DEVELOPMENT OF TITANOCENE-CATALYZED MULTICOMPONENT COUPLING REACTIONS

A Dissertation

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A titanocene catalyst system is described herein for the synthesis of tertiary carbon centers. Using catalytic titanocene, phosphine, and zinc dust, zinc acetyldies can be generated from the corresponding iodoalkynes to affect sequential nucleophilic additions to aromatic aldehydes. The intermediate propargylic alkoxides are trapped in situ with acetic anhydride, which are susceptible to a second nucleophilic displacement upon treatment with a variety of electron rich species, including acetyldies and electron-rich aromatics. The use of two acetylide units as the nucleophilic components provides symmetrical and unsymmetrical 1,4-diynes. This adaptable methodology also includes electron-rich arenes as the third nucleophilic component, to provide substituted butenolides and diarylethynyl methanes in good yields. Additional investigation into the catalytic metatation capability of titanocene provides novel entries to chalcones from \( \alpha \)-halo ketones and aldehydes, and homopropargyl alcohols from propargylic acetates and aldehydes. Finally, an alternative approach to diarylethynyl methanes from terminal alkynes and Brønsted acid is described using indium catalysis.
The developed titanocene-catalyzed diarylethynyl methane reaction was then applied to the synthesis of various diarylheptanoid natural product analogues bearing tertiary carbon centers, including a calyxin B derivative. En route to analogue synthesis, a novel ortho-selective phenol deprotection reaction was discovered and investigated. In addition, the biological activities of the synthetic diarylheptanoids were investigated and found not to have substantial cytotoxicity against glioblastoma and neuroblastoma cell lines. However, compounds provided by C. Campos possessed anti-glioblastoma and neuroblastoma activity, while not displaying toxicity to human progenator cells.
This is for Bart, Anne, Danny, Vinnie, and Gabrielle.
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1.1 Selected Synthetic Strategies

The tertiary all-carbon center is defined as a tetrahedral carbon bearing three carbon substituents and one hydrogen. This structural motif is found in a variety of pharmaceuticals and biologically important molecules. As such, there is a wide array of methods for their construction. Nucleophilic addition to a disubstituted olefin (conjugate addition), or attack of a secondary allylic electrophile (allylic substitution), are common ways of constructing all carbon tertiary centers. These strategies are just a few of a vast array of methodologies that have been extensively reviewed and scrutinized. Nucleophilic addition to propargylic carbons (propargylic substitution), by contrast, is relatively underdeveloped. The synthetic potential of the alkyne moiety makes the development of novel propargylic substitution reactions highly desirable. Three-component coupling strategies to forge tertiary centers are similarly underutilized. This mode of reactivity potentially offers maximum convergence about the tertiary carbon, and could greatly streamline synthetic routes toward biologically important molecules. This section of the chapter will give an overview on recent developments in the area with a specific focus on propargylic substitution, three-
component couplings, and will conclude with a description of an important class of natural products baring the carbon tertiary center motif.

1.1.1 Propargylic Substitution

The substitution reaction of propargyl electrophiles is an important and well-studied reaction in organic synthesis. The synthetic potential of the alkyne functionality to be converted to virtually any functional group makes this reaction extremely important in the synthesis of organic compounds. Mechanistically, substitution at a propargylic carbon can be grouped into different types: Lewis-acid assisted substitution, in which there is the formation of a discrete carbocation intermediate, via metal-alkylidine species using terminal alkynes, and via propargyl or allenyl metal intermediates. Each of these reaction types has advantages and disadvantages, with common issues being regioselectivity (allenyl or propargyl products), stereoselectivity (enantio or diastereoselective), and substitution of the alkyne.

1.1.1.1 The Nicholas Reaction

A classic approach toward these propargylic adducts is the Nicholas reaction, in which a propargylic substitution of an alcohol derivative occurs, mediated by dicobalt hexacarbonyl. \(^1\) Through the course of this transformation, an alkyne forms a complex with dicobalt hexacarbonyl. These metal complexes can then be subjected to Lewis-acidic conditions to generate a cobalt-stabilized carbocation that is intercepted by a wide range of nucleophiles (eq 1). This methodology allows not only for substitutions to occur with much greater facility, but also gives exclusively the propargylic substitution
without any allene observed. Schreiber and coworkers investigated the synthetic utility of these complexes in early extensions of this work, including analysis of diastereoselective transformations (eq 2).³

The cations generated from dicobalt hexacarbonyl and propargyl alcohols have comparable stability to triaryl methane carbocations, and in some cases can be stored for extended periods of time at 0 °C under an inert atmosphere. Once a substitution reaction has been carried out, the alkyne can be regenerated from the cobalt complex under oxidative or reductive conditions (eq 3).

Carbon-based nucleophiles were observed to participate in the reaction, and include electron-rich aromatics, β-dicarboxyls, ketones and enols, allyl silanes, organometallics, etc. In addition, hydride, nitrogen, oxygen, and sulfur can participate in efficient substitutions. Interestingly, The cobalt-alkyne complexes can also stabilize propargyl radicals to effect reductive carbon–carbon bond formation. Treatment of the
stabilized cations with zinc affords a propargylic radical species, which can dimerize or append to a radical acceptor (eq 4).4

1.1.1.2 Catalytic Propargylic Substitution

Since the initial discovery of the Nicholas reaction, reports of catalytic methods for propargylic substitution in the literature have proliferated. The use of a catalyst to carry out this type of transformation allows for a more atom economical reaction, without the need to generate stoichiometric cobalt waste byproducts. In addition, catalytic methods obviate the need for discrete complexation/decomplexation steps. Titanium tetrachloride as well as titanium tetraisopropoxide can be used to catalyze the substitution of propargyl acetates. In this case, oxygen and nitrogen based nucleophiles can participate in the reaction using catalytic amounts of metal catalyst (eq 5).5

Ytterbium(III) triflate catalyzes the substitution of propargyl alcohols by carbon nucleophiles (eq 6). Interestingly, when tertiary alcohols were utilized as substrates, the allenyl regioisomers were observed. The authors rationalized these results through steric approach control wherein the substitution occurs at the least hindered site on the cationic π system.6
Matsuda reported that the use of iridium catalyst [Ir(cod){P(OPh)3}2]OTf with a loading of 1 mol% could facilitate the coupling of internal propargylic acetates and phosphates (eq 7). A wide variety of nucleophiles including silylenol ethers, silyl ketene acetals and thioketene acetals served as propargylic coupling partners. Interestingly, regioselectivity was reversed to give substituted allenes when the propargylic acetate was diphenyl-substituted.7

A variety of substitution reactions were described by Chatterjee and Roy using the hetero-bimetallic Ir–Sn catalyst [Ir(cod)(SnCl3)Cl(µ-Cl)2]. Under their conditions, terminal and internal propargyl alcohols can be substituted with a variety of carbon and heteroatom based nucleophiles.8 Iron(III) chloride and bismuth(III) chloride can be used as catalysts as described by Zhan and coworkers to substitute propargyl alcohols with C, N, O, and S-based nucleophiles.9,10,11 Gold(III) complexes have found extensive use as efficient propargylation catalysts. Campagne and coworkers discovered propargyl alcohols were converted to the corresponding substitution products using NaAuCl4·2H2O (eq 8). In all cases, propargylic substitution is observed over allene products. However, in certain cases, α,β-unsaturated ketones were obtained via a Meyer-Schuster type
rearrangement. These reactions require a tertiary, or benzyl/allyl, propargyl alcohol in order for the cation to be generated.

Due to the capacity for gold to act as an oxophillic and π-Lewis acid, tandem reactions were developed by Campagne using dual nucleophiles. Following the propargylic substitution, another nucleophilic residue can attack the activated alkyne in an intramolecular fashion to construct a variety of heterocycles (eq 9).\textsuperscript{12}

Hidai with Nishibayashi and Uemura found that terminal propargyl alcohols undergo substitution via ruthenium alkylidine intermediates. This distinct mechanistic substitution manifold was an important development in the field of propargylic substitution, as it created an opportunity for stereocontrol by modulation of the ligand environment around the metal center. Using a catalytic amount of [Cp*RuCl(μ₂-SMe)$_2$RuCp*Cl] (5 mol%), a variety of propargyl alcohols can be substituted at the propargylic carbon with amines, thiols, alcohols, and phosphines.\textsuperscript{13}
Scheme 1.1: Ruthenium-Catalyzed Propargyl Substitution

The reaction is proposed to proceed through ruthenium vinylidene species 1.25. Elimination of water would give an electrophilic allenylidene complex 1.26 susceptible to attack by a nucleophile. Protonation, followed by dissociation of the product from 1.29 regenerates the active catalyst. Remarkably, this mode of reactivity was rendered asymmetric by employing chiral thiolate ligands on ruthenium. Good enantiomeric excess was first established using acetone as the pronucleophile (eq 10), and this reactivity was further extended to arenes in a Friedel-Crafts process as well. The asymmetric ruthenium catalysis was only effective for terminal alkynes, in accord with the proposed mechanism wherein vinylidene intermediates are generated.
Copper has also been used as a catalyst to substitute terminal propargyl electrophiles. Murahashi employed copper(I) chloride (1 mol%) to a substitution reaction using aliphatic and aromatic amines and propargyl phosphates. Under their conditions, propargyl amines could be produced in high yields. Nishibayashi was able to produce enantioenriched propargyl amines from propargyl acetates using chiral diphosphine ligands and copper(I) triflate. Concurrently, van Maarseveen accomplished the synthesis of enantioenriched propargyl amines with copper(I) iodide and pybox (pyridine-2,6-bisoxazoline) ligand 1.34 (eq 11). Both of these copper-catalyzed methods are limited to terminal alkynes, and vinylidene intermediates have been invoked.

The Toste group reported the rhenium-catalyzed allylation of propargyl alcohols, and was able to apply the developed methodology to the synthesis of several natural products. The reaction was typically limited to propargylic benzylic alcohols, but in some
cases, with the addition of AgSbF₆ as a co-catalyst the reaction could proceed on nonaryl substituted alcohols. Here again, a dibenzylc propargylic tertiary alcohol produced exclusively the allene regioisomer. With substituted allyl silanes, modest diastereoselectivity was observed. The relative and absolute stereochemistries were assigned by synthesis of the natural product \((-\text{-di-O-Me-calopin 1.39 from adduct 1.38})\).\(^8\)

\[
\begin{align*}
\text{Me} & \\
\text{O} & \\
\text{O} & \\
\text{TMS} & \\
\end{align*}
\]  \[ \text{Me} \]  \[ \text{O} \]  \[ \text{Me} \]  \[ \text{TMS} \]  \[ 1.36 \]  \[ \text{Me} \]  \[ \text{O} \]  \[ \text{Me} \]  \[ \text{O} \]  \[ \text{TMS} \]  \[ 1.37 \]

\[
\begin{align*}
\text{CO}_2\text{Me} & \\
\text{DMPS} & \\
\end{align*}
\]  \[ \text{Me} \]  \[ \text{O} \]  \[ \text{Me} \]  \[ \text{O} \]  \[ \text{Me} \]  \[ \text{TMS} \]  \[ 1.38 \]

\[
\begin{align*}
\text{Me} & \\
\text{O} & \\
\text{O} & \\
\text{OH} & \\
\end{align*}
\]  \[ \text{Me} \]  \[ \text{O} \]  \[ \text{Me} \]  \[ \text{O} \]  \[ \text{Me} \]  \[ \text{TMS} \]  \[ 1.39 \]

\text{Scheme 1.2: Synthesis of \((-\text{-di-O-Me-calopin 1.39})\)}

Toste synthesized several other small molecules featuring his rhenium-catalyzed propargylation technology. Mimosifoliol (1.43) and O-Me-detrol were assembled in a few short steps. In addition, the biologically important lignan podophyllotoxin was accessed in a formal synthesis. The authors intercept \(\beta\)-apopicropodophyllin 1.48, a known intermediate \textit{en route} to podophyllotoxin (Scheme 1.4).\(^9\)
Evans and coworkers established a rhodium-catalyzed protocol for the propargylic substitution of carbonates (Scheme 1.5). Interestingly, they observed the allene regiosomer 1.51 when aryl or 1,1-disubstituted propargyl carbonates are used.
Significantly, in certain cases the regiochemical outcome can be reagent controlled. They attributed this to a base induced isomerization of the resultant propargyl sulfonamide, and propargylic sulfonamide 1.52 could be isolated as the major product when the weaker base potassium carbonate was used. The rhodium catalyst did not seem to be effective for internal alkynes as only one example was reported in a low yield.20

![Scheme 1.5: Diverted Product Distribution in Rhodium-Catalyzed Propargylic Amination](image)

Sawamura and coworkers described the propargylic substitution to give allenylsilanes with chirality transfer from enantioenriched propargyl carbonates. In this case allene products were the exclusive regioisomer observed, and the reaction was proposed to proceed via a vinyl rhodium species that then undergoes elimination to give the allene (Scheme 6).21
Propargylic alkylation can also be achieved through the use of more conventional cross-coupling catalysts. Palladium and nickel complexes can be employed along with propargyl halides and pseudohalides to couple with organometallic reagents. Marshall demonstrated a stereoretentive propargylic substitution reaction with a palladium catalyst. Interestingly, introduction of a CO atmosphere leads to generation of the corresponding allenyl amide 1.59 (eq 12).\(^{22}\)

Fu demonstrated Negishi couplings with secondary propargyl bromides to give the corresponding coupling products. This was the first nickel-based system for the coupling of sterically-demanding secondary electrophiles and secondary nucleophiles (eq 13).\(^{23}\)

Soon after this initial report, Fu and Smith reported an asymmetric protocol. Under the similar conditions, with the addition of a pybox ligand, high yields and ee’s were achieved. Importantly, the asymmetric transformation is stereoconvergent, and
racemic halides give the desired enantiomer due to the planar radical intermediate.\textsuperscript{24}

Finally, organic Brønsted acid catalysts such as PTSA were found to affect propargylation as demonstrated by Sanz and Rodriguez. This method proved fairly general, as it was able to incorporate allyl silanes, ethers, amines, and arenes as effective nucleophilic components.\textsuperscript{25}

1.1.2 Three-component Coupling Reactions (MCRs)

1.1.2.1 Symmetrical Nucleophilic Substitutions

Three-component coupling reactions to construct tertiary carbon centers often proceed via Friedel-Crafts type processes. In 2005, Nair described the symmetrical substitution of aldehydes catalyzed by gold(III) chloride. Several electron-rich arenes and heteroarenes were incorporated into tertiary carbon centers, performing two carbon–carbon bond forming events in a single synthetic operation (eq 13).\textsuperscript{26} Jaratiaroonphong and coworkers reported a similar method using catalytic iodine. Aliphatic and aromatic aldehydes are effective substrates, as well as electron-rich arenes (eq 14).\textsuperscript{27}
Wang developed a clever approach for the unsymmetrical aryl substitution of aldehydes catalyzed by iron(III) chloride. By using an aniline and a less electron-rich second arene, unsymmetrical arylmethanes were obtained in moderate to good yields (eq 15).28

![Chemical reaction image]

Warner and coworkers described an incident of a bisallylation reaction with an aromatic aldehyde. Ytterbium(III) chloride catalyzed the double alkylation in nitromethane (eq 16).29

![Chemical reaction image]

1.1.2.2 Unsymmetrical Three Component Couplings

Recent investigations by the Van Vranken and Wang groups, however, more completely addressed the unsymmetrical substitution selectivity problem. By employing diazo compounds into palladium cross-coupling technology, three functionally distinct components can be incorporated into the reaction manifold. Initial studies by the Van Vranken group focused on the construction of allylic amines, where an amine is a nucleophilic coupling partner.30 In 2008 Van Vranken and coworkers extended this methodology to allow for two carbon–carbon bond formations (eq 17).
The authors provided a mechanistic hypothesis in which oxidative addition of palladium into the vinyl iodide bond preceded diazo decomposition to generate a vinyl palladium carbene species (Scheme 1.7). A migratory insertion then provided the electrophilic allyl palladium complex, which suffered nucleophilic attack to release palladium(0) to complete the catalytic cycle. The initially described methodology was limited to highly stabilized carbon nucleophiles, vinyl iodides and (trimethylsilyl)diazomethane. The reaction could be rendered intramolecular to produce an indane derivatives by appending an $\alpha,\beta$-unsaturated ester on to an aryl halide (eq 18).
Wang and coworkers were able to produce diarylethynyl methanes from aryl hydrazones, aryl halides and terminal acetylenes (eq 19). The tosyl hydrazones converted to the corresponding diazo compounds in situ, and then the acetylide unit was incorporated from a copper acetylide in a Sonogashira-type process. Diaryl substituted acetylene resulting from a direct Sonogashira could be suppressed by judicious ligand and halide choice to compensate for slow palladium carbene generation. Although the halide and tosylhydrazone were limited to aryl groups, aliphatic and silyl groups were incorporated into the acetylide piece.33

Liang and coworkers then described the construction of tertiary carbon centers using aryl iodides, malonates and unsaturated tosylhydrazones (eq 20). In the intermolecular sense, they obtained regioisomeric mixtures.34
1.2 Diarylheptanoids: A Biologically Active Subclass

Compounds bearing tertiary carbon centers are ubiquitous in nature. One class of natural products that universally bares this motif is the calyxins. This class of compounds is a subset of diarylheptanoids, and has garnered some synthetic interest since their isolation the early 1990’s.

