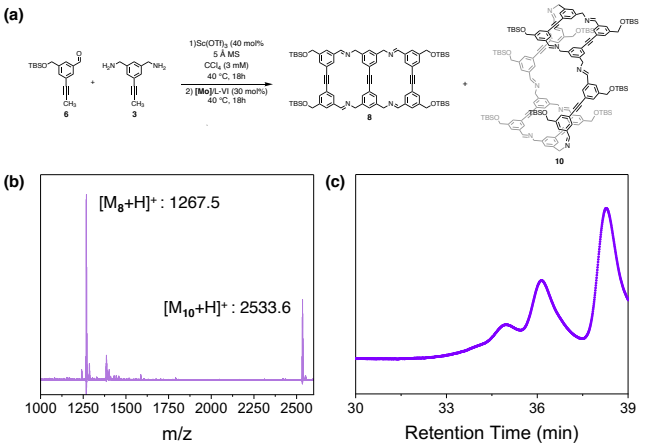


Figure 6. Assembly of ladder **8** in the presence of a Lewis Acid catalyst. (a) Reaction conditions and the proposed structure of **10**. (b) MALDI-MS mass spectrum of the assembly reaction mixture. (c) SEC chromatogram of the reaction mixture. The presence of both high and low molecular weight byproducts indicates potential strand misregistration *via* AM. Expected mass $[M_{10}^{\bullet}]^+$ = 2533.3 g mol^{-1}.

The presence of mass peaks corresponding to **10** in earlier assembly experiments also suggests that this structure may represent a particularly stable kinetic trap for this system, and thus might have error-corrected to **8** at higher temperatures, catalyst loadings, or longer reaction times.[35] The absence of other oligomers and out-of-register species in the mass spectrum further support this notion and suggests only limited cross-reactivity between the catalysts.

In ODCC with multitopic precursors, access to a particular product distribution may require continuous dynamic exchange for multiple parallel reactions. Thus, we next turned our attention to the nature of imine exchange in our system. Previous studies have demonstrated that amine-imine interchange proceeds even in the absence of an acid catalyst.[36] Therefore, we suspected that imine exchange occurs under our reaction conditions. To probe the equilibrium and dynamic nature of the system, a stationary state perturbation experiment was performed. Precursors **3** and **6** (1:2 ratio) were allowed to react *via* sequential imine formation and AM, either in the presence or absence of $Sc(OTf)_3$, to generate **8**. Then, the reaction mixtures were charged with 30 equiv of methylamine and stirred at RT for 18 h. Analysis by ^{1}H NMR spectroscopy revealed an abundance of ladder disassembly product **9a** and a disappearance of peaks corresponding to metathesis products in both cases (Fig. 7 and S8-11[†]). Together, these results indicate that imine exchange is dynamic under orthogonal reaction conditions, even in the absence of a molecular Brønsted or Lewis acid catalyst.

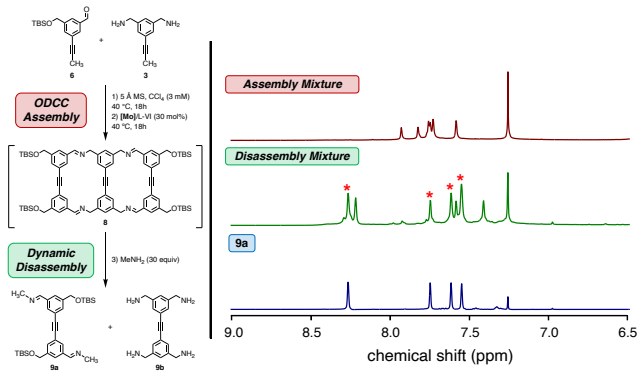


Figure 7. Disassembly of ladder **8** proceeds even in the absence of a molecular acid catalyst, indicating amine/imine exchange is dynamic. Left: ODCC assembly and disassembly of ladder **8** *via* dynamic imine exchange. Right: Comparison of ^{1}H NMR spectra of the assembly mixture (top), the disassembly mixture (middle), and the independently synthesized imine **9a** (bottom). The reaction mixtures were filtered through basic alumina and concentrated to dryness. Peak labels correspond to the disassembly product **9a**. NMR performed in $CDCl_3$, 500 MHz, 25 °C.