1.2.1 Background

The diarylheptanoid family of natural products is a diverse group of compounds that contain two aromatic rings linked by a seven-carbon unit. These compounds display a wide range of interesting biological activities and have been extensively studied in recent years. Perhaps the most biologically intriguing member of this family is curcumin. Recent attention has been paid to its neuroprotective, anticancer and anti-inflammatory activity. However, clinical application of curcumin has been hampered by its low water-solubility, low potency, and low *in vivo* bioavailability. Consequently, there have been efforts to develop analogues to overcome these obstacles while maintaining biological activity. An intriguing subclass of diarylheptanoids, the calyxins were first described by Kadota and coworkers, and display a rich structural diversity. The calyxins contain the diarylheptanoid substructure, appended to a chalcone or flavanone unit to form the all carbon tertiary center. The “cyclic” calyxins contain a pyran embedded in the heptanoid chain, whereas the “acyclic” calyxins are the open form. The blepharocalyxins refer to fused oxabicyclic pyran containing compounds. Preliminary biological testing revealed intriguing biological *in vitro* against HT-1080 human fibrosarcoma and 26-L5 murine colon carcinoma cell lines in the low micromolar range.
with the most potent members of the calyxins displaying ED\textsubscript{50} values more potent than curcumin and comparable to the clinical anticancer agent 5-fluorouracil (Figure 1.1).

Figure 1.1: Selected Biologically Active Diarylheptanoids and ED\textsubscript{50} values (µM)
1.2.2 Synthetic Efforts

Recent efforts have focused on assembling the central pyran ring of the cyclic calyxins, which in turn has led to the development of new synthetic routes. Rychnovsky and coworkers developed an arene-terminated Prins-cyclization to construct the substituted pyran 1.97 (Scheme 1.8). This synthetic strategy was applied to the syntheses of calyxin L, G, F, M and epicalyxins G and M.\textsuperscript{42}

![Scheme 1.8: Total Synthesis of Calyxin L](image)

Hashimoto completed a formal synthesis of calyxin L using an asymmetric Diels-Alder approach to construct the pyran. A subsequent Suzuki coupling and reduction installed the tertiary carbon center.\textsuperscript{43} Conversely, an intramolecular conjugate addition was used to establish the tertiary carbon center in calyxin F (Scheme 1.9).\textsuperscript{44}
Rychnovsky further explored the relationship among the cyclic calyxs by investigation of their interconversion (Scheme 1.10). Subjection of calyxin L to acidic conditions led to a mixture of calyxs L, F, M, G, and epicalyxins M and G. Presumably facile carbocation formation at the benzylic ether allows for the observed isomerization.
Eun Lee described the first synthesis of the cytotoxic blepharocalyxin D. This unique natural product contains a 2,8-dioxabicyclo[4.4.0]decane core, which was assembled by two key Prins-type cyclizations. Their synthesis commenced with an oxidation followed by asymmetric allylation described by the Maruoka group to establish absolute stereochemistry to produce 1.103. The enantioenriched homoallylic alcohol was subjected to a cross-metathesis to produce diacetate 1.104. A diastereoselective Prins cyclization with anisaldehyde established the first pyran ring (1.105).

Scheme 1.11: Synthesis of Pyran 1.105

Pyran 1.105 was then deacylated and converted to the thionocarbonate 1.106. Generation of cyclic acetal 1.107 set the stage for the second key Prins cyclization. Curiously, the kinetic aldehyde diastereomer was produced, but could be epimerized using sodium hydroxide to the thermodynamic isomer 1.109. Julia olefination followed by demethylation revealed blepharocalyxin D (1.111).45
Scheme 1.12: Lee’s Total Synthesis of Blepharocalyxin D

Willis and coworkers subsequently developed an elegant route to blepharocalyxin D using a Lewis-acid mediated cascade sequence as the key step. From a known alcohol 1.112, TBS-protection and oxidative cleavage yielded aldehyde 1.114. Wittig olefination followed by conjugate addition of boronic acid 1.116 gave ketone 1.117 as an inconsequential mixture of diastereomers. Chugaev elimination of the alcohol to reveal a symmetrically substituted tertiary carbon center proceeded in good yield. Silyl ether cleavage revealed the key cascade-cyclization intermediate 1.119.
Remarkably, four stereogenic centers are established in a single operation, as the bicycle was isolated in 75% as a single diastereomer (Scheme 1.14). The preference for the substituents to sit equatorial in the six-membered transition state was stated as the reason for the selectivity. To complete the synthesis of blepharocalyxin D, the side chain was appended via Grignard addition to 1.120, followed by a deoxygenation of the lactol. Concomitant deprotection of the methyl and phenylsulfonyl groups completed the synthesis of 1.111.46
1.3 Conclusion

The calyxins are an interesting class of natural products biologically and structurally. To date, they have been tested against only a small number of biological assays but have showed promising results. There is little known in terms of the structure-activity relationship of the calyxins or how they behave in vivo. Total synthesis has only been realized in a few members of the cyclic and blepharocalyxins, but has nonetheless inspired creative methodological advancement. No general strategy for synthetic access to the calyxins has been established, and new synthetic methodologies will likely need to be developed to realize the full potential of these compounds.

Scheme 1.14: Willis’ Total Synthesis of Blepharocalyxin D
The prevalence of tertiary carbons in nature and biologically relevant molecules displays their synthetic importance. When thinking about synthetic strategies to maximize efficiency and economy, the ideal situation is the three-component coupling reaction. The lack of methods available to effectively stitch three carbon components together hampers the utility of these three component strategies in the total synthesis arena. The use of allylic or propargylic substitution reactions in the multicomponent carbon–carbon bond forming repertoire has not been realized.
CHAPTER 2:  
TITANOCENE CATALYZED REACTIONS

Since the 1950’s, organotitanium reagents have found broad applicability in organic synthesis. Titanium reagents can perform a wide variety of transformations, including aldol reactions, asymmetric epoxidations, olefinations, cyclopropanations, hydrogenations, reductive couplings, and polymerizations. Many of these powerful methods have been established as indispensable tools to the synthetic chemist.

Biscyclopentadienyl (titanocene) species offer unique properties owing to their stabilization by the cyclopentadienyl ligands. Although divalent “titanocene(II)” has never been fully characterized due to its instability, it is often invoked as an intermediate for a variety of reductive transformations. It’s affinity for $\pi$-unsaturation allows for binding to alkenes and alkynes to generate organo-titanocene (IV) complexes. These complexes are generally nucleophilic, and can interact with a variety of electrophiles. Derivatives of titanocene(III) and (IV) have been well characterized over the past decades. Trivalent titanocene(III) is well known to be an effective single electron reductant, and can reduce epoxides, ozonides, carbonyls, and N–O bonds. The distinct reactivity of each of titanocene’s oxidation states has allowed for its mechanistic flexibility. These versatile complexes have frequently been studied as reagents for organic and polymer synthesis, and even as biologically active
pharmaceutical agents themselves. More recently, titanocene reagents have developed into effective catalysts. Titanocenes in catalysis have been purported to operate through +2 to +4, and +3 to +4 redox cycles. This chapter will focus on highlighting the development of titanocene derivatives as catalysts for organic transformations. Titanocenes as stoichiometric reagents and polymer catalysts in Ziegler-Natta type processes have been extensively reviewed and will not be discussed here. The following discussion will be divided into catalytic methods for the generation of reactive organometallics, reductions, reductive cyclizations, and single electron transfer (SET) catalysis.

2.2 Metalation Catalysis

Titanocene(III) chloride is an effective catalyst for the alkylation of electrophiles. In this mode of reactivity, titanocene(IV) dichloride is reduced with a stoichiometric metal such as zinc, magnesium or manganese to generate titanocene(III) chloride in situ, which is thought to be the active catalyst. Structurally, titanocene(III) chloride exists in solution as a mixture between the monomer and dimer, depending on the conditions employed. Mechanistically, titanocene acts to activate the halide by sequential electron transfer processes to generate a transient alkyl titanocene species.

2.2.1 Alkylations of Ketones and Aldehydes using “Regenerative Reagents”

The alkylation of carbonyl derivatives is a fundamental tool in synthetic organic chemistry. Traditionally, this is most often achieved by use of Grignard and Barbier reagents, where an organometallic reagent is stoichiometrically generated from the
corresponding organohalide and metal. This process suffers from a number of drawbacks, including functional group incompatibility and the use of corrosive and pyrophoric materials. Since the initial Barbier reaction was reported in 1899, many alternatives have emerged. Several other protocols use other metals including tin, chromium, indium, zinc, samarium and lead. Each of these metals has limitations, including high-toxicity in some cases. Cuerva and Oltra sought to establish a more environmentally friendly catalytic protocol, and thus provide a milder alternative method. Titanium is the seventh-most abundant metal on earth, and the authors first investigated the titanocene-catalyzed allylation of aldehydes and ketones. The proposed mechanism proceeds through the generation of an allyl radical species that then adds across an aldehyde to give homoallylic titanium alkoxide intermediate 2.2. The reaction requires the use of a “regeneration reagent”, to turnover the titanocene catalyst. $N$-trimethylsilyl collidine (2.3) is necessary to liberate the titanium from the alkoxide (Scheme 2.1).
Allyl, benzyl and propargyl halides were found to be effective coupling partners to produce secondary alcohols (2.5) (eq. 21). Significantly, the authors demonstrated the first example of an intramolecular Barbier-type reaction. Importantly, in most cases, crotylations proceeded with γ-selectivity, which is often not observed through chelation-controlled transition states. The natural product 12-hydroxysqualene (2.8) was prepared from allyl chloride 2.7 and α,β-unsaturated aldehyde 2.6, demonstrating the utility of this regioselective alkylation procedure (eq 22).
Rosales and Oltra then investigated propargylations and allenylations of aldehydes and ketones. Using terminal propargyl halides such as 2.10 the homopropargyl alcohols (2.11) were observed as the major products (eq 23). However, with certain aldehydes (2.12), employing internal propargyl halides (2.13) led to allenyl alcohols (2.14) as the major product (eq 24).\textsuperscript{51,52}

\begin{equation}
\begin{array}{c}
\text{CHO} \\
\text{OAc}
\end{array}
\begin{array}{c}
\text{OAc}
\end{array}
\xrightarrow{\text{Cp}_2\text{TiCl}_2 \ (20 \text{ mol\%}), \text{Mn collidine, TMSCl, THF}, \ \text{99\%}}
\begin{array}{c}
\text{CHO} \\
\text{OAc}
\end{array}
\begin{array}{c}
\text{OH} \\
\text{Cp}_2\text{TiCl}_2 (20 \text{ mol\%}), \text{Mn collidine, TMSCl, THF}
\end{array}
\begin{array}{c}
\text{99\%}
\end{array}
\begin{array}{c}
\text{2.10}
\end{array}
\begin{array}{c}
\text{2.11}
\end{array}
\end{equation}

The products observed were substrate dependant, and rationalized by formation of an equilibrium between propargyl (2.15) and allenyl (2.16) titanocene intermediates (eq 25).

\begin{equation}
\text{XCP}_2\text{Ti} \xleftrightarrow{\text{R}} \text{TiCp}_2\text{X}
\end{equation}

To survey the feasibility of a catalytic asymmetric method, the authors described an example using homochiral Brintzinger’s catalyst (2.18) to afford a low yield of mildly enantioenriched homopropargyl alcohol (2.19, eq 26). The enantioselectivity observed was low, and in agreement with previously reported values for additions of homochiral allyl-titanocene additions to aldehydes.\textsuperscript{53}

\begin{equation}
\text{MeO} \\
\text{2.17}
\xrightarrow{\text{Cp}_2\text{TiCl}_2 \ (20\%, \ 23\% \ ee)}
\begin{array}{c}
\text{MeO} \\
\text{2.18} \ (\text{cat.})
\end{array}
\begin{array}{c}
\text{2.10}
\end{array}
\begin{array}{c}
\text{2.19}
\end{array}
\end{equation}
2.2.2 Carbonyl Allylations via Organozinc and Magnesium Reagents

Fleury and Ashfeld reported the use of catalytic titanocene dichloride and zinc dust as a reductant to affect similar types of allylations. Ketones and aldehydes were allylated in good yields, without the need for any regenerating reagents. The authors propose a transmetalation of the allyl group from a titanocene species to Zn (II) salts present in the reaction mixture, which presumably obviates the need to turnover a titanium alkoxide. Additionally, the allylations could proceed with much lower catalyst loadings. In a typical reaction, aldehyde 2.20 could be converted to the homoallylic alcohol 2.21 in excellent yield (eq 27).

\[
\text{Me}_2\text{N} + \text{CHO} + \text{Br} \rightarrow \text{Cp}_2\text{TiCl}_2 (1 \text{ mol}) \rightarrow \text{Zn, THF} \rightarrow 91\%
\]

Also intriguing, the authors observed addition of catalytic amounts of certain phosphines allowed the reaction to proceed at lower temperatures (–40 °C). The addition of a chiral ligand 2.22 led to a low yield of a moderately enantioenriched homoallylic alcohol 2.5 (eq 28). Importantly, the use of enantioenriched titanium or phosphine species did not show any enantiomeric excess.54 The same authors similarly employed magnesium as a reductant for the in situ generation of Grignard reagents (eq 29).

\[
\text{CHO} + \text{Br} \rightarrow \text{Cp}_2\text{TiCl}_2 (1 \text{ mol}) \rightarrow \text{Mg, THF} \rightarrow 93\%
\]
The above methodologies demonstrate the mechanistic flexibility of titanocene catalysis to affect carbon–carbon bond formation through either organotitanium or other organometallic species.

2.2.3 Titanocene-catalyzed Reformatsky Reactions

In addition to benzyl, propargyl and allyl halides, α-halo carbonyl derivatives can be effectively used as organometallic precursors in titanocene-catalyzed Reformatsky reactions. The Cozzi group investigated the titanocene-catalyzed Reformatsky reaction using titanocene dichloride and manganese (eq 30). Trifluoroacetic anydride was used as a turnover reagent to trap the resultant alkoxide and release titanocene(IV) to turnover the catalytic cycle. The second hydrolysis step revealed β-hydroxyester 2.24. Aliphatic and aromatic aldehydes could be used, but the reaction appeared to be limited to α-bromoesters as the organohalide.56

Concurrently, Oltra, Cuerva and Robles described a similar Reformatsky process. They utilized titanocene dichloride, manganese and trimethylsilyl collidine to turnover titanocene. This protocol generally led to higher yields, and a variety of α-chloro carbonyl derivatives could be effective substrates (eq 31). Substituted α-chloroketones could also be used to give mildly diastereoselective examples (up to 4:1 dr).57
2.3 Reductions

The formal addition of hydride to unsaturated functional groups is of immense importance in the synthesis of pharmaceuticals. Titanium, relatively abundant and environmentally benign, would be desirable to carry out these types of transformations. Importantly, titanocene catalysts have been employed to several different types of reductions, including hydrogenations, hydrosilylations, hydroborations, and reductive cyclizations. Kagan first showed titanocene could be used as a catalyst for the homogenous hydrogenation of olefins. The active catalyst is believed to be a titanocene (III) hydride species generated from reduction of titanocene(IV) dichloride and an alkyl metal reductant in situ. The titanium hydride adds across the olefin, and subsequent addition of hydrogen releases the saturated alkane and the titanium hydride species to turn over the catalyst. Low ee values were reported using chiral titanocene derivatives 2.29 (eq 32), but for the first time showed the viability of chiral titanocene complexes in hydrogenation catalysis.58

Buchwald further illustrated the potential of asymmetric titanocene catalysis by developing an asymmetric protocol for the hydrogenations of imines. In this case, Brintzinger’s catalyst 2.29 afforded good yields and ee’s of benzylic amines (2.32) (eq
Later the Buchwald group described an asymmetric reduction of ketones using a similar precatalyst (2.34) and phenyl silane as the hydride source (eq 34). They also found that employing lactones as the starting electrophile gives the corresponding lactol products (eq 35). This method provided an attractive alternative to stoichiometric reduction using pyrophoric and highly reactive metal hydrides. Silane additives were required not only as the reductant, but also to turnover the titanium alkoxide.

Titanocene(II) has also been shown to catalyze the hydroboration of carbonyl derivatives. Using titanocene(II) biscatecholborane, a number of aldehydes and ketones underwent reduction to the boron alkoxide (eq 36). The reaction worked for several
aliphatic and aromatic ketones and aldehydes, with electron-poor carbonyls displaying a faster rate of hydroboration.\textsuperscript{62}

\[
\begin{array}{c}
\text{Me} \quad \text{O} \\
\text{Me} \quad \text{O} \\
\end{array}
\quad \text{Me} \quad \text{O}
\]

Schwartz employed catalytic titanocene dichloride in an intriguing reductive dehalogenation of arenes using sodium borohydride as the reductant. The reaction was limited to aryl bromides and polychlorides. The authors propose a single electron transfer from titanocene(III) chloride to form a radical anion, followed by expulsion of the halide ion to release an aryl radical that is trapped by the borohydride. When an olefin is appended to the aryl bromide (2.42), cyclization products (2.43) are observed, indicating the formation of a transient aryl radical species (eq 37).\textsuperscript{63}

\[
\begin{array}{c}
\text{Me} \quad \text{O} \\
\text{Me} \quad \text{O} \\
\end{array}
\quad \text{Me} \quad \text{O}
\]

While the above examples show effective titanocene(II)/(III) redox catalysis, a titanocene(III)/(IV) cycle would be a milder and more functional group tolerant method due to the reactive nature of titanocene(II) species. Gansäuer, Oltra and Cuerva investigated this type of reactivity in the reduction of ketones in aqueous media. Mechanistically, two equivalents of titanocene(III) are thought to serve as single-electron-transfer agents to generate an acyl titanocene species, which is protonated by amine hydrochloride salts present in the reaction mixture. This process is an \textit{umpolung} to the titanocene(II) catalyzed reductions in that the polarity of the hydrogen atom
incorporation is reversed. This reactivity was observed for aliphatic and aromatic cyclic and acyclic ketones (eq 38).^64

\[ \text{Cp}_2\text{TiCl}_2 (10 \text{ mol\%}), \text{Zn} \text{H}_2\text{O}, 2,4,6\text{-collidine HCl} \text{THF, 80\%} \]

2.44

\[ \text{O} \]

2.45

Ashfeld subsequently reported the selective 1,4-reduction of $\alpha,\beta$-unsaturated carbonyl derivatives. Using catalytic titanocene dichloride, zinc dust and amine hydrochloride salts, unsaturated aldehydes, ketones, esters, and amides could be reduced to the corresponding saturated product. Mechanistically, a series of single electron transfers from titanocene(III) species are thought to reduce the unsaturated carbonyl derivative via protonation of an allyl titanocene species. Significantly, the resultant ketone is stable to the reaction conditions (eq 39).^65

\[ \text{MeO}_2\text{C} \]

2.46

\[ \text{O} \]

2.47

2.4 Carbon–Carbon Bond Formation by Single Electron Transfer from Titanocene

In recent years, radical chemistry has proliferated in organic synthesis. Chemistry that has been traditionally thought of as unselective can be an effective means to construct organic molecules. Titanocene reagents are well known to be an effective single electron reductant, and over the years these effective catalytic methods have emerged at the forefront of reaction development. The oxidation of titanocene(III) to (IV) by select organic functional groups provides a mild and selective way of generating transient carbon-centered organic radicals as intermediates in important
transformations. In particular, aldehydes, ketones, epoxides, and halides are known to effectively engage titanocene catalysts, which further expands the utility of these motifs.

2.4.1 Pinacol Couplings

The pinacol coupling is a fundamental organic reaction for the synthesis of vicinal diols. The reaction can be facilitated by many different kinds of reducing reagents, but most commonly involves intermediate ketyl radicals followed by dimerization. The use of titanocene in pinacol coupling represents a catalytic method, and also demonstrates the ability of titanocene(III) complexes to affect carbon–carbon bond formation by SET processes. In 1998 Gansäuer reported that titanocene(III) chloride with trimethylsilyl chloride and magnesium(II) bromide could serve as an effective pinacol coupling catalyst. Diols such as 2.50 were generated in high dr, and the authors speculate the high diastereomeric ratio could be attributed to a bi-metallic titanocene catalyst in which two ketyl radicals are coupled in close proximity (2.49, eq 40). The reaction was limited to aromatic aldehydes.66

The authors also reported diastereoselective pinacol couplings that avoided the use of TMSCl and magnesium salts. In this case, 2,4,6-collidine hydrochloride served as a turnover reagent by protonation of titanium alkoxides to release titanocene(IV)
dichloride. Shortly after, Nicholas reported a similar pinacol coupling reaction using titanocene(IV) dichloride with manganese as the reductant and TMSCl to generate the bis-silylated vicinal diols. However, the observed diastereoselectivities were lower, but showed a greater substrate scope to include aromatic and aliphatic aldehydes (eq 41).

\[
\begin{array}{c}
\text{CHO} \\
\text{CHO} \\
\end{array}
\xrightarrow{\text{Cp}_2\text{Ti(Ph)Cl (10 mol%), Zn}}
\begin{array}{c}
\text{OH} \\
\text{OH} \\
\end{array}
\]

Itoh and coworkers also reported a diastereoselective pinacol coupling protocol. In their case, titanocene(IV) phenyl chloride was used as the precatalyst. This titanocene species is purported to be monomeric in nature, which is in accord with low levels of diastereoselection in the intermolecular examples. The authors report much higher diastereomeric ratios in the cyclization of dialdehydes. Aromatic and aliphatic aldehydes underwent facile pinacolization. The reactions were thought to proceed via diradical titanocene species. The observed trans diol products are opposite than for related samarium(II) diiodide promoted couplings that proceed through a chelated transition structure to give cis diols (eq 52).

2.4.2 Reductive epoxide opening

The titanocene catalyzed reductive opening of epoxides is perhaps the most powerful method in the repertoire of titanocene catalysis. Gansäuer and coworkers have extensively explored the ability of titanocene to cleave oxiranes regio and
chemoselectively. Initial examples focused on the use of catalytic titanocene, manganese as the reductant, and 1,4-cyclohexadiene as a hydrogen atom donor (eq 53).

The authors propose a kinetic preference for the observed selectivity, where the titanocene catalyst sits opposite the more sterically demanding side of the epoxide. The opening of oxetanes using titanocene was investigated computationally by density functional theory (DFT) calculations with the BP functional and a TZVP basis set. The oxetane opening is less exothermic and slower compared to the opening of epoxides. Dimerization products were more frequently than reductive opening, which the authors attribute to the generated radicals being further from the shielding effect of the titanocene catalyst (eq 54).

Similarly, when Barrero and coworkers employed vinyl epoxides to the catalytic titanocene conditions, they could obtain good yields of the reductive opening dimerization product.

Oltra and Cuerva have extended this reductive epoxide opening methodology to the synthesis of terpenoid natural products. The cascade cyclization methodology allowed for the reductive cyclization of polyenes. The tricyclic product depicted in eq 55 is an intermediate en route to the terpenoid dauca-4(11),8-diene. Alkenes and alkynes can also be used in intermolecular cyclization protocols employing acrylates and acrylamides as the radical acceptors. In the case of alkynes, this strategy allows for the
synthesis of stereodefined olefins from vinyl radical intermediates (eq 56). In order for the cyclization of alkynes to be successful, ethyl acetate had to be substituted for THF due to quenching of the vinyl radical to form the protonated cyclized product.\textsuperscript{74}

The reaction pathway could be diverted to form carbon–oxygen bonds in the absence of a radical trap. Using DFT calculations with BP and B3LYP methods, the authors discovered that the homolytic breaking of the titanium–oxygen bond to form cyclic ethers is thermodynamically favorable. A lower relative concentration of titanocene(III) was found to be beneficial owing to the deceleration of radical trapping of the generated tertiary radical. Thus ethyl acetate and zinc were used in combination due to the relatively slow reduction of titanocene(IV) with this system to produce the desired bicycles 2.65 (eq 57). To rule out a cationic reaction pathway, the authors subjected the starting materials to a variety of Lewis and Brønsted acids, and did not observe appreciable (<15%) yields of the desired products.\textsuperscript{75}

Four-member carbocycles could also be produced from the corresponding epoxides \textit{via} four-exo cyclizations (eq 58). Several titanocene catalysts were investigated in terms of yield and diastereoselectivity, with more bulky titanocenes generally
increasing the dr. This was one of very few radical-based methods for four-member carbocycle formation.\(^{76}\)

![Reactive scheme 1](image1.png)

In an effort to establish an environmentally benign reductive opening of epoxides, the authors sought to use hydrogen gas as the source of hydrogen as opposed to 1,4-cyclohexadiene. Hydrogen gas would be the optimal hydrogen source in terms of atom economy. They found that Wilkinson’s catalyst was an effective hydrogen transfer catalyst that was compatible with the titanocene catalyst. The dual-catalyst system was effective at inducing the reductive epoxide opening, and was compatible with a variety of functional groups including sulfonates, pivalates and chlorides (eq 59).\(^{77}\)

![Reactive scheme 2](image2.png)

Similarly, reductive cyclizations could be terminated with hydrogen gas by employing Vaska’s complex, IrCl(CO)(PPh\(_3\))\(_2\) to donate hydrogen to alkyl and vinyl radicals.\(^{78}\) To further their quest for a sustainable reductive epoxide opening, the Gansäuer group developed a system using a titanocene(III) hydride catalyst. Generated from dimethyl titanocene(IV) and silanes, epoxides could be reductively opened without the use of reducing metals or turnover reagents. The resulting silyl ethers were mildly deprotected to reveal the alcohol with aqueous potassium carbonate (eq 60).
Intriguingly, the observed diastereoselectivities associated with this catalyst system were much higher when compared to the previously reported external reductant system. The authors attributed this increase in diastereoselectivity to their postulated ordered cyclic transition states in which the hydrogen is transferred from the alkoxy-titanocene hydride to the adjacent carbon-centered radical. Importantly, this reaction was observed to be stereoconvergent, and agreed with the authors’ proposed intramolecular hydride delivery hypothesis.\textsuperscript{79} The atom-economical titanocene-catalyzed reaction was fully realized in the arylation of epoxides. Gansäuer and Flowers demonstrated that titanocene could catalyze the arylative opening of epoxides using catalytic amounts of titanocene, manganese and 2,4,6-collidine·HCl. In their proposed mechanism, the \(\alpha\)-alkoxy radical \textit{2.74} adds into the aniline to produce the delocalized radical species \textit{2.75}. Electron transfer to the pendant titanocene alkoxide produces zwitterion \textit{2.76}, which undergoes elimination to generate the product and titanocene(III) to close the cycle. The reaction scope reported was limited to aniline derivatives (Scheme 2.2), but this importantly demonstrated for the first time the ability of titanocene to be reduced within the catalytic cycle, thus rendering the reaction catalytic in all reagents.\textsuperscript{80}
2.5 Miscellaneous Reductive Couplings

Titanocene complexes can facilitate a wide variety of reductions, owing partially to the fact that titanocene(III) or titanocene(II) catalysts can be accessed, depending on the conditions employed for reduction. Importantly, amides, alkynes and olefins are can be reduced/ coupled to other functionality. Functional groups that are potentially inert to SET catalysis by titanocene can engage the much more reactive titanocene(II) species. This mechanistic flexibility allows for exploration of a wide variety of organic transformations.

Harrod reported the reductive coupling of amides to form vicinal diamines using a titanocene catalyst and a silane as the reductant. The reaction was limited to aryl amides and a titanocene hydride species is assumed to be the active catalyst,
importantly displaying the ability of a titanocene catalyst to affect a reductive coupling in which two equivalents of hydride are incorporated into the product (eq 61).\(^{81}\)

Buchwald and coworkers reported the reductive coupling of enynes (2.80) with isocyanide insertion to form cyclopentenones (2.81, eq 62). This reaction could proceed using titanocene(II) generated from titanocene(IV) dichloride and alkyl lithium or magnesium reagents, but was found to be optimal when titanocene(II) bistrimethyl phosphine was used as the precatalyst. The respective zirconocene reagents were ineffective catalysts when oxygenated functional groups were examined, which the authors attributed to an irreversible Zr–O interaction. Ti–O bonds are substantially weaker by about 20 kcal/mol. This work offered a significant advance over the previously known stoichiometric titanocene and zirconocene processes developed by Negishi and Buchwald. With this method, a variety of fused bicyclic cyclopentenones were synthesized. Esters and carbamates were well tolerated under the reaction conditions, however terminal alkynes and bulky alkyne substituents (Ph, TMS) resisted cyclization.
The reductive cyclization is catalyzed by a titanocene(II) species, which undergoes cyclization to give titanacycle 2.83, which then intercepts isocyanide to form the 6,5-fused bicycle 2.84. Reductive elimination produces the cyclic imine 2.85, which is then hydrolyzed to form cyclopentenone 2.86. This method was extended to the reductive cyclization and CO insertion of ketones to generate substituted butyrolactones (2.88, eq 63).

Aliphatic and aromatic ketones could undergo the cyclization reaction, however, the catalytic activity of titanocene(II) bistrimethylphosphine was only observed for aromatic ketones. The authors speculate this difference is due to displacement of CO ligands on titanocene by aryl ketones as it accepts electron density from titanocene prior to metallacycle formation. This mode of reactivity was further exploited to ene-type cycloisomerizations. Using titanocene(II) dicarbonyl, a variety of exo-cyclopentene
derivatives were produced in good yields with titanocene loadings ranging from 5 – 25 mol\% (eq 64).84

Crowe showed the reductive cyclization of $\delta,\epsilon$-unsaturated ketones and aldehydes using titanocene(II) bisdimethylphosphine.85 Terao and Kambe demonstrated the carbosilylation of alkenes and dienes with alkyl and silyl halides catalyzed by a titanium(II) species (eq 65).86

Titanocene(III) complexes have been shown to facilitate reductive couplings in a dual-catalytic system employing titanocene(III) chloride and palladium(0) as the active catalysts (eq 66). In this system propargyl carbonates succumb to oxidative addition from palladium. The propargyl palladium species then undergoes transmetalation via two sequential SET processes from titanocene(III) chloride, at which point the propargyl titanocene(IV) complex adds to a carbonyl to give a titanium alkoxide, which is liberated by 1-trimethylsilyl-2,4,6-collidine to regenerate titanocene(IV) chloride.87

Barrero and coworkers demonstrated a reductive dimerization of benzyl halides. Titanocene (III) chloride catalyzed the formation of bibenzyl derivatives, while *geminal*
dihalides gave the corresponding stilbene products. Products of benzyl addition to aldehydes could also be produced, although in much lower yields (5 – 60%).

Conclusion

The versatility of titanocene complexes has spurred the development of a variety of synthetic methods. Most notably, titanocene has the ability to act as a strong π-Lewis acid or as a mild SET reductant depending on the conditions employed. Important opportunities in titanocene reaction development remain. Differing reaction conditions with regard to the necessity for “turnover reagents” and other subtle changes can have profound effects on observed reactivity. Issues that have been addressed more completely in the reductive opening of epoxides, for example, have yet to be addressed in metalation catalysis. Is it possible to increase enantioselectivity or avoid the use of stoichiometric reductants? Given the versatility of titanocene complexes, can they be exploited as bifunctional catalysts? That is to say, the use of titanocene complexes to carry out multiple distinct transformations to a given substrate in a single pot is underexplored. The ability to facilitate carbon–carbon as well as carbon–heteroatom bond formations will undoubtedly allow for the continued development of titanocene as an effective, economical, and environmentally benign catalyst for years to come.
CHAPTER 3:
TITANOCENE CATALYZED MULTICOMPONENT COUPLING REACTIONS

Guided by our interest in the tertiary carbon center for its prevalence in nature, and the diarylheptanoids in particular, we sought to develop a protocol for a three-component coupling reaction that targeted this structural motif. A multicomponent strategy would allow for improved convergence and synthetic efficiency in assembling the tertiary carbon unit. The ability of titanocene catalysis to affect multiple carbon–carbon bond formations has been elegantly demonstrated by Gansäuer, Oltra, Cuerva, and others in radical-cascade reactions, which have been employed in the total synthesis of several natural products.\textsuperscript{73,74} In previous efforts by our lab, my colleagues investigated the catalytic Barbier reaction catalyzed by titanocene and phosphine. They found that titanocene and phosphine complexes could effectively promote the generation of reactive organometallic reagents from allylic and benzylic halides.\textsuperscript{54,55} In contrast to this work, and the work described above, the use of titanocene complexes to facilitate a convergent three-component coupling reaction was not yet known.

We speculated that a titanocene catalyst could enable metal-acetylide generation and allow access to propargyl alkoxide intermediates, which would provide an opportunity for further functionalization at the propargylic carbon. Owing to the preponderance of literature on propargylic activation, we reasoned that proper tuning
of the reaction conditions would allow us access to potentially two mechanistically distinct processes catalyzed by titanocene: a catalytic acetylide addition followed by either a Lewis-acid or SET reductive functionalization of the propargylic intermediate (Figure 3.1).

![Figure 3.1: Titanocene-Catalyzed Three Component Assembly of Tertiary Carbon Centers](image)

Due to the redox and Lewis-acidic properties of titanocene catalysts described above, we set out to develop a three-component coupling reaction that would rely on titanocene to mediate two carbon–carbon bond forming events in a single synthetic operation. In light of our laboratory’s experience in the catalytic generation of reactive organometallics, we reasoned the first step in the transformation would involve the nucleophilic alkylation of an aldehyde. The use of a nucleophilic acetylide would serve the two-fold purpose of incorporating a versatile functional handle while generating an activated propargylic center, which given the array of propargylic activation strategies described above, could enable a second bond forming event to occur.