The measured success of these experiments indicates the robustness of catalyst **VI** to catalytic imine exchange conditions, as well as the potential for self-assembly by catalytic ODCC using multitopic imine and alkyne-bearing precursors. However, the apparent sensitivity of even the most stable canopy-type catalyst to water and primary amines poses a challenge for future synthetic applications of AM in ODCC. Jia and coworkers recently reported novel Re(V) AM catalysts that are stable to air and moisture as well as polar and protic moieties.[37,38] These systems, which have been demonstrated to promote catalytic metathesis in wet solvent, hold tremendous promise for the evolution of AM in ODCC systems and will require further investigation in the future.

CONCLUSIONS

In summary, a one-pot ODCC approach to imine exchange and AM has been developed. The efficacy of the sequential reaction strategy was demonstrated in the synthesis of a 3-rung molecular ladder, as well as its disassembly by transimination in the presence and absence of a Lewis acid catalyst. The protocols developed herein open the door to facile syntheses of well-defined molecular architectures bearing both imine and ethynylene functionalities, expanding the scope of DCC further to increasingly complex materials and chemical systems.

EXPERIMENTAL SECTION

General Information. All reactions were performed in oven (c.a. 165 ^{o}C) or flame-dried glassware under an atmosphere of dry argon or nitrogen unless otherwise noted. All solvents used were either anhydrous commercial grade (Aldrich/Fisher) or purified by a solvent purification system unless otherwise noted. All alkyne metathesis reactions were conducted in an argon- filled glovebox in oven-dried glassware, using anhydrous (Aldrich), argon-degassed solvents. All reagents were purchased from commercial sources and used without further purification. Molybdenum(VI) propylidyne precatalyst **[Mo]**, (5-iodo-1,3-phenylene)dimethanol, and ligand **L-III** were each prepared according to published literature procedures.[11,39,40] Triphenol ligand **L-VI** was generously gifted to us by the Zhang group and used as received. Molecular sieves (5 Å powdered) were dried in a vacuum oven at 200 ^{o}C for 5 days prior to use in alkyne metathesis reactions.[25] Chromatographic purifications were conducted via MPLC on a Biotage Isolera 1 using Silicycle SiliaSep cartridges (230-400 mesh, 40-63 μm). Column separation conditions are reported in column volumes (CV) of gradient solvent mixtures. ^{1}H and ^{13}C nuclear magnetic resonance spectra (NMR, 500 MHz) were recorded at room temperature (298 K) and chemical shifts were referenced to the residual solvent peak. Structural assignments were made with additional information from gCOSY, gHSQC, and gHMBC experiments. Elemental analysis was obtained through the Microanalysis Laboratory, School of Chemical Sciences, University of Illinois using an Exeter Analytical CE 440 Analyzer. Mass spectra were obtained through the Mass Spectrometry Facility, School of Chemical Sciences, University of Illinois. High resolution electron impact (EI) mass spectra were obtained on a Micromass 70-VSE TOF spectrometer and electrospray ionization (ESI) mass spectra were obtained on a Waters Synapt G2-Si TOF spectrometer. Matrix-assisted laser desorption/ionization (MALDI) mass spectrometry was performed on a Bruker Daltonics UltrafleXtreme MALDI using DCTB matrix. MALDI spectra were plotted using OriginPro 2018 software. ^{1}H and ^{13}C NMR were processed using MestReNova software v12.0.4-22023. Reported yields are of isolated material which in some cases were corrected for trace residual solvent.

Synthesis and Characterization of Compounds.

2,2'-(2,2'-(5-iodo-1,3-phenylene)bis(acetyl))dibenzoic acid (**1**). In a 250 mL round bottom flask charged with stir bar, triphenylphosphine (4.75 g, 18.2 mmol, 2.4 equiv) and (5-iodo-1,3-phenylene)dimethanol (2.00 g, 7.57 mmol, 1 equiv) were combined and dissolved in THF (75 mL). Diisopropyl azodicarboxylate (3.67 g, 18.2 mmol, 2.4 equiv) was added dropwise and the mixture was stirred for 3 h at room temperature. After adding water and stirring briefly, the white precipitate was collected by filtration and washed thoroughly with water (ca. 100 mL) and dried under vacuum to give the product as a white powder (3.64 g, 92% yield). The ^{1}H and ^{13}C NMR spectra corresponded to the values reported in literature for this compound.[41] m.p. = 245–247 ºC; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.85 (dd, J = 5.5, 3.1 Hz, 4H), 7.72 (dd, J = 5.4, 3.2 Hz, 4H), 7.64 (d, J = 1.4 Hz, 2H), 7.47 (s, 1H), 4.76 (s, 4H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 168.0, 138. 9, 136.9, 134.3, 132.2, 128. 5, 123.7, 94.9, 77.4, 77.2, 76.9, 40.8.

2,2'-((5-(prop-1-yn-1-yl)-1,3-phenylene)bis(methylene))bis(isoindoline-1,3-dione) (**2**). In a 100 mL Schlenk tube charged with stir bar, iodide **7** (3.42 g, 6.98 mmol, 1 equiv), $Pd(PPh_3)_2Cl_2$ (49 mg, 0.070 mmol, 1 mol %), 1,4-(bisdiphenylphosphino)butane (60 mg, 0.14 mmol, 2 mol%), and 2-butynoic acid (733 mg, 8.72 mmol, 1.25 equiv) were dissolved in DMSO. To the mixture was added DBU (3.23 g, 20.9 mmol, 3 equiv), then the tube was sealed and the reaction was stirred at 110 °C overnight in an oil bath. After cooling to room temperature, saturated aqueous NH_4Cl was added. The layers were then separated and the aqueous layer was extracted 3x with DCM. The combined organic layers were washed with water and brine, dried with Na_2SO_4, and filtered over celite. The reaction mixture was purified *via* silica gel chromatography using DCM to afford **2** as a yellow solid (1.38 g, 46% yield). m.p. = 240–243 ºC; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.85 (dd, J = 5.4, 3.1 Hz, 4H), 7.71 (dd, J = 5.5, 3.1 Hz, 4H), 7.41 (s, 1H), 7.31 (s, 2H), 4.78 (s, 4H), 1.98 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 168.0, 137.0, 134.2, 132.2, 130.9, 128.1, 125.1,

123.6, 86.8, 77.4, 77.2, 76.9, 41.2, 4.4; HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{25}H_{20}N_2O_4Na$ 435.1321; Found 435.1335.

(5-(prop-1-yn-1-yl)-1,3-phenylene)dimethanamine (**3**). In a three-neck 500 mL round bottom flask charged with stir bar and jacketed condenser, bis-phthalimide **2** (1.34 g, 3.08 mmol, 1 equiv) was dissolved in ethanol (100 mL) and toluene (50 mL). The reaction mixture was then charged with hydrazine hydrate (926 mg, 18.5 mmol, 6 equiv) and stirred at 85 °C overnight in an oil bath. After cooling to room temperature, the mixture was concentrated and redissolved in 10 % NaOH. The aqueous layer was extracted 3x with $CHCl_3$ and separated. The combined organic layers were then acidified with 10% HCl and the aqueous layer was collected, neutralized to pH ~9 with 1M HCl, and extracted 5x with $CHCl_3$. The mixture was then dried over Na_2SO_4, filtered over celite, and concentrated to afford **3** as a yellow oil (420 mg, 78% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.21 (s, 2H), 7.17 (s, 1H), 3.81 (s, 4H), 2.03 (s, 3H), 1.38 (s, 4H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 143.8, 128. 7, 125.3, 124.4, 85.8, 79.8, 77.4, 77.2, 76.9, 46.3, 4.4; HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{11}H_{15}N_2$ 175.1235; Found 175.1234.