3.1 Symmetrical 1,4-Diyne Synthesis (Performed by C. Campos)

Ashfeld and Campos initially set out to generate the all-carbon tertiary center focusing on aromatic aldehydes and iodoacetylenes as pronucleophiles. Early trials
employing catalytic titanocene, zinc dust and TMSCl as an additive led to low conversion of the propargylic intermediate (eq 67).

\[
\text{CHO} \quad \text{MeO} \\
\text{3.1a} \\
\]
\[
\text{Cp}_2\text{TiCl}_2 (2 \text{ mol%}), \text{Zn, TMSCl, CH}_2\text{Cl}_2, \text{rt} \\
\text{OH} \\
\text{3.3a} \\
\text{MeO} \\
\text{3.4a} \\
\text{Ph} \\
\]

Acetic anhydride in place of TMSCl alleviated this problem to ensure complete conversion of the propargylic intermediate. However, the addition of phosphine additives proved crucial to obtain high yields of the 1,4-dynes (eq 68).

\[
\text{CHO} \quad \text{MeO} \\
\text{3.1b} \\
\]
\[
\text{Cp}_2\text{TiCl}_2 (2 \text{ mol%}), \text{Zn, TMSCl, CH}_2\text{Cl}_2, \text{rt} \\
\text{OH} \\
\text{3.3b} \\
\text{MeO} \\
\text{3.4b} \\
\text{Ph} \\
\]

Additional studies demonstrated the need for zinc dust as the reducing metal (Table 3.1, entries 4 – 6), as well as the requirement of titanocene for the reaction to proceed. In these reactions, titanocene(IV) dichloride is reduced to titanocene(III) by excess zinc dust. This is followed by addition of phosphine, then addition of the organic reagents iodoalkyne, aldehyde and acetic anhydride at room temperature to prepare the 1,4-dynes after 2 – 4 h. Campos showed the applicability of this reaction to the synthesis of a variety of symmetrical 1,4-dynes from aromatic aldehydes and iodoalkynes (eq 69).
TABLE 3.1:  
INITIAL 1,4-DIYNE INVESTIGATIONS

<table>
<thead>
<tr>
<th>Entry</th>
<th>M</th>
<th>Cp₂TiCl₂ (mol%)</th>
<th>Time (h)</th>
<th>Yield (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>100</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>Zn</td>
<td>-</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>Zn</td>
<td>-</td>
<td>2</td>
<td>0&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>4</td>
<td>Zn</td>
<td>2</td>
<td>2</td>
<td>83</td>
</tr>
<tr>
<td>5</td>
<td>Mn</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>Mg</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

<sup>a</sup>Reaction conditions: <sub>3.1a</sub>(0.26 mmol), <sub>3.1a</sub>(0.62 mmol), Ac₂O (0.80 mmol), and phosphine (0.10 mmol) at 0.25 M for 2 h at rt.)<sup>b</sup>Yields determined by 500 MHz <sup>1</sup>H-NMR

3.2 Unsymmetrical 1,4-Diyne Synthesis (Gianino and Ashfeld)

While mechanistic questions remained, we were prompted to move further toward establishing a flexible methodology in which we could employ three distinct coupling partners. Thus our attention turned to the synthesis of unsymmetrical diynes for the unsymmetrical substitution of aldehydes. Unsurprisingly, when two different iodoacetylenes were employed under the standard reaction conditions, statistical mixtures of symmetrical and unsymmetrical 1,4-diynes were recovered. To address this issue, we modified our original procedure to include a stepwise addition protocol for the
in situ generation of a propargyl alkoxide intermediate. The first step was therefore more closely examined to investigate optimal zinc and phosphine conditions. First, the alkynylation was monitored in the absence of a phosphine additive (Table 3.2).

TABLE 3.2

TITANOCENE-CATALYZED ACETYLIDE ADDITION

<table>
<thead>
<tr>
<th>Entry</th>
<th>Zn (equivalents)</th>
<th>Solvent</th>
<th>3.3b (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.0</td>
<td>CH₂Cl₂</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>3.0</td>
<td>CH₂Cl₂</td>
<td>12</td>
</tr>
<tr>
<td>3</td>
<td>2.0</td>
<td>CH₂Cl₂/THF (1:1)</td>
<td>55</td>
</tr>
</tbody>
</table>

<sup>a</sup>Reaction conditions: 2.48 (0.37 mmol), 3.2a (0.37 mmol), Cp₂TiCl₂ (0.007 mmol), and Zn (0.73 mmol) at 0.5 M <sup>b</sup>Isolated yields

Interestingly, low yields of propargyl alchohol were obtained using just catalytic titanocene and zinc. By TLC analysis of the reactions, an initial low conversion of aldehyde to propargyl alcohol 3.3b was observed, followed by decomposition to complex mixtures of unidentified byproducts. However, when THF was used as a cosolvent, a moderate yield was obtained without extensive decomposition (entry 3). Phosphine and zinc were therefore examined further (Table 3.3). Under the conditions described below, zinc metal and diethyl zinc performed comparably well with tri-tert-
butyl phosphine to give propargyl alcohol \textit{3.3c}. Interestingly, the use of bidentate phosphines led to low conversion of starting aldehyde and iodoalkyne.

TABLE 3.3

TITANOCENE-CATALYZED ACETYLIDE ADDITION REVISITED

<table>
<thead>
<tr>
<th>Entry</th>
<th>Zinc Source</th>
<th>Phosphine</th>
<th>\textit{3.3c} (%)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Zn$^0$</td>
<td>$t^\prime$Bu$_3$P</td>
<td>66</td>
</tr>
<tr>
<td>2</td>
<td>Et$_2$Zn</td>
<td>$t^\prime$Bu$_3$P</td>
<td>67</td>
</tr>
<tr>
<td>3</td>
<td>Zn$^0$</td>
<td>Ph$_3$P</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>Zn$^0$</td>
<td>(Ph$_2$P)$_2$(CH)$_2$</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>Zn$^0$</td>
<td>(Ph$_2$P)$_2$(CH)$_3$</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>Zn$^0$</td>
<td>(Ph$_2$P)$_2$(CH)$_4$</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>Zn$^0$</td>
<td>(±)-BINAP</td>
<td>0</td>
</tr>
</tbody>
</table>

$^a$Reaction conditions: \textit{3.1b} (0.37 mmol), \textit{3.2a} (0.37 mmol), Cp$_2$TiCl$_2$ (0.007 mmol), phosphine (0.08 mmol), and Zn (0.73 mmol) at 0.5 M. $^b$Isolated yields

While the exact role of phosphine remains unclear to this point, studies carried out in our laboratory tangential to this work indicate that phosphine ligates to zinc acetylides in dichloromethane, while solvent ligation occurs in predominantly THF.\textsuperscript{89} The fact that this correlates to an efficient acetylide addition with phosphine is tantalizing. One possible explanation for this observation may be that ligation to zinc facilitates C–C bond formation by distortion of the zinc–acetylide bond angle (R–Zn–X) analogous to
Zn(II) aminoalcohol additions to carbonyls.\textsuperscript{90} Further, one cannot ignore the possibility of phosphine ligation to titanocene as well. While the effect of phosphine in these reactions remains perplexing, a plausible rationale includes the ligation of phosphine to both titanocene and zinc to provide for the mild reactivity observed.

Unfortunately, attempts to apply this reactivity to unsymmetrical diynes failed to provide the desired adducts in good yields. Additionally, alternative Zn sources (e.g. Et\textsubscript{2}Zn) led to complete recovery of the intermediate propargyl acetate (eq 68). Moving away from diethyl zinc, the sequential addition protocol was assessed for yield of unsymmetrical 1,4-diyne 3.4d. Unfortunately, low yields were observed irrespective of the phosphine employed (Table 3.4).
TABLE 3.4

PHOSPHINE SURVEY IN THE SYNTHESIS OF UNSYMMETRICAL 1,4-DIYNES

<table>
<thead>
<tr>
<th>Entry</th>
<th>Phosphine (x mol%)</th>
<th>3.4d (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>tBu₃P (40)</td>
<td>34</td>
</tr>
<tr>
<td>2</td>
<td>tBu₃P (20)</td>
<td>12</td>
</tr>
<tr>
<td>3</td>
<td>(4-OMe-C₆H₄)₃P (40)</td>
<td>16</td>
</tr>
<tr>
<td>4</td>
<td>(tHex)₃P (40)</td>
<td>17</td>
</tr>
<tr>
<td>5</td>
<td>(2,4,6-OMe-C₆H₄)₃P (40)</td>
<td>0</td>
</tr>
</tbody>
</table>

*Reaction conditions: 3.1b (0.37 mmol), 3.2a (0.37 mmol), 3.2b (0.55 mmol), Cp₂TiCl₂ (0.007 mmol), phosphine, Zn (0.73 mmol), and Ac₂O (0.84) at 0.2 M. "Isolated yields"

While many attempts at unsymmetrical 1,4-diyne generation produced intractable mixtures, a closer analysis of the crude material shed light on a potential problem. In many cases, symmetrical 1,5-diyne dimer (3.5) was detected in the reaction mixtures (eq 71). These results, combined with our inability to see comparable yields to the symmetrical 1,4-diynes led us to presume the occurrence of multiple unproductive pathways originating from the propargyl acetate intermediate.
The dimerization to symmetrical 1,5-diynes may arise through a radical combination process, or a metal-mediated substitution reaction. While mechanistically intriguing in its own right, we initially focused on minimizing this side reaction by decreasing the concentration of propargyl acetate relative to the second alkyne. To this end, we investigated a slow addition protocol of the acetic anhydride (eq 72). Adding a solution of Ac₂O via syringe pump over 5 hours led to an increase in yield of the 1,4-diyne 3.4f. An increase to 6.5 hours further improved the yield of 3.4f with an optimal time of addition found to be 11 h. With this protocol, we were able to synthesize 10 examples of unsymmetrical 1,4-diynes with isolated yields up to 56% (Table 3.5). In all cases, the starting aldehyde and intermediate acetate were fully consumed. We attribute the low yields to unproductive degradative pathways from the propargyl acetate species. With this initial dataset in hand, we moved to explore other nucleophilic components in the second step of the reaction, as the question remained of whether the inclusion of a non-acetylide nucleophile was feasible.
### TABLE 3.5

**SYNTHESIS OF UNSYMMETRICAL 1,4-DIynes**

<table>
<thead>
<tr>
<th>R1</th>
<th>R2</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>Me</td>
<td>52%</td>
</tr>
<tr>
<td>Cl</td>
<td>Me</td>
<td>56%</td>
</tr>
<tr>
<td>CF3</td>
<td>Me</td>
<td>50%</td>
</tr>
<tr>
<td>Me</td>
<td>MeO</td>
<td>53%</td>
</tr>
<tr>
<td>MeO</td>
<td>MeO</td>
<td>57%</td>
</tr>
<tr>
<td>CF3</td>
<td>OMe</td>
<td>55%</td>
</tr>
</tbody>
</table>

*Reaction conditions: 3.1b (0.37 mmol), 3.2a (0.37 mmol), 3.2b (0.55 mmol), Cp₂TiCl₂ (0.007 mmol), phosphine (0.15 mmol), Zn (0.73 mmol), and Ac₂O (0.84) at 0.2 M* [isolated yields]

#### 3.3 Diarylethynyl Methane Synthesis

We next examined electron-rich arenes as a second nucleophile to provide diarylethynyl methanes, upon which we expected to access calyxin substructures. We prepared a series of biaryls in order to first examine an entropically favored intramolecular arylation. When we subjected biaryl 3.1c to the reaction conditions
employed for the unsymmetrical 1,4-diynne synthesis, we discovered tricycle 3.6a produced in 14% yield. A brief survey of activating agents to facilitate propargyl substitution was conducted (Table 3.6). Acetic anhydride and methyl chloroformate performed comparably, and acetic anhydride was used moving forward due to expense and ease of handling.

**TABLE 3.6**

LEAVING GROUP EXAMINATION IN THE ARYLATION REACTION

<table>
<thead>
<tr>
<th>Entry</th>
<th>Activating Agent</th>
<th>3.6a Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ac₂O</td>
<td>14</td>
</tr>
<tr>
<td>2</td>
<td>AcCl</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>methyl chloroformate</td>
<td>21</td>
</tr>
<tr>
<td>4</td>
<td>Boc₂O</td>
<td>0</td>
</tr>
</tbody>
</table>

*aReaction conditions: 3.1c (0.20 mmol), 3.2a (0.20 mmol), Cp₂TiCl₂ (0.004 mmol), iBu₃P (0.08 mmol), Zn (0.44 mmol), and the activating agent (0.44 mmol), at 0.13 M *Yields determined by ¹H-NMR

Next the amounts of titanocene and types of phosphine were examined (Table 3.7). Lowering the loading of titanocene decreased the yield of the desired product (entry 1 – 2), while increasing the amount did not significantly increase the yield (entry 3). Additionally, the use of an alternate phosphine or phosphite was detrimental in
these cases (entry 4 – 5). In general, full conversion of the aldehyde and intermediate propargyl species was observed, often resulting in complex mixtures of products. Prior to acetic anhydride addition, however, it appeared as though the aldehyde was not fully converted to the propargyl intermediate (by TLC analysis).

In an attempt to ensure full conversion of the aldehyde to the propargyl alkoxide, the amount of iodoacetylene in the reactions was systematically examined (Table 3.8). Increasing the amount of iodoalkyne seemed to have a beneficial effect (entries 1 -3), however, increasing the amount of zinc along with the iodoalkyne led to

<table>
<thead>
<tr>
<th>Entry</th>
<th>( \text{Cp}_2\text{TiCl}_2 ) (mol%)</th>
<th>Phosphine</th>
<th>3.6a Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.0</td>
<td>(^t)Bu_3P</td>
<td>38</td>
</tr>
<tr>
<td>2</td>
<td>0.5</td>
<td>(^t)Bu_3P</td>
<td>29</td>
</tr>
<tr>
<td>3</td>
<td>10.0</td>
<td>(^t)Bu_3P</td>
<td>39</td>
</tr>
<tr>
<td>4</td>
<td>2.0</td>
<td>(^n)Bu_3P</td>
<td>&lt;5</td>
</tr>
<tr>
<td>5</td>
<td>2.0</td>
<td>(MeO)_3P</td>
<td>&lt;5</td>
</tr>
</tbody>
</table>

*Reaction conditions: 3.1c (0.20 mmol), 3.2a (0.20 mmol), \(^t\)Bu_3P (0.08 mmol), Zn (0.44 mmol), and Ac_2O (0.44 mmol) at 0.13 M *Yields determined by \(^1\)H-NMR
an additional increase in yield (entry 5). Presumably, the increase in concentration of
the acetylide leads to better conversion of the aldehyde to the propargylic alkoxide.
Additionally, cesium carbonate was found to have a beneficial effect on reaction yield,
possibly mitigating acetic acid formation in the arylation event.

### TABLE 3.8

<table>
<thead>
<tr>
<th>Entry</th>
<th>Iodoalkyne 3.2a</th>
<th>Zn</th>
<th>3.6a Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.5</td>
<td>2.2</td>
<td>29</td>
</tr>
<tr>
<td>2</td>
<td>2.0</td>
<td>2.2</td>
<td>39</td>
</tr>
<tr>
<td>3</td>
<td>2.5</td>
<td>2.2</td>
<td>43</td>
</tr>
<tr>
<td>4</td>
<td>3.0</td>
<td>2.2</td>
<td>26</td>
</tr>
<tr>
<td>5</td>
<td>3.0</td>
<td>3.0</td>
<td>45</td>
</tr>
<tr>
<td>6</td>
<td>3.0</td>
<td>3.0</td>
<td>55</td>
</tr>
</tbody>
</table>

*Reaction conditions: 3.1c (0.20 mmol), 3.2a, Cp₂TiCl₂ (0.004 mmol), Bu₃P (0.08 mmol), Zn (0.44 mmol),
and Ac₂O (0.44 mmol) at 0.13 M *Yields determined by ¹H-NMR *Cs₂CO₃ (0.20 mmol) added

Unable to increase the yield beyond 55%, a starting aldehyde modified with a
two-carbon tether was synthesized to test if larger rings were generated with this
method. Aryl bromide 3.1d was subjected to Sonogoshira conditions with known alkyne
followed by global reduction and then oxidation to the aldehyde 3.1e (eq 73).

Interestingly, seven-membered ring formation gave an increased yield to 77% (eq 74),
and the intermolecular variant of the reaction proved equally effective (eq 75).