(5-(prop-1-yn-1-yl)-1,3-phenylene)dimethanol (**4**). In a 500 mL round bottom flask charged with stir bar, 5-iodo-1,3-phenylene)dimethanol (8.3 g, 31 mmol, 1 equiv), $Pd(PPh_3)_2Cl_2$ (1.1 g, 1.6 mmol, 5 mol %), CuI (600 mg, 3.14 mmol, 10 mol%), and triphenylphosphine (412 mg, 1.57 mmol, 5 mol%) were dissolved in triethylamine (100 mL) and toluene (100 mL). The reaction mixture was then cooled to -78 ^{o}C using a dry ice/acetone bath and propyne gas was added to the reaction mixture. (**Note:** excess propyne was used. The propyne gas was bubbled through the mixture and into the headspace of the reaction from a small lecture bottle via an 18-gauge metal needle with an argon balloon as pressure release. The gas was added in approximately 4 ten-second bursts.) The reaction mixture was allowed to stir at -78 ^{o}C for 5 minutes after which the bath was removed, and the mixture was stirred at RT for 24 hours. The black reaction mixture was then filtered through a short plug of silica gel with Et_2O and concentrated directly onto celite. The reaction was purified *via* silica gel flash chromatography with a 10 CV gradient of 0-80% EtOAc/Hexane (CV = column volume) to afford **4** as an off-white solid (5.37g, 97% yield). m.p. = 86–90 ºC. ^{1}H NMR (500 MHz, Acetone-d_6): δ 7.28 (s, 1H), 7.24 (s, 2H), 4.59 (d, J = 6.4 Hz, 4H), 4.24 (t, J = 5.8 Hz, 2H), 2.01 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, Acetone-d_6): δ 203.2, 140.6, 125.7, 121.9, 121.6, 82.8, 77.6, 61.1, 27.3, 27.1, 27.0, 26.8, 26.7, 26.5, 26.4, 0.9; HRMS (EI+) m/z: $[M^•]^+$ Calcd for $C_{11}H_{12}O_2$ 176. 0837; Found 176.0840.

(3-(((*tert*-butyldimethylsilyl)oxy)methyl)-5-(prop-1-yn-1-yl)phenyl)methanol (**5**). In a two-neck 100 mL round bottom flask charged with stir bar, diol **4** (717 mg, 4.07 mmol, 1 equiv) was added to a solution of imidazole (277 mg, 4.07 mmol, 1 equiv) in DCM (40 mL). The reaction mixture was charged with TBSCl (624 mg, 4.14 mmol, 1.01 equiv) and allowed to stir at room temperature. After 1 h, the reaction slurry was filtered over celite and the filtrate was concentrated onto silica. The reaction mixture was purified *via* silica gel flash chromatography using a gradient of 0-10-30-60% EtOAc/Hexanes to afford **5** as a colorless oil which solidified into a white solid upon further drying (752 mg, 64% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.97 (s, 1H), 7.76 (s, 1H), 6.63 (s, 1H), 7.58 (s, 1H), 4.75 (s, 2H), 2.07 (s, 3H), 0.95 (s, 9H), 0.11 (s, 6H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 142.0, 141.1, 128.7, 128.5, 124.3, 124.1, 85.9, 79.8, 77.4, 77.2, 76.9, 65.2, 64.7, 26.1, 18.6, 4.5, -5.1; HRMS (EI+) m/z: $[M-H^-]^+$ Calcd for $C_{17}H_{25}O_2Si$ 289.1624; Found 289.1634.

3-(((tert-butyldimethylsilyl)oxy)methyl)-5-(prop-1-yn-1-yl)benzaldehyde (**6**). In a 50 mL round bottom flask charged with stir bar, alcohol **5** (877 mg, 3.02 mmol, 1 equiv), PCC (976 mg, 4.53 mmol, 1.5 equiv), and celite (1.5 g) were combined in dry DCM (14 mL). The reaction was stirred overnight at room temperature, then passed over a short silica pad with DCM as eluent. The filtrate was further purified *via* flash column chromatography using a gradient of 0-10% EtOAc/Hexanes to afford **6** as a colorless oil (545 mg, 63% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.97 (s, 1H), 7.76 (s, 1H), 7.73 (s, 1H), 7.58 (s, 1H), 4.75 (s, 2H), 2.07 (s, 3H), 0.95 (s, 9H), 0.11 (s, 6H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 191.8, 142.7, 136.4, 134.6, 131.6, 125.8, 125.1, 87.4, 78.6, 77.3, 77.0, 76.8, 64.0, 25.9, 18.4, 4.4, -5.3; HRMS (EI+) m/z: $[M^•]^+$ Calcd for $C_{17}H_{24}O_2Si$ 288.1546; Found 288.1551.