In a similar protocol to that developed for diyne synthesis, titanocene is first
reduced with excess zinc dust, followed by addition of phosphine. The aldehyde, arene
and iodoalkyne are then added, and for the intermolecular three-component couplings,
a slow Ac2O addition protocol of 11 hours was necessary to give the desired
diarylethynyl methanes in good yields. Upon examination, we discovered that the
titanocene-catalyzed multicomponent coupling of aryl aldehydes 3.1 and arenes 3.8
with 3.2a proved general for a wide array of functionally diverse substrates (Table 3.9).
Alkylation of neutral, electron-rich and electron- poor aldehydes 2.48, 3.1a and 3.1b
with indole 3.8b provided the expected diarylethynyl methanes in good yields (entries 1
The coupling of aldehydes bearing an indole (3.1g), furyl (3.1h), or thienyl (3.1i) heteroaryl ring with indole 3.8b and 3.2a yielded the unsymmetrical diarylethynyl methanes 3.6g–i, respectively in 68–71% yields (entries 4 – 6). The three-component coupling reaction was then assessed with regard to the arene employed (Table 3.12). The presence of an N-acyl protecting group on indole 3.8c did not adversely effect the formation of 3.6j (entry 1). The addition of C2-substituted indole 3.8d and 3.2a to aldehyde 3.1a provided adduct 3.6k in 80% yield (entry 2). Aniline 3.8e also proved effective in the coupling of aldehydes 3.1a and 3.1g to yield 3.6l and 3.6m (entry 3, 4). Consistent with our initial findings, electron-rich aryl rings proved superior to their neutral and electron-deficient counterparts, as the use of benzene or toluene did not result in any diarylethynyl methane. The titanocene-catalyzed coupling also proved general for a range of iodoalkynes 3.2 in the alkylation of aldehyde 3.1a and indole 3.8b (Table 3.13). Electron-rich and electron-poor aryl iodoalkynes provided the corresponding diarylethynyl methanes 3.6n–o in good yields (entries 1–3). Aliphatic alkynyl iodides gave propargyl indoles 3.6q and 3.6r in 80% and 58% yield, respectively (entries 4 and 5). Triisopropylsilyl iodoalkyne, an effective acetylene surrogate, coupled efficiently to yield diarylethynyl methane 3.6s (entry 6). It is noteworthy that, although both iodoalkyne and Ar–H nucleophiles are present throughout the reaction, the formation of 1,4-diynes or triaryl- methanes was not observed.
### TABLE 3.11

ALDEHYDE SCOPE IN THE SYNTHESIS OF DIARYLETHYNYL METHANES

![Chemical reaction diagram]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me</td>
<td><img src="image" alt="Molecule 3.6d" /></td>
<td>68</td>
</tr>
<tr>
<td>2</td>
<td>MeO</td>
<td><img src="image" alt="Molecule 3.6e" /></td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>Cl</td>
<td><img src="image" alt="Molecule 3.6f" /></td>
<td>63</td>
</tr>
<tr>
<td>4</td>
<td><img src="image" alt="Molecule 3.1g" /></td>
<td><img src="image" alt="Molecule 3.6g" /></td>
<td>69</td>
</tr>
<tr>
<td>5</td>
<td><img src="image" alt="Molecule 3.1h" /></td>
<td><img src="image" alt="Molecule 3.6h" /></td>
<td>68</td>
</tr>
<tr>
<td>6</td>
<td><img src="image" alt="Molecule 3.1i" /></td>
<td><img src="image" alt="Molecule 3.6i" /></td>
<td>71</td>
</tr>
</tbody>
</table>

*Reaction conditions: 3.1 (0.20 mmol), 3.2a (0.60 mmol), 3.8b (0.40), Cp₂TiCl₂ (0.04 mmol), tBu₃P (0.16 mmol), Zn (0.44 mmol), Cs₂CO₃ (0.20 mmol) and Ac₂O (0.44 mmol) at 0.13 M. Isolated yields*
### TABLE 3.12

**ARENE SCOPE IN THE SYNTHESIS OF DIARYLETHNYL METHANES**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar–H</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Image" /></td>
<td><img src="image2" alt="Image" /></td>
<td>63</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3" alt="Image" /></td>
<td><img src="image4" alt="Image" /></td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td><img src="image5" alt="Image" /></td>
<td><img src="image6" alt="Image" /></td>
<td>81</td>
</tr>
<tr>
<td>4</td>
<td><img src="image7" alt="Image" /></td>
<td><img src="image8" alt="Image" /></td>
<td>68</td>
</tr>
</tbody>
</table>

*Reaction conditions: 3.1a (0.20 mmol), 3.2a (0.60 mmol), 3.8 (0.40 mmol), Cp$_2$TiCl$_2$ (0.04 mmol), tBu$_3$P (80 mol%), Zn (0.44 mmol), Cs$_2$CO$_3$ (0.20 mmol) and Ac$_2$O (0.44 mmol) at 0.13 M.*

*Isolated yields*
## TABLE 3.13

**IODOALKyne SCOPE IN THE SYNTHESIS OF DIARYLETHYNYL METHANES**

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Product</th>
<th>Yield (%)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="3.2b" /></td>
<td><img src="image" alt="3.6n" /></td>
<td>83</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="3.2d" /></td>
<td><img src="image" alt="3.6o" /></td>
<td>83</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="3.2c" /></td>
<td><img src="image" alt="3.6p" /></td>
<td>80</td>
</tr>
<tr>
<td>4</td>
<td>$^n$Bu (3.2e)</td>
<td><img src="image" alt="3.6q" /></td>
<td>80</td>
</tr>
<tr>
<td>5</td>
<td>BnOCH$_2$ (3.2f)</td>
<td><img src="image" alt="3.6r" /></td>
<td>58</td>
</tr>
<tr>
<td>6</td>
<td>TIPS (3.2g)</td>
<td><img src="image" alt="3.6s" /></td>
<td>67</td>
</tr>
</tbody>
</table>

$^a$Reaction conditions: **3.1a** (0.20 mmol), **3.2** (0.60 mmol), **3.8b** (0.40 mmol), Cp$_2$TiCl$_2$ (0.04 mmol), $^t$Bu$_3$P (0.16 mmol), Zn (0.44 mmol), Cs$_2$CO$_3$ (0.20 mmol) and Ac$_2$O (0.44 mmol) at 0.13 M $^b$Isolated yields

65
Whereas aromatic aldehydes proved effective substrates for the three-component coupling reaction, the use of cyclohexane carboxaldehyde 3.1j as the starting aldehyde resulted in propargyl acetate 3.9 isolated in 92% yield. These results are consistent with the idea that ionization of a propargylic intermediate precedes the second carbon–carbon bond forming event. We postulate that an adjacent aliphatic substituent does not sufficiently stabilize a carbocation intermediate. Interestingly, we observed one instance of a double aryl addition to an aldehyde. The use of iodopropionate 3.2h produced exclusively triaryl methane 3.10 in 67% (eq 77) and recovered iodoalkyne 3.2h. This result seemed to stem from an extremely slow metalation of the iodoalkyne, which allowed nucleophilic attack by N-methylinodole to the aldehyde under the Lewis-acidic conditions.  

\[
\text{C}_{6}H_{5}CHO + \text{C}_{6}H_{5}NMe + \text{CO}_{2}Et \xrightarrow{\text{Cp}_{2}TiCl}_{2} (5 \text{ mol%), Zn PBU}_{3} (80 \text{ mol%), Cs}_{2}CO_{3} \text{Ac}_2O, DCE} 3.10
\]

In an effort to construct fused indole structures from aliphatic aldehydes, indole 3.1k was subjected to more forcing conditions (Table 3.14). Acetic anhydride addition did not produce desired product 3.12, but propargyl acetate 3.11 was recovered at room temperature, and complex mixtures were produced at elevated temperatures. To
increase the lability of the propargyl leaving group, trifluoroacetic anhydride was tested. Again, at elevated temperatures, only decomposition was observed.

TABLE 3.14

ATTEMPTED ALKYLATIVE CYCLIZATION

<table>
<thead>
<tr>
<th>Entry</th>
<th>Activating Agent</th>
<th>Temperature</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ac₂O</td>
<td>room temp.</td>
<td>3.11 (quant.)</td>
</tr>
<tr>
<td>2</td>
<td>Ac₂O</td>
<td>80 °C</td>
<td>complex mixture</td>
</tr>
<tr>
<td>3</td>
<td>(CF₃CO)₂O</td>
<td>room temp.</td>
<td>3.11 (quant.)</td>
</tr>
<tr>
<td>4</td>
<td>(CF₃CO)₂O</td>
<td>80 °C</td>
<td>complex mixture</td>
</tr>
</tbody>
</table>

*aReaction conditions: 3.1k (0.20 mmol), 3.2a (0.60 mmol), Cp₂TiCl₂ (0.04 mmol), Bu₃P (0.16 mmol), Zn (0.44 mmol), Cs₂CO₃ (0.20 mmol) and activating agent (0.44 mmol) at 0.13 M bIsolated yields

3.4 Miscellaneous Nucleophile Examination

To further investigate the scope of the three-component coupling, various other nucleophiles were examined. As many natural products contain the butenolide motif, investigation of an electron rich oxyfuran as a nucleophilic component was carried out. Gratifyingly, the electron-rich siloxyfuran 3.8f provided butenolide 3.6t in 60% yield as a 1:1 mixture of diastereomers after a brief screen of conditions (Table 3.15).³
Further attempts to expand the scope of this reactivity revealed the chemoselective nature of the metatlation conditions. Attempts to produce unsymmetrical triarylmethanes were unsuccessful due to the inability to break the C–X bond in aryl halides. Similarly, vinyl halides did not undergo metatlation under our conditions (eq 78).
3.5 Access of Propargyl Titanocenes as Nucleophiles

In an effort to extend the scope of the three-component coupling reaction, and to further investigate activated propargyl species in titanocene catalysis, we sought an *umpolung* approach to utilize the propargyl acetate as a pronucleophile rather than an electrophile (Figure 3.2). It is well known in the literature that propargyl titanocene complexes, studied most prominently by the Yamamoto, Sato, and Ding labs, are formed through a variety of methods (including titanocene and zinc) and are readily added to electrophiles.\(^94-97\) In spite of this, no catalytic metalation of propargyl acetates by titanocene was reported, and thus we set out to study how we could access propargyl metal species first starting from propargyl acetates, with the goal of extending this method to a three-component coupling.

![Figure 3.2: Titanocene-Catalyzed *Umpolung* Approach to Tertiary Carbon Centers](image)

---

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TABLE 3.16

CATALYTIC PROPARGYLIC METALATION

<table>
<thead>
<tr>
<th>Entry(^a)</th>
<th>Metal</th>
<th>Additive</th>
<th>Solvent</th>
<th>3.16 (% yield)(^b,c)</th>
<th>3.5a (% yield)(^b,c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Mg</td>
<td>-</td>
<td>THF</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>Mn</td>
<td>-</td>
<td>THF</td>
<td>&lt;5</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>Zn</td>
<td>-</td>
<td>THF</td>
<td>&lt;5</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>Zn</td>
<td>-</td>
<td>CH(_2)Cl(_2)</td>
<td>36</td>
<td>34</td>
</tr>
<tr>
<td>5</td>
<td>Zn</td>
<td>-</td>
<td>CH(_2)Cl(_2):THF (1:1)</td>
<td>&lt;5</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>Zn</td>
<td>-</td>
<td>Et(_2)O</td>
<td>&lt;5</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>Zn</td>
<td>-</td>
<td>toluene</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>Zn</td>
<td>tBu(_3)P</td>
<td>CH(_2)Cl(_2)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>Zn</td>
<td>Ph(_3)P</td>
<td>CH(_2)Cl(_2)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>Zn</td>
<td>(MeO)(_3)P</td>
<td>CH(_2)Cl(_2)</td>
<td>&lt;5</td>
<td>0</td>
</tr>
<tr>
<td>11</td>
<td>Zn</td>
<td>2,4,6-collidine·HCl</td>
<td>THF</td>
<td>&lt;5</td>
<td>0</td>
</tr>
<tr>
<td>12</td>
<td>Zn</td>
<td>2,4,6-collidine·TMSCl</td>
<td>THF</td>
<td>&lt;5%</td>
<td>0</td>
</tr>
</tbody>
</table>

\(^a\)Reaction conditions: 3.15 (0.20 mmol), 3.1a (0.20 mmol), Cp\(_2\)TiCl\(_2\) (10 mol%), Zn (0.44 mmol), and Ac\(_2\)O (0.44 mmol) at 0.13 M \(^b\)Isolated yields \(^c\)Isolated as 1:1 mixture of diastereomers

Propargyl acetate 3.15 was treated with a catalytic amount of titanocene dichloride and reducing metal (Table 3.16, entries 1 – 3) in THF, resulting in quantitative recovery of starting aldehyde and acetate, even in the presence of known titanocene “turnover reagents” (entries 11, 12). Interestingly, employing dichloromethane as
solvent gave a mixture of homopropargyl alcohol 3.16 and 1,5-diyne 3.5a, each as a 1:1 mixture of diastereomers (entries 3,4). Additionally, doping the reactions with phosphines prevented conversion of the propargyl acetate (entries 8 – 10). The inhibition of reactivity in the presence of phosphine or THF is intriguing, as these additives were found to be crucial in the efficient production of propargyl alcohols from aldehydes and iodoalkynes described at the beginning of this chapter. One could speculate that phosphine or THF serve to narrow the reactivity profile of titanocene, thus inhibiting this type of propargylic activation. In regards to the three-component coupling, it appears that at least under these conditions, a three-component umpolung process is not currently feasible due to the requirement of phosphine in the first alkynylation step, which would inhibit the activation of the resultant propargylic species. However, my colleague Jennifer Meloche optimized the above two-component reaction, and explored the reaction scope and limitations.\textsuperscript{98} Importantly, this work extended the catalytic capabilities of titanocene to include propargylic metalation, one of many avenues this catalyst will continue to traverse.

3.6 Synthesis of $\alpha,\beta$-unsaturated Ketones

Continuing to utilize the metalation capabilities of titanocene complexes, we sought to expand the multicomponent-coupling manifold to include a greater number of tertiary carbon types. Based on literature-precedented titanocene-catalyzed Reformatsky reactions,\textsuperscript{56,57} we explored the use of $\alpha$-halo ketones as our starting pronucleophile in place of iodoacetylenes (Figure 3.3). In this case, in the presence of
acetic anhydride, we speculated there would be a facile elimination of the $\beta$-acetoxy ketone, followed by a Lewis-acid mediated 1,4-addition to the chalcone.

![Figure 3.3: Titanocene-Catalyzed Assembly of Tertiary Carbon Centers via a Tandem Reformatsky/ Michael Addition](image)

As seen in Table 3.17, acetic anhydride was essential for turnover of the titanocene catalyst, in accord with a literature precedent using trifluoroacetic anhydride. The use of 2.0 equivalents of triethylamine proved optimal, and to the best of our knowledge, this is the first example of $\alpha,\beta$-unsaturated ketone synthesis using titanocene catalysis. Curiously, attempts to use different bases such as DBU, carbonates, or imidazole gave complex mixtures.
TABLE 3.17
TITANOCENE-CATALYZED REFORMATSKY INVESTIGATION

<table>
<thead>
<tr>
<th>Entry</th>
<th>( \text{Ac}_2O ) (equiv)</th>
<th>base (equiv)</th>
<th>( 3.18 ) (%)</th>
<th>( 3.19 ) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>-</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>-</td>
<td>-</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>1.0</td>
<td>-</td>
<td>55</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>1.0</td>
<td>( \text{Et}_3\text{N} ) (1.0)</td>
<td>24</td>
<td>27</td>
</tr>
<tr>
<td>6</td>
<td>1.0</td>
<td>( \text{Et}_3\text{N} ) (2.0)</td>
<td>0</td>
<td>70</td>
</tr>
<tr>
<td>7</td>
<td>1.0</td>
<td>( \text{ImH} ) (2.0)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>1.0</td>
<td>( \text{K}_2\text{CO}_3 ) (2.0)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>1.0</td>
<td>( \text{DBU} ) (2.0)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

\(^a\)Reaction conditions: \( 3.1f \) (0.20 mmol), \( 3.15 \) (0.40 mmol), \( \text{Cp}_2\text{TiCl}_2 \) (0.01 mmol), and \( \text{Zn} \) (0.40 mmol), at 0.20 M \(^b\)Isolated yields

Next, 1,3,5-trimethoxybenzene was introduced to the reaction conditions in an effort to carry out a three-component coupling. The results seemed to indicate that improved Lewis acidity was necessary for the conjugate addition to occur. However, doping the reaction mixtures with a full equivalent of Lewis acids \( \text{TiCl}_4 \), \( \text{Ti(O}^{\text{OPr}})\text{)}_4 \), \( \text{BF}_3\text{OEt}_2 \), and \( \text{SnCl}_4 \) similarly failed to convert the enone to the \( \beta \)-substituted ketone, and only the chalcone remained. This may be due to the Lewis basic triethylamine
interacting with Lewis acids in solution. These initial results, therefore, prompted us to set aside this strategy for tertiary center synthesis.

3.7 Indium Mediated Tertiary Center Synthesis

While effective, our titanocene-catalyzed methodology requires the iodoalkyne functionality to induce metal-acetylide formation. Could we establish a three-component coupling strategy from terminal acetylenes? Further guided by our interest in tertiary carbon center synthesis, we sought to investigate the reactivity of a different catalyst. To address this question, we looked to a metal known to both facilitate acetylide additions from terminal alkynes and initiate propargylic activation chemistry.