(1E,1'E)-N,N'-((5-(prop-1-yn-1-yl)-1,3-phenylene)bis(methylene))bis(1-(3-(((tert-butyldimethylsilyl)oxy)methyl)-5-(prop-1-yn-1-yl)phenyl)methanimine) (**7**). In a 2-dram vial charged with magnetic stir bar and 4 Å molecular sieves, diamine **3** (100 mg, 0.57 mmol, 1 equiv) and aldehyde **4** (480 mg, 1.66 mmol, 2.9 equiv) were dissolved in $CHCl_3$ (3 mL) and EtOH (3 mL). Acetic acid (34 µL) was added and the mixture was allowed to stir overnight at 55 °C. After cooling to room temperature, the mixture was diluted with $CHCl_3$ and filtered. The organic layer was washed with methanol and concentrated to afford a colorless oil. The residue, which contained residual aldehyde **4**, was further purified by column chromatography using 1:9 triethylamine/hexanes as eluent to afford **7** as a colorless oil (54 mg, 13% yield). The Note: NMR indicates the presence of residual **4**. The purity of **7** was determined to be 90% by ^{1}H NMR. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.32 (s, 2H), 7.67 (s, 2H), 7.63 (s, 2H), 7.43 (s, 2H), 7.21 (s, 1H), 4.76 (s, 4H), 4.72 (s, 4H), 2.05 (s, 6H), 2.03 (s, 3H), 0.95 (s, 18H), 0.10 (s, 12H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 161.7, 142.2, 139.7, 136.2, 134.8, 131.4, 130.3, 129.8, 127.1, 125.0, 124.6, 86.35, 85. 9, 79.9, 79.5, 77.4, 77.2, 76.9, 64.8, 64.5, 29.9, 26.1, 18.6, 4.5, -5.1; HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{45}H_{59}N_2O_2Si_2$ 715.4115; Found 715.4109; Anal. Calcd for $C_{45}H_{58}N_2O_2Si_2$: C, 75.58; H, 8.17; N, 3.92. Found: C, 75.61; H, 8.26; N, 3.81.

General Procedure for Ladder Assembly from 7. In an argon-filled glovebox, a solution of **7** (10 mg, 14 µmol, 1 equiv) was dissolved in a slurry of 5 Å molecular sieves (120 mg) in CCl_4 (1 mL). In a separate vial, precatalyst **[Mo]** (2.8 mg, 4.2 µmol, 30 mol % relative to **7**) and either ligand L-III or L-VI (each 1.5 mg, 4.2 µmol, 1 equiv relative to **[Mo]**) were combined in 3.6 mL CCl_4 and stirred at 25 or 70 °C, respectively, for 10 minutes in a heating block. The reactant and catalyst mixtures were then combined and stirred overnight at 40 °C. After cooling to room temperature, the mixture was filtered over a short pad of neutral alumina with chloroform as eluent, concentrated, and redissolved in 5 mL of dry THF. The resulting solution was analyzed by MALDI-MS with DCTB as a matrix.