![Figure 3.4: Indium/ Brønsted Acid Catalyzed Synthesis of Tertiary Carbon Centers](figure)

Indium(III) salts are known to facilitate terminal acetylene additions to aldehydes, and also enable propargylic substitution reactions of free alcohols.\textsuperscript{99,100} For these reasons we chose to investigate an indium-mediated three-component coupling reaction (Figure 3.4). Initial studies in this reaction system evaluated the reactivity using a full equivalent of indium. While the absence of additives only led to recovered propargyl alcohol, the addition of Brønsted-acid additives facilitated the propargylic substitution reaction (Table 3.18). Indium(III) chloride worked comparably well, but
indium(III) triflate gave no reaction, likely due to a lack of solubility of the complex. Importantly, this established the feasibility of the requisite reactivity to produce diarylethynyl methanes in a “dual-catalyst” system.

**TABLE 3.18**

**INDIUM-CATALYZED DIARYLETHYNYL METHANE SYNTHESIS**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Additive (1.0)</th>
<th>3.3d Yield (%)^b</th>
<th>3.6u Yield (%)^b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>94</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>p-TsOH</td>
<td>-</td>
<td>70</td>
</tr>
<tr>
<td>3</td>
<td>Ac₂O</td>
<td>89</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>(±)-CSA</td>
<td>-</td>
<td>75</td>
</tr>
</tbody>
</table>

^bReaction conditions: **1.63** (0.41 mmol), **3.20** (0.82 mmol), **3.8g** (0.82 mmol), InBr₃ (0.41), and DIPEA (0.82 mmol), at 0.20 M *^b*isolated yields

We next investigated whether we could render this protocol catalytic in indium and acid. Lowering the amount of indium to 20 mol% did not impede the reaction, and diarylethynyl methane **3.6v** was produced in 85% yield (eq 79).
However, Lowering the amount of Brønsted acid proved detrimental (eq 80). Intriguingly, when an excess of indium(III) bromide relative to base was employed, a catalytic amount of acid could be used to achieve a moderate yield (eq 81). The lack of conversion of aldehyde to propargyl alcohol in these reactions led to the diminished yields.

This indium / Brønsted acid methodology establishes a new platform for tertiary carbon center synthesis moving forward. Work remains to optimize this protocol, and to fully explore the scope and limitations.
3.8 Conclusion

The convergent synthesis of tertiary carbon centers was described herein. Aromatic aldehydes effectively coupled to a variety of alkynes and electron-rich nucleophilic components in a one-pot operation. The use of the adaptable titanocene catalyst not only facilitated efficient carbon–carbon bond formations, but also established a reaction manifold that spurred innovations in other catalytic arenas. This work takes a small step toward realizing the potential of these types of three-component couplings. Future work will undoubtedly focus on systems that allow for catalyst-controlled stereoselection, and enhancements in breadth of scope.
Cancers of the brain and central nervous system (CNS) are devastating diseases with characteristically aggressive tumors, and of these perhaps the type with the most bleak prognosis is glioblastoma.\textsuperscript{101} With an estimated 20,000 diagnoses per year and a median survival of less than one year, new treatments are desperately needed. Currently, the most effective treatment options include a combination of chemotherapy and radiation, as surgery is often prohibited due to the diffuse nature of metastatic tumors. With regard to available chemotherapeutic options, major limiting factors include high systemic toxicity and the inability of many compounds to cross the blood-brain-barrier (BBB).\textsuperscript{102} Presently, prescribed medicines include carmustine and temozolomide (Figure 4.1), both harsh DNA-alkylating agents that show limited success in glioblastoma patients.\textsuperscript{103} Cognizant of these hurdles, our group has an ongoing interest in the exploration of compounds that show promising biological activity against brain and CNS cancers.

Figure 4.1: Temozolomide and Carmustine
A compound that has captured our attention in this regard is curcumin (Figure 4.2). This diarylheptanoid is a major component of turmeric and has a wide array of biological activity. Curcumin generated substantial interest in recent years as a potential pharmaceutical agent, but its use in the clinic has not been realized due to low potency and poor bioavailability.\textsuperscript{35}

![Curcumin](image)

Figure 4.2: Curcumin

However, because curcumin possesses many favorable attributes including low toxicity and BBB permeability,\textsuperscript{104} substantial interest from the medicinal chemistry community exists in the study of analogues. Recent reports detailing, the antiglioblastoma activity of curcumin led us to investigate natural and synthetic analogues for anti-tumor activity in order to search for lead compounds in the fight against brain and CNS cancers.\textsuperscript{105,106,107} The calyxins are a biologically active subclass of diarylheptanoids that display a broad structural diversity, and show promising biological activity as discussed in Chapter 1 (Figure 4.3). We postulate the array of structural variation of the calyxins provides an opportunity to explore synthetic and biological properties of these variants with regard to structure and function. Specifically, long-term goals include evaluation of calyxins and synthetic analogues for cytotoxicity and BBB permeability. As the calyxins incorporate a modular structural nature, structure-activity relationships can potentially be investigated with regard to modifications of the
arylheptanoid chain, the chalcone appendage, and polarity modulation of hydroxyl groups (Figure 4.4).

![Chemical structures](image)

**Figure 4.3: Representative Calyxin Natural Products**

**Figure 4.4: General Calyxin Archetype with Highlighted Characteristic Structural Elements**

Synthetically, access to these compounds remains a formidable challenge. The Rychnovsky group described the total syntheses of a number of pyran-containing (cyclic) calyxins, which importantly led to the structural reassignment of calyxin L and calyxin F.
Additionally, biosynthetic hypotheses could be drawn from their efforts as described in chapter 1. However, these syntheses require many linear steps, and a route with a high degree of convergency is desired. As a general entry into the calyxin family is not presently available, we speculated that our titanocene-catalyzed three component coupling regime would address these synthetic challenges by honing in on the tertiary carbon centers present in all calyxins to give a general and convergent entry.

4.1 Synthesis

4.1.1 Initial Synthesis of Calyxin Framework

With a developed method for diarylethynyl methane construction, we moved into studies aimed at the synthesis of diarylheptanoid and calyxin analogues. We targeted calyxin B and epicalyxin B because they are the most biologically active of the acyclic calyxins, and have not yet succumbed to total synthesis. We envisioned calyxin B (4.1) to arise from diarylethynyl methane 4.2 after a *trans*-selective reduction of the internal alkyne (Figure 4.5). The ketone in 4.2 comes from an acylation of 4.3, which is the product of the titanocene-catalyzed three-component coupling between 4.4, 4.5 and 4.6. The requisite iodoalkyne 4.4 is assembled through iodination and protection of the free alcohol, which stems from an asymmetric propargylation of an aldehyde. The more electron-rich arene 4.6 serves as the second nucleophile in the three-component coupling, while the *para*-phenolic aryl ring carries the aldehyde in 4.5.
Figure 4.5: Retrosynthesis of Calyxin B

To test the feasibility of the three-component coupling, racemic iodoalkyne 4.10 was prepared and subjected to the reaction conditions with phloroglucinol derived aldehydes 4.11a and 4.11b (Scheme 4.1).

Scheme 4.1: Synthesis of rac-iodoalkyne 4.10
Unfortunately, the reaction failed to yield any coupling product, and only ortho-selective monodeprotection was observed to give aldehydes 4.13a and 4.13b (eq 82). Together with my colleague Lauren Fleury, we explored this curious result further. We discovered that Zn\textsuperscript{II} salts facilitated the deprotection, with ZnCl\textsubscript{2} giving the best yields. Interestingly, deprotection of ethereal protecting groups benzyloxymethyl and ethylethoxymethyl led to complex mixtures unless diethyl ether was used as the solvent (eq 83). When ketone 4.11e was subjected to ZnCl\textsubscript{2} in ether, the BOM group was selectively removed. However, in 1,2-dichloroethane, a 1:1 mixture of deprotection products was obtained (eq 84). The observed reactivity was found to be selective for a variety of carbon and silicon groups, while leaving sulfanyl groups intact. In the context of the ortho-phenol deprotection methods, this was an incredibly mild and general method compared to known literature procedures.\textsuperscript{108,109,110,111}

\[\text{R = BOM 4.11c, 71%} \quad \text{R = EOM 4.11d, 55%}\]

\[\text{solvent = Et}_2\text{O, 4.13e, 86%} \quad \text{solvent = DCE, 4.13e/4.13f, (1:1), 81%}\]
After exploration of the Zn\(^{II}\) reactivity, the task remained to establish an enatioselcetive route to the alkyne component. Our first attempts at the preparation of enantioenriched iodoalkyne 4.16 featured a Keck propargylation employing Ti(OiPr)\(_4\), (R)-BINOL and allenyltributylstannane.\(^{112}\) These conditions led to low conversion of the starting aldehyde and allene even under stoichiometric conditions. However, conditions developed by Maruoka and coworkers afforded the optically active homopropargylic alcohol 4.15 in 81% yield and 83% ee (Scheme 4.2).\(^{113}\)

Subsequent silyl protection and iodination produced the desired iodoalkyne 4.16. Gratifyingly, treatment of 4.16 with aldehyde 4.17 and 1,3,5-trimethoxybenzene (3.8g) employing our optimized protocol gave the desired diarethynyl methane 4.18 in 99% yield as a 1:1 mixture of diastereomers (eq 85). The lack of diastereoselectivity here is perhaps unsurprising given the distance of the existing stereocenter from the site of carbon–carbon bond formation.
Attempts to demethylate compound 4.18 were unsuccessful and led only to complex mixtures upon treatment with BBr₃ or BrI. However, treatment with TBAF resulted in the isolation of secondary alcohol 4.19, which was subsequently treated with a range of hydride reagents in an attempt to direct an E-selective reduction (Scheme 4.3). These conditions again led to complex mixtures. Fortunately, the catalytic ruthenium protocol developed independently by the Trost and Fürstner laboratories led to selective reduction of the internal alkyne to give vinyl siloxane 4.20.¹¹⁴

Scheme 4.3: Synthesis of Vinyl Siloxane 4.20

Unfortunately, this intermediate failed to couple with the cinnamoyl derivative as hoped under Lewis acid mediated Friedel-Crafts acylation conditions. We therefore attempted a different route of acylation involving halogenation and subsequent lithium-halogen exchange to add into an appropriate electrophile. Bromination of the most electron-rich aryl ring present in 4.20 gave aryl bromide 4.21 (Scheme 4.4). While a variety of conditions were evaluated for metal-halogen exchange (tBuLi, sBuLi, PhLi, PhMgBr, etc.), each resulted in complex mixtures of products. We postulated that the
vinyl siloxane was problematic under the conditions employed, and alternate avenues of chalcone appendage were explored.

In an attempt to avoid these issues of lithium-halogen exchange, we attempted to append the chalcone at an earlier stage, starting with homopropargyl silylether 4.18. Bromination proceeded smoothly, and after some experimentation PhLi (as described by Rychnovsky) proved successful in the lithium-halogen exchange. Addition of \( \alpha,\beta \)-unsaturated aldehyde 4.23 resulted in the formation of a mixture of diastereomeric allylic alcohol products. Failed oxidation attempts with \( \text{MnO}_2 \), TPAP/NMO, and DMP led to the use of DDQ followed by silyl deprotection with TBAF to give chalcone 4.24 in 39\% over three steps. Silylation of the resultant homopropargyl alcohol with chlorodimethylsilane followed by addition of the Ru-catalyst gave a vinyl siloxane. Desilylation to give \textit{trans}-alkene 4.25 was realized with TBAF in DMF at 120 °C (Scheme 4.6). Thus, a synthesis of a protected analogue of calyxin B was achieved. One of the remaining hurdles to gain access to calyxin B is to establish a route that allows for the
differentiation of the phenolic ether para to the established tertiary carbon center (Figure 4.5).

Scheme 4.5: Calyxin Analogue Synthesis

Figure 4.6: Phenolic Substitution Pattern in Calyxin B

4.1.2 Modified Protecting Group Strategies

As the appropriate methyl/phenolic substitution on the phloroglucinol appeared not plausible (as highlighted in Figure 4.6), new strategies for the synthesis of calyxin B
had to be devised (Figure 4.7). Three avenues were considered as options: 1) a regioselective arylation event directed by judicious protecting group choice on the phloroglucinol residue 2) a post-three-component coupling differentiation of the para-phenol group and 3) an appropriate substitution pattern on an aromatic aldehyde electrophile. Although our previous efforts to carry ortho-substituted aldehydes through our three-component coupling failed (eq 82), we thought a more robust protecting group would ameliorate this problem. Initial studies directed at appropriate differentiation of the phenolic residues employed differentially protected aldehyde **4.11g**, iodoalkyne **4.16** and the silyl ether **4.12**.

![Scheme 4.6: Strategies for the Appropriate Methyl-Ether Substitution for Calyxin B](image)

Subjection of these components to the titanocene-catalyzed three-component coupling conditions led to low and irreproducible yields (Scheme 4.6). By TLC analysis, the initial propargyl alkoxide formation was inefficient, as only a low amount of the aldehyde was converted. We speculated that the steric bulk of the two flanking
phenylsulfonyl groups inhibited the addition of the acetylide. To further probe the nature of ortho-substitution on the aldehyde, an aldehyde similar to one previously used with success (4.17) was subjected to the alkynylation protocol. Surprisingly, a complex mixture of products was observed after 2 hours at room temperature. At this point it became apparent that ortho-substituents on the aldehyde component would not be feasible, and an alternate route would have to be devised.

Scheme 4.7: Investigation of ortho-Substituted Aldehydes in the Three-Component Coupling Reaction

To investigate the second strategy (vide supra), we synthesized a phloroglucinol derivative capped with one methyl group and two triethylsilyl groups. We chose to look at this regiochemical question to get a handle on the protecting group size on product distribution. To this end, phloroglucinol derivative 4.27 was subjected to the three-component coupling reaction as the nucleophilic arene. Interestingly, only a trace amount of the para-methoxy isomer was detected, with the major product being the ortho-derivative (eq 86). Although this reaction provided rapid access to a potentially
interesting regiochemical analogue, we deemed this strategy as an ineffective approach to synthesize calyxin B.

To appropriately substitute the phenolic residue, we carried out the titanocene-catalyzed three-component coupling with tris-TES-protected phloroglucinol \(4.28\). With this strategy, the para-phenol could be differentiated, being the least sterically encumbered phenol residue. The coupling proceeded smoothly to give diarylethynyl methane \(4.29\) in good yield (Scheme 4.7), and fortunately, under Brønsted acidic conditions we observed selective deprotection at the phenol para to the newly forged tertiary carbon center to give \(4.30\). Methylation of the free phenol then gave methyl ether \(4.31\).

Scheme 4.8: Post-Coupling Phenolic Differentiation
Once the phloroglucinol fragment was appropriately differentiated, the challenge remained to reduce the alkyne component under the new protecting group regime. Initially we attempted to perform an intermolecular Ruthenium-catalyzed trans-hydrosilylation strategy (eq 87). This hydrosilylation methodology has not been demonstrated on a substrate as elaborate as ours, and initial attempts proved unsuccessful, only leading to recovered starting material. This result could possibly be attributed to the steric encumbrance surrounding our alkyne, which is why the intramolecular reaction works efficiently.

![Reaction Scheme]

\[ \text{OBn} \quad \text{OTES} \quad \text{OTES} \quad \text{OTES} \quad \text{OTES} \quad \text{Cp}^*\text{Ru(\text{CH}_3\text{CN})}_3\text{PF}_6 \,(5\,\text{mol\%}) \quad \text{hydride source} \quad \text{(EtO)}_3\text{Si–H} \quad \text{Bu}_3\text{Sn–H} \quad \text{H–H} \quad \text{no conversion of alkyne} \quad (87) \]

Future directions of this project in the short term include the completion of the total synthesis of calyxin B (Figure 4.8). In order to accomplish this goal, a suitable alkyne reduction strategy needs to be found. In contrast to the analogue, completion of calyxin B likely involves careful protecting group manipulation to maintain differentiation among the phenolic residues, but also provide a handle for a hydroxyl-directed alkyne reduction.
4.2 Biological Activity

Motivated by our interest in biologically active compounds against glioblastoma and neuroblastoma, our laboratory, in a collaboration led by Dr. Karen Pollok at the Indiana University School of Medicine, evaluated a series of diarylheptanoid analogues against human glioblastoma and neuroblastoma cell lines \textit{in vitro}. Together with Catherine Campos, we synthesized six synthetic diarylheptanoid analogues (Figure 4.9), with my compounds being synthetic intermediates ND5 (4.19) and ND6 (4.20) prepared \textit{en route} to calyxin B (see Chapter 4).\textsuperscript{115}
Accordingly, these compounds were exposed to U87-MG human glioblastoma cells in increasing concentrations (Figure 4.10). Gratifyingly, two of our compounds, ND1 and ND2 showed good biological activity at 7.5 and 8.0 μM, respectively. Next, the compounds were evaluated for their dependence on p53, a protein often associated with cancer resistance. Wild-type, p53-knock down and the vector control cell lines were exposed to our compounds. The inhibition displayed was retained irrespective of p53 status, indicating that inhibition was not dependent on the p53 pathway. Similarly, SK-NF-1 human neuroblastoma cell lines were exposed to the diarylheptanoids. Again ND1 and ND2 showed promising activity at 18.1 and 11.7 μM, respectively. The activity was retained regardless of p53 expression as before. Overall, these compounds display comparable activity when compared to curcumin, which showed 8.1 and 6.4 μM activity against U87-MG and SK-NF-1 cell lines.
Decrease cell growth in glioblastoma and neuroblastoma cells irrespective of p53 status. (A) U87 MG GBM cells were exposed in triplicate to vehicle or increasing concentrations of compound and growth was measured at 5 days post-exposure. To quantify cell mass, cells were stained with methylene blue, solubilized in 0.1N HCl, and absorbance determined at 610nm. (B) Effect of ND1 and ND2 on U87 parental, U87 vector control (U87gfpcontrol), and cells with knock down of p53 (U87shp53) was determined as described above.

Figure 4.9: Anti Glioblastoma and Neuroblastoma Activity of Diarylethananoid Analogues

In light of these promising results, our compounds were then evaluated for toxicity against non-tumor cells. Human CD34+ stem cells were grown in increasing concentrations of ND1, ND2 and ND6 (Figure 4.11). After 14 days, cell death was not
pronounced. This initial study indicated cancer cell selectivity in vitro, and provides an intriguing initial dataset on diarylheptanoid analogues.

![Graph showing results of toxicity evaluation](image)

Human CD34+ cells (2000 per plate) were exposed in triplicate to 0.3-30 µM of compounds ND1, ND2, or ND6. Progenitor cell frequency was determined after 14 days by visual examination under an inverted microscope. *p < 0.05, vehicle vs ND2 at 30 µM.

**Figure 4.10: In Vitro Toxicity Evaluation of Diarylheptanoid Analogues**

4.3 Conclusion

The synthesis and biological evaluation of diarylheptanoid analogues described above represents our continued efforts to develop a rapid entry into biologically interesting molecules. The ability to form multiple carbon–carbon bonds in a single synthetic operation increases efficiency as we continue to strive for ideal synthetic methodology. The titanium-catalyzed three component coupling reaction has proven an effective method to construct diarylethynyl methanes. Importantly, the reactivity has shown to be robust while using more advanced substrates in the context of diarylheptanoid synthesis. We also explored the limits of reactivity and found that ortho-substituted substrates are not tolerated, but importantly we found a new method for the selective ortho-monodeprotection of aryl carbonyl derivatives.
In the long term, continued study of the synthesis of the calyxins and other diarylheptanoids will advance synthetic methodology and spur innovation in other unexpected ways. Total synthesis not only establishes unique entry into important molecules, but also inspires creative advancement of chemical science.
CHAPTER 5:

EXPERIMENTAL PROCEDURES

All solvents and reagents were ACS reagent grade, obtained from commercial sources, and used without further purification unless otherwise stated. Acetonitrile (CH$_3$CN), dimethylformamide (DMF), toluene (PhMe), tetrahydrofuran (THF), dichloromethane (CH$_2$Cl$_2$) and diethyl ether (Et$_2$O) were degassed with argon, passed through a column of molecular sieves, and stored under argon. 1,2-Dichloroethane (DCE) was distilled over CaH$_2$, stored over 4 Å molecular sieves, and degassed with argon thoroughly prior to use. All reactions were carried out in oven-dried glassware under argon unless otherwise specified.

$^1$H nuclear magnetic resonance (NMR) spectra were obtained at either 300, 400, 500 or 600 MHz. $^{13}$C NMR were obtained at 100, 125 or 150 MHz, Chemical shifts are reported in parts per million (ppm, δ), and referenced from chloroform or tetramethylsilane (TMS). Coupling constants are reported in Hertz (Hz). Spectral splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; p, pentet; m, multiplet; comp, complex; app, apparent; hom, higher order multiplet; and br, broad. Infrared (IR) spectra were obtained using a Thermo Electron Nicolet 380 FT-IR using a silicon (Si) crystal in an attenuated total reflectance (ATR) tower and reported as wavenumbers (cm$^{-1}$). High and Low resolution electrospray ionization (ESI)
measurements were made with a Bruker MicroTOF II mass spectrometer, Analytical thin layer chromatography (TLC) was performed using EMD 250 micron 60 F254 silica gel plates, visualized with UV light (254 nm lamp) and stained with either p-anisaldehyde, ceric ammonium nitrate (CAN) or potassium permanganate (KMnO₄) solutions. Flash column chromatography was performed according to Still’s procedure (Still, W.C.; Kahn, M.; Mitra, A. J. Org. Chem. 1978, 43, 2923) using EMD 40-63 µm 60 Å silica gel. Melting points were determined in capillary tubes using an Electrothermal Mel-Temp apparatus and are uncorrected.

5.1 Synthetic Procedures From Chapter 3

5.1.1 General

The following compounds were purchased from a commercial source and used without further purification unless otherwise noted: 1.63, 2.48, 3.1a, 3.1b, 3.1d, 3.1f, 3.1h-j, 3.8a, 3.8b, 3.8d, 3.8e-g, 3.13, 3.15, and 3.20. The following compounds were prepared following previously reported literature procedures: 3.1c, 3.1g, 3.1k, 3.2a-h, 3.7, 3.8c, and 3.14. Zinc dust was rinsed with 1M HCl, filtered and washed thoroughly with water, acetone and ether and dried under vacuum.

5.1.2 Synthesis of Substrates and Reagents

3-Phenyl-1-(p-tolyl)prop-2-yn-1-ol (3.3b). A vial, equipped with a magnetic stir bar, was charged with Cp₂TiCl₂ (1.8 mg, 7.0 µmol), and zinc dust (50 mg, 0.73 mmol) then purged
with argon for 5 min. A solution of dry, degassed CH₂Cl₂/THF (1:1, 0.25 mL) was added and the resulting gray slurry was stirred vigorously at 25 °C until it took on a blue/green color. A solution of para-tolualdehyde (42 µL, 0.37 mmol) and phenyliodoacetylene (84 mg, 0.37 mmol) in CH₂Cl₂/THF (1:1, 0.50 mL) was then added dropwise. The resulting mixture was stirred at 25 °C until TLC analysis indicated full conversion of the aldehyde (3-4 hours). Purification by flash chromatography eluting with hexanes/EtOAc (3:1) provided 45 mg (55%) of 3.3b as a yellow oil. The ¹H-NMR data for 3.3b was consistent with literature reported data.¹²⁸

![Chemical structure of 3.3c](image)

**1-(4-Chlorophenyl)-3-phenylprop-2-yn-1-ol (3.3c).** A vial, equipped with a magnetic stir bar, was charged with Cp₂TiCl₂ (1.8 mg, 7.0 µmol), and purged with argon for 5 min. Dry, degassed CH₂Cl₂ (0.25 mL) was added and the resulting solution stirred at 25 °C for 5 min. Diethyl zinc (1 M in hexanes) (0.73 mL, 0.73 mmol) was added, followed by addition of a solution of tri-tert-butylphosphine (30 mg, 0.15 mmol) in CH₂Cl₂ (0.25 mL). A solution of 4-chlorobenzaldehyde (52 mg, 0.37 mmol) and phenyliodoacetylene (84 mg, 0.37 mmol) in CH₂Cl₂ (0.50 mL) was then added, dropwise. The resulting mixture was stirred at 25 °C until TLC analysis indicated full conversion of the aldehyde (3-4 hours). Purification by flash chromatography eluting with hexanes/EtOAc (3:1) provided 60 mg (67%) of 3.3c as a yellow oil. The ¹H-NMR data for 3.3c was consistent with literature reported data.¹²⁸
Hexa-1,5-diyne-1,3,4,6-tetrayltetrabenzene (3.5). A vial, equipped with a magnetic stir bar, was charged with titanocene dichloride (1.8 mg, 7.0 μmol) and zinc dust (50 mg, 0.77 mmol), and then purged with argon for 5 min. Dry, degassed CH₂Cl₂ (0.25 mL) was added and the resulting gray slurry was stirred vigorously at 25 °C until it took on a blue/green color. A solution of phosphine (0.15 mmol) in CH₂Cl₂ (0.25 mL) was added slowly, followed by the dropwise addition of a solution of 4-methoxybenzaldehyde (44 μL, 0.37 mmol) and phenyliodoacetylene (84 mg, 0.37 mmol) in CH₂Cl₂ (0.50 mL). The resulting mixture was stirred at 25 °C until TLC indicated full conversion of the starting aldehyde (~3-4 hrs), at which time 1-(iodoethynyl)-4-methoxybenzene (142 mg, 0.55 mmol) was added neat and in one portion. A solution of Ac₂O (80 μL, 0.84 mmol) in CH₂Cl₂ (0.80 mL) was then added dropwise. The solution was stirred until conversion of the intermediate alcohol was observed by TLC analysis. The reaction mixture was then diluted with CH₂Cl₂ (2.0 mL) and filtered through a plug of silica gel eluting with 100% Et₂O (50 mL). The filtrate was concentrated under reduced pressure and purified by flash column chromatography eluting with the indicated solvent system to yield the 1,5-dimer 3.5. Purification by flash chromatography eluting with hexanes provided 15 mg (38%) of 3.5 as a yellow oil. The ¹H-NMR data for 3.5 was consistent with literature reported data.⁹⁷

General Procedure for the synthesis of unsymmetrical 1,4-diynes: A vial, equipped with a magnetic stir bar, was charged with titanocene dichloride (1.8 mg, 7.0 μmol) and zinc
dust (50 mg, 0.77 mmol), and then purged with argon for 5 min. Dry, degassed CH₂Cl₂ (0.25 mL) was added and the resulting gray slurry was stirred vigorously at 25 °C until it took on a blue/green color. A solution of tri-tert-butylphosphine (30 mg, 0.15 mmol) in CH₂Cl₂ (0.25 mL) was added slowly, followed by the dropwise addition of a solution of aldehyde 3.1 (0.37 mmol) and the first alkynyl iodide 3.2 (0.37 mmol) in CH₂Cl₂ (0.50 mL). The resulting mixture was stirred at 25 °C until TLC indicated full consumption of the starting aldehyde (3-4 hrs), at which time the second alkynyl iodide (0.55 mmol) was added neat and in one portion via syringe. A solution of Ac₂O (86 mg, 80 μL, 0.84 mmol) in CH₂Cl₂ (0.80 mL) was then added at the indicated temperature over 11 h via syringe pump. Once the addition of Ac₂O was complete, the resulting crude mixture was diluted with CH₂Cl₂ (2.0 mL) and filtered through a plug of silica gel eluting with 100% Et₂O. The filtrate was concentrated under reduced pressure and purified by flash column chromatography eluting with the indicated solvent system to yield the desired unsymmetrical 1,4-diyne 3.4.

4,4'-(5-Phenylpenta-1,4-diyne-1,3-diyl)bis(methoxybenzene) (3.4d). 1,4-diyne 3.4d was obtained in 53% yield (0.37 mmol scale, 69 mg) after 14 hr at 25 °C, eluting with 4:1, hexanes/CH₂Cl₂, as a clear orange oil. ¹H NMR (500 MHz) δ 7.59-7.60 (m, 2 H), 7.47-7.49 (comp, 2 H), 7.42-7.44 (m, 2 H), 7.30-7.31 (comp, 3 H), 6.93-6.95 (m, 2 H), 6.84-6.85 (m,
2 H), 5.16 (s, 1 H), 3.84 (s, 3 H), 3.82 (s, 3 H); $^{13}$C (125 MHz) δ 159.7, 159.1, 133.4, 132.0, 130.5, 128.6, 128.4, 123.3, 115.3, 114.3, 114.0, 87.3, 85.6, 82.7, 82.6, 55.6, 55.5, 29.5; IR (thin film) 3055, 3004, 2958, 2935, 2837, 1602, 1509, 1462, 1291, 1250, 1174, 1071, 1032 cm$^{-1}$; mass spectrum (ESI) m/z 353.1535 [C$_{25}$H$_{21}$O$_2$ (M+1) requires 353.1536].

[Diagram of the compound]

1-Chloro-4-(1-(4-methoxyphenyl)-5-phenylpenta-1,4-diyn-3-yl)benzene (3.4e). 1,4-diyn 3.4e was obtained in 55% yield (0.37 mmol scale, 72 mg) after 2 h at 50 °C, eluting with 4:1, hexanes/CH$_2$Cl$_2$, as an orange solid. $^1$H NMR (500 MHz) δ 7.60-7.62 (m, 2 H), 7.47-7.49 (comp, 2 H), 7.40-7.42 (m, 2 H), 7.36-7.37 (m, 2 H), 7.30-7.32 (comp, 3 H), 6.83-6.85 (m, 2 H), 5.16 (s, 1 H), 3.81 (s, 3 H); $^{13}$C (125 MHz) δ 159.9, 136.9, 133.4, 132.0, 129.0, 128.9, 128.6, 128.5, 123.0, 115.0, 114.1, 96.1, 86.5, 83.2, 83.2, 55.5, 29.8; IR (thin film) 3055, 2957, 2933, 2836, 1605, 1509, 1488, 1289, 1249, 1173, 1070, 1033, 1015 cm$^{-1}$; mass spectrum (ESI) m/z 357.1031 [C$_{24}$H$_{18}$ClO (M+1) requires 357.1041].
4,4’-(5-Phenylpenta-1,4-diyn-1,3-diyl)bis(chlorobenzene) (3.4f). 1,4-diyn 3.4f was obtained in 50% yield (0.37 mmol scale, 66 mg) after 14 h at 25 °C, eluting with 20:1, hexanes/CH₂Cl₂, as a clear yellow oil. ¹H NMR (500 MHz) δ 7.58-7.60 (m, 2 H), 7.47-7.49 (comp, 2 H), 7.36-7.41 (m, 4 H), 7.28-7.32 (comp, 5 H), 5.16 (s, 1 H); ¹³C (125 MHz) δ 136.5, 134.7, 133.7, 133.3, 132.0, 129.1, 128.9, 128.8, 128.7, 128.5, 122.8, 121.4, 87.3, 85.9, 83.5, 82.2, 29.8; IR (neat) 3057, 2925, 2852, 1594, 1487, 1443, 1401, 1373, 1294, 1243, 1092, 1046, 1015 cm⁻¹; mass spectrum (ESI) m/z 377.0466 [C₂₃H₁₅Cl₂O (M+O) requires 377.0494].

2,2’-(5-Phenylpenta-1,4-diyn-1,3-diyl)bis(methylbenzene) (3.4g). 1,4-diyn 3.4g was obtained in 52% yield (0.37 mmol scale, 72 mg) after 14 h at 25 °C, eluting with 20:1, hexanes/CH₂Cl₂, as a clear yellow oil. Product was isolated as a mixture of 3.4g and the corresponding symmetrical diynes. The combined yield of the minor symmetrical adducts (11%) was determined by comparison of their benzylic protons at 5.30 ppm and
5.22 ppm in the $^1$H NMR spectrum of the mixture. $^1$H NMR (500 MHz) $\delta$ 7.78-7.80 (m, 1 H), 7.41-7.47 (comp, 3 H), 7.16-7.30 (comp, 8 H), 7.09-7.12 (comp, 1 H), 5.26 (s, 1 H), 2.56 (s, 3 H), 2.43 (s, 3 H); $^{13}$C (125 MHz) $\delta$ 140.6, 136.5, 136.0, 132.2, 131.9, 131.0, 129.6, 128.4, 128.4, 127.9, 127.8, 126.7, 125.6, 123.3, 123.0, 90.5, 86.7, 82.5, 81.8, 28.5, 20.9, 19.6; IR (neat) 3057, 2923, 2853, 1655, 1592, 1489, 1443, 1399, 1293, 1176, 1092, 1015 cm$^{-1}$. mass spectrum (ESI) m/z 321.1625 [C$_{25}$H$_{21}$ (M+1) requires 321.1638].

![Structure](image)

1-(1-(4-Chlorophenyl)-5-phenylpenta-1,4-diyn-3-yl)-2-methylbenzene (3.4h). Reaction was run in dichloroethane. Mixture was stirred at 25 °C for 3 h and heated to 45 °C upon addition of Ac$_2$O for 11 h. 1,4-diyne 3.4h was obtained in 56% yield (0.37 mmol scale, 70 mg) eluting with 15:1, hexanes/CH$_2$Cl$_2$, as a clear orange oil. H NMR (500 MHz) $\delta$ 7.74-7.75 (m, 1 H), 7.45-7.47 (comp, 2 H), 7.37-7.39 (m, 2 H), 7.20-7.31 (comp, 8 H), 5.21 (s, 1 H), 2.54 (s, 3 H); $^{13}$C (125 MHz) $\delta$ 136.1, 136.0, 134.4, 133.2, 132.0, 131.0, 128.7, 128.5, 128.4, 128.0, 127.8, 126.7, 123.1, 121.7, 87.5, 86.2, 82.8, 81.5, 28.4, 19.5; IR (neat) 3063, 3022, 2926, 1596, 1488, 1462, 1443, 1398, 1380, 1265, 1176, 1091, 1014 cm$^{-1}$; mass spectrum (ESI) m/z 341.1072 [CH$_2$Cl$_2$ (M+1) requires 341.1092].

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1-Methyl-2-(1-phenyl-5-(4-(trifluoromethyl)phenyl)penta-1,4-diyne-3-yl)benzene (3.4i).