General Procedure for ODCC Assembly of Ladder 8 from Diamine 3 and Aldehyde 6. In an argon-filled glovebox, diamine **3 (**2.4 mg, 14 µmol, 1 equiv) and aldehyde **6** (8.9 mg, 31 µmol, 2.2 equiv) were each dissolved in 500 µL CCl_4. The mixtures were combined in a slurry of 5 Å molecular sieves (120 mg) in CCl_4 (1 mL) and stirred overnight at 40 °C. In a separate vial, precatalyst **[Mo]** (2.8 mg, 4.2 µmol, 30 mol %) and L-VI (1.5 mg, 4.2 µmol, 1 equiv relative to **[Mo]**) were combined in

3.6 mL CCl_4 and stirred at 70 °C for 10 minutes in a heating block. Following catalyst activation, the mixtures were combined and stirred at 40 °C overnight. The reaction mixture was then cooled to room temperature, passed over a short silica plug with chloroform as eluent, and concentrated to dryness. The resultant oil was redissolved in 5 mL dry THF and analyzed by MALDI-MS with DCTB as a matrix.

Metathesis of 3 and 6. In an argon-filled glovebox, diamine 6 (5.0 mg, 28 μmol, 1 equiv) and aldehyde 3 (18.3 mg, 63 μmol, 2.2 equiv) were each dissolved in 500 μL CCl_4. Meanwhile, precatalyst [Mo] (5.7 mg, 8.5 μmol, 30 mol%) and L-VI (3.1 mg, 8.5 μmol, 1 equiv relative to [Mo]) were combined in 8.2 mL CCl_4 and stirred at 70 °C for 10 minutes. Following catalyst activation, the solutions of 3 and 6 were added to a slurry of 5 Å molecular sieves (100 mg) in CCl_4 (200 μL), followed by the catalyst solution. The mixture was stirred at 40 °C overnight in a heating block, then allowed to cool to room temperature and filtered over a short pad of neutral alumina with chloroform as eluent. The mixture was then concentrated, redissolved in 5 mL dry THF, and analyzed by MALDI-MS with DCTB as a matrix.

Assembly of Ladder 8 without Molecular Sieves: The general procedures for assembly of ladder **8** from strand **7**, or from precursors **3** and **6**, were followed. For assembly in open air conditions, solutions of substrate and catalyst **VI** were combined, then removed from the glovebox and stirred at 40 °C in a heating block for 18h in a 20 mL reaction vial without a cap. For vacuum-driven reactions, the solutions of substrate and catalyst **VI** were combined in the glovebox, then stirred at 40 °C for 5h, during which a dynamic vacuum was applied to the mixture in 30-minute intervals. The mixture was then stirred overnight in a heating block inside the glovebox at 40 °C. Reaction mixtures were then filtered over plugs of neutral alumina and concentrated. The resulting oily residues were redissolved in 5 mL dry THF and analyzed by SEC and MALDI-MS.

Assembly of Ladder 8 in the Presence of $Sc(OTf)_3$. The general procedures for assembly of ladder **8** from strand **7**, or from precursors **3** and **6**, were followed. When solutions of substrate and catalyst were combined, a solution of $Sc(OTf)_3$ (2.8 mg, 5.6 μmol, 40 mol%) in 0.4 mL CCl_4 was also added to the mixture. Following analysis by MALDI-MS and SEC, the residue obtained from reaction of **7** (8 mg) was redissolved in CCl_4 (1 mL) and subjected to the general procedure for the synthesis of ladder **8**. After stirring for 18h in a heating block, the mixture was filtered over a pad of neutral alumina, concentrated, and redissolved in THF. The solutions were then analyzed by SEC and MALDI-MS.

General Procedure for Ladder Disassembly Experiments. Following the general procedure for ODCC assembly of molecular ladder **8**, a 100 μL aliquot of the reaction mixture was taken, filtered through a short pad of neutral alumina, concentrated to dryness, and analyzed by ^{1}H NMR. The remaining reaction mixture was charged with methylamine (840 μL of a 2 M solution in THF, 30 equiv relative to **3** or **7**) and stirred overnight at room temperature. The mixture was then filtered over neutral alumina and solvent and excess methylamine were removed *in vacuo*. The mixture was then redissolved in 750 μL $CDCl_3$ and analyzed by ^{1}H NMR.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Ladder assembly and disassembly experimental details, characterization data, and NMR spectra for all new compounds. (PDF)

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Notes

The authors declare no competing financial interest.

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