Reaction was run in dichloroethene. Mixture was stirred at 25 °C for 3 hours and heated to 45 °C upon addition of Ac₂O for 11 h. 1,4-diyne 3.4i was obtained in 50% yield (0.37 mmol scale, 68 mg) eluting with 15:1, hexanes/CH₂Cl₂, as a clear orange oil. ¹H NMR (500 MHz) δ 7.75 (d, J = 7, 1 H), 7.55 (s, 4 H), 7.46-7.48 (m, 2 H), 7.22-7.31 (comp, 6 H), 5.24 (s, 1 H), 2.55 (s, 3 H); ¹³C (125 MHz) δ 136.0, 135.9, 132.2, 132.0, 131.1, 128.5, 128.4, 128.1, 127.8, 126.8, 125.3 (q, J = 3.6 Hz), 123.0, 89.2, 85.9, 83.0, 81.3, 28.4, 19.6; IR (neat) 3062, 3023, 2928, 1735, 1677, 1615, 1490, 1461, 1323, 1265, 1168, 1129, 1068, 1017 cm⁻¹; mass spectrum (ESI) m/z 375.1361 [C₂₅H₁₈F₃ (M+1) requires 375.1355].

1-(1-(4-Methoxyphenyl)-5-(4-(trifluoromethyl)phenyl)penta-1,4-diyne-3-yl)-2-methylbenzene (3.4j). 1,4-diyne 3.4j was obtained in 57% yield (0.37 mmol scale, 85 mg) after 14 h at 25 °C, eluting with 10:1, hexanes/CH₂Cl₂, as a clear orange oil. ¹H NMR
(500 MHz) δ 7.74-7.75 (m, 1 H), 7.55 (s, 4 H), 7.39-7.41 (m, 2 H), 7.21-7.29 (comp, 3 H), 6.82-6.84 (m, 2 H), 5.23 (s, 1 H), 3.80 (s, 3 H), 2.55 (s, 3 H); $^{13}$C (125 MHz) δ 159.8, 136.1, 136.0, 133.4, 132.2, 131.1, 128.0, 127.8, 126.8, 125.3 (q, $J = 4.0$ Hz), 115.1, 114.1, 89.4, 84.4, 82.8, 81.2, 55.5, 28.4, 19.6; IR (neat) 3072, 2957, 2932, 2839, 1607, 1509, 1462, 1323, 1289, 1249, 1171, 1068, 1036, 1018 cm$^{-1}$; mass spectrum (ESI) $m/z$ 405.1434 [C$_{26}$H$_{20}$OF$_3$ (M+1) requires 405.1461].

2-(3,5-Dimethoxyphenethyl)benzaldehyde (3.1e). A solution of 2-bromobenzaldehyde (3.1d) (745 mg, 4.03 mmol, 0.47 mL) and 1-ethynyl-3,5-dimethoxybenzene (3.7) (594 mg, 3.66 mmol) in Et$_3$N (4 mL) was added to a solution of Pd(OAc)$_2$ (9 mg, 0.04 mmol), Cul (15 mg, 0.08 mmol), and Et$_3$N (4 mL) at room temperature. The resulting mixture was warmed to 80 °C and stirred for 12 h. The reaction was then diluted with H$_2$O (8 mL), the layers were separated, and the aqueous phase extracted with with CH$_2$Cl$_2$ (3 x 10 mL). The combined organic fractions were dried (Na$_2$SO$_4$), and concentrated under reduced pressure. The resulting crude material was then dissolved in MeOH (70 mL) and placed under an atmosphere of H$_2$. To this solution was added 5% Pd/C (800 mg, 0.376 mmol) and stirred at room temperature for 24 h. The resulting mixture was filtered through a pad of Celite eluting with Et$_2$O (200 mL), and concentrated under reduced pressure. The crude material was dissolved in 1:1 DMSO/CH$_2$Cl$_2$ (26mL) and cooled to 0
°C. iPr₂NEt (1.9 mL, 10.98 mmol) was then added dropwise followed by a portionwise addition of SO₃·pyr (1.7 g, 10.98 mmol). The resulting mixture was allowed to warm to room temperature by removal of the ice bath and stirred for 1 h. The mixture was diluted with CH₂Cl₂ (25 mL) and water (10 mL), and extracted with CH₂Cl₂ (3 x 10 mL). The combined organic extracts were dried (Na₂SO₄) and concentrated under reduced pressure. The resulting crude mixture was purified by flash chromatography eluting with hexanes/CH₂Cl₂ (1:1) to provide 314 mg (32% over 3 steps) of 3.1e as a clear, colorless oil. ¹H NMR (500 MHz) 10.21 (s, 1H), 7.84 (dd, J = 7.5, 1.0, 1 H), 7.50 (td, J = 8.0, 2.0, 1 H), 7.40 (td, J = 7.5, 1.5, 1 H), 7.24 (d, J = 7.5, 1 H), 6.35 (d, J = 2.0, 2 H), 6.32 (t, J = 2.5, 1 H), 3.76 (s, 6 H), 3.30-3.33 (m, 2 H), 2.83-2.86 (m, 2 H); ¹³C (125 MHz) δ 192.6, 161.0, 144.5, 143.8, 134.0, 133.9, 132.7, 131.5, 126.9, 106.8, 98.4, 55.5, 38.7, 34.9; IR (neat) cm⁻¹ 3050, 2963, 2907, 1696, 1597, 1461, 1205, 1153, 1066; mass spectrum (EI) m/z 270.1255 [C₂₅H₂₅O₃ (M+1) requires 270.1256].

General procedure for the synthesis of diarylethynylmethanes: A two-dram screw cap vial, equipped with a magnetic stir bar, was charged with Cp₂TiCl₂ (2.6 mg, 10.3 μmol) and zinc dust (40.0 mg, 0.165 mmol) then purged with argon for 5 min. Dry, degassed DCE (0.50 mL) was added and the suspension stirred at 25 °C until a blue/green color persisted. A solution of tBu₃P (33.0 mg, 0.165 mmol) in DCE (0.25 mL) was then added dropwise, and the mixture stirred for an additional 10 min. A solution of aldehyde 3.1 (0.206 mmol), iodoacetylene 3.2 (0.618 mmol) and arene 3.8 (0.418 mmol) in DCE (0.75 mL) was then added and the reaction stirred at 25 °C until full consumption of aldehyde
3.1 was observed by TLC (1-4 hours). Cs₂CO₃ (67.0 mg, 0.206 mmol) was then added in one portion followed by the slow addition of Ac₂O (46 mg, 0.453 mmol, 43 µL) in DCE (0.5 mL) over 11 hours via syringe pump. The reaction was then diluted with CH₂Cl₂ (2.0 mL), filtered through a short plug of silica gel eluting with 100% CH₂Cl₂ (50 mL), and the filtrate concentrated under reduced pressure. The crude mixture was purified by flash column chromatography eluting with the indicated solvent mixture to give the corresponding diarylethynyl methane 3.6.

![Diarylethynyl Methane](image)

1,3-Dimethoxy-9-(phenylethynyl)-9H-fluorene (3.6a). The coupling of 3.1c and 3.2a was performed on 0.206 mmol scale with a total reaction time of 11 h. Purification by flash chromatography eluting with hexanes/CH₂Cl₂ (1:1) provided 37 mg (55%) of 3.6a as a yellow solid. ¹H NMR (500 MHz, CDCl₃) δ 7.69-7.40 (m, 2 H), 7.42-7.35 (m, 4 H), 7.26-7.23 (m, 3 H), 6.91 (d, J = 2.0 Hz, 1 H), 6.49 (d, J = 2.0 Hz, 1 H), 4.95 (s, 1 H) 3.96 (s, 3 H), 3.91 (s, 3 H); ¹³C NMR (125 MHz) δ 162.2, 157.5, 145.2, 142.9, 140.6, 132.0, 128.3, 127.9, 127.86, 127.82, 125.36, 124.1, 123.1, 120.2, 98.7, 98.8, 87.3, 81.2, 55.9, 37.4, 29.9; IR (neat) 3052, 3000, 2926, 2837, 1947, 1607, 1593, 1494, 1451, 1206; HRMS (ESI) m/z 327.1377 [C₂₃H₁₉O₂ (M+1) requires 327.1380]; m.p. = 89-93 °C.
2,4-Dimethoxy-5-(phenylethynyl)-10,11-dihydro-5H-dibenzo[a,d][7]annulene (3.6b).

The coupling of 3.1e and 3.2a was performed on 0.206 mmol scale with a total reaction time of 11 h. Purification by flash chromatography eluting with hexanes/CH$_2$Cl$_2$ (1:1) provided 56 mg (77%) of 3.6b as a white solid. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.34-7.29 (m, 3 H), 7.22-7.10 (m, 6 H), 6.33-6.32 (m, 2 H), 5.81 (s, 1 H), 4.02-3.96 (m, 1 H), 3.84 (s, 3 H), 3.81-3.75 (m, 4 H), 2.95-2.82 (m, 2 H); $^{13}$C NMR (125 MHz) $\delta$ 159.5, 157.1, 142.8, 140.1, 138.7, 131.7, 130.8, 130.6, 128.2, 127.7, 127.5, 126.3, 124.2, 120.1, 106.6, 96.6, 92.2, 82.1, 56.2, 55.4, 33.5, 32.8, 32.5; IR (neat) 3058, 2963, 2906, 2360, 2335, 2194, 1747, 1605, 1594, 1204, 1145; HRMS (ESI) m/z 354.1607 [C$_{25}$H$_{25}$O$_2$ (M+1) requires 354.1620]; m.p. = 109-111 °C.

2,4-Dimethoxy-1-(3-phenyl-1-(o-tolyl)prop-2-yn-1-yl)benzene (3.6b). The coupling of 3.1f, 3.2a, and 3.8a was performed on 0.206 mmol scale with a total reaction time of 11 h. Purification by flash chromatography eluting with hexanes/EtOAc (10:1) provided 50 mg (77%) of 3.6b as a clear, yellow oil. $^1$H NMR (500 MHz) $\delta$ 7.46-7.45 (m, 1 H), 7.43-7.41 (m, 2 H), 7.33 (d, $J$ = 6.0 Hz, 1 H), 7.26-7.24 (comp, 3 H), 7.18-7.12 (comp, 3 H), 6.48-6.44
(m, 2 H), 5.64 (s, 1 H), 3.78 (s, 3 H), 3.77 (s, 3 H), 2.35 (s, 3 H); $^{13}$C (125 MHz) δ 160.1, 157.5, 140.0, 136.1, 131.9, 130.5, 129.9, 128.3, 128.2, 127.8, 126.8, 126.1, 124.1, 122.1, 104.4, 98.8, 91.1, 83.4, 55.8, 55.5, 33.5, 19.6; IR (neat) 3071, 3014, 2936, 2835, 2247, 2220, 1672, 1611, 1502, 1418, 1378, 1334, 1293, 1208, 1156, 1115, 1036; mass spectrum (ESI) m/z 343.1692 [C$_{24}$H$_{13}$O$_{2}$ (M+1) requires 343.1693].

1-Methyl-3-(3-phenyl-1-(p-tolyl)prop-2-yn-1-yl)-1H-indole (3.6d). The coupling of 2.48, 3.2a, and 3.8b was performed on 0.206 mmol scale with a total reaction time of 11 h.

Purification by flash chromatography eluting with hexanes/CH$_2$Cl$_2$ (3:1) provided 47 mg (68%) of 3.6d as a yellow oil. $^1$H NMR (500 MHz, CDCl$_3$) δ 7.67 (dt, $J = 8.0$, 1.0 Hz, 1 H), 7.52-7.49 (m, 2 H), 7.47 (d, $J = 8.0$ Hz, 2 H), 7.32-7.30 (m, 5 H), 7.27-7.24 (m, 1 H), 7.18 (d, $J = 7.5$ Hz, 2 H), 7.01 (s, 1 H), 5.47 (s, 1 H), 3.76 (s, 3 H), 2.37 (s, 3 H); $^{13}$C NMR (125 MHz) δ 138.7, 137.7, 136.5, 131.9, 129.4, 128.4, 128.0, 127.9, 127.4, 126.7, 124.0, 121.9, 119.9, 119.2, 115.7, 109.5, 91.1, 83.2, 35.2, 32.9, 21.3; IR (neat) 3051, 3023, 2974, 2244, 1614, 1598, 1571, 1488; HRMS (ESI) m/z 336.1769 [C$_{25}$H$_{22}$N (M+1) requires 336.1747].
3-(1-(4-Methoxyphenyl)-3-phenylprop-2-yn-1-yl)-1-methyl-1H-indole (3.6e). The coupling of 3.1a, 3.2a, and 3.8b was performed on 0.206 mmol scale with a total reaction time of 11 h. Purification by flash chromatography eluting with hexanes/CH₂Cl₂ (1:1) provided 65 mg (90%) of 3.6e as a yellow solid. ¹H NMR (500 MHz, CDCl₃) δ 7.60 (dt, J = 7.5, 1.0 Hz, 1 H), 7.46-7.43 (m, 4 H), 7.29-7.26 (m, 4 H), 7.75-7.04 (m, 1 H), 6.95 (d, J = 0.5 Hz, 1 H), 6.87-6.85 (m, 2 H), 5.41 (s, 1 H), 3.78 (s, 3 H), 3.73 (s, 3 H); ¹³C NMR (125 MHz) δ 158.7, 137.7, 133.9, 132.0, 129.2, 128.4, 128.0, 127.4, 126.7, 124.1, 122.0, 120.0, 119.3, 115.9, 114.1, 110.0, 91.2, 83.3, 55.6, 34.9, 33.0; IR (neat) 3051, 2935, 2836, 2302, 1609, 1265, 738; HRMS (ESI) m/z 352.1670 [C₂₅H₂₂NO (M+1) requires 352.1696]; m.p. = 120-121 °C.

3-(1-(4-Chlorophenyl)-3-phenylprop-2-yn-1-yl)-1-methyl-1H-indole (3.6f). The coupling of 3.1b, 3.2a, and 3.8b was performed on 0.206 mmol scale with a total reaction time of 11 h. Purification by flash chromatography eluting with hexanes/CH₂Cl₂ (4:1) provided 46 mg (63%) of 3.6f as a green solid. ¹H NMR (500 MHz, CDCl₃) δ 7.55 (d, J = 8.0 Hz, 1 H), 7.46-7.44 (m, 4 H), 7.29-7.26 (m, 5 H), 7.23-7.19 (m, 1 H), 7.08-7.04 (m, 1 H), 6.97 (s, 1 H), 5.41 (s, 1 H), 3.72 (s, 3 H); ¹³C NMR (125 MHz) δ 140.2, 137.6, 132.7, 131.9, 129.5,
128.8, 128.4, 128.2, 127.5, 126.5, 123.7, 122.1, 119.7, 119.4, 114.9, 110.0, 90.2, 83.7, 35.0, 32.9; IR (neat) 3078, 3054, 2928, 2305, 1596, 1486, 1086; HRMS (ESI) m/z 356.1178 [C_{24}H_{18}ClN (M+1) requires 356.1201]; m.p. = 140-147 °C.

![Image of 3.6g molecule]

1-Methyl-3-(3-phenyl-1-(1-tosyl-1H-indol-3-yl)prop-2-yn-1-yl)-1H-indole (3.6g). The coupling of 3.1g, 3.2a, and 3.8b was performed on 0.206 mmol scale with a total reaction time of 11 h. Purification by flash chromatography eluting with hexanes/CH\(_2\)Cl\(_2\) (4:1) provided 74 mg (69%) of 3.6g as a pale yellow solid. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.98 (dt, \(J = 8.5, 1.0 \text{ Hz}, 1 \text{ H}\)), 7.68 (dt, \(J = 8.5, 2.0 \text{ Hz}, 2 \text{ H}\)), 7.66 (dt, \(J = 7.5, 1.0 \text{ Hz}, 1 \text{ H}\)), 7.53 (dt, \(J = 8.0, 1.0 \text{ Hz}, 1 \text{ H}\)), 7.48 (d, \(J = 1.0 \text{ Hz}, 1 \text{ H}\)), 7.43-7.41 (m, 2 H), 7.31-7.26 (m, 5 H), 7.24-7.21 (m, 1 H), 7.19-7.16 (m, 3 H), 7.06-7.02 (m, 1 H), 7.01 (d, \(J = 0.5 \text{ Hz}, 1 \text{ H}\)), 5.59 (s, 1 H), 3.73 (s, 3 H), 2.32 (s, 3 H); \(^{13}\)C NMR (125 MHz) \(\delta\) 144.9, 137.7, 136.0, 135.3, 131.9, 130.0, 129.9, 128.4, 127.6, 127.0, 126.5, 124.9, 124.5, 123.6, 123.3, 123.2, 122.0, 120.7, 119.7, 119.2, 114.0, 112.7, 109.7, 89.2, 82.8, 33.0, 27.1, 21.8; IR (neat) 3053, 2985, 2305, 1598, 1371, 1174; HRMS (ESI) m/z 515.1772 [C_{33}H_{26}N_{2}O_{2}S (M+1) requires 515.1788]); m.p. = 112-116 °C.

![Image of 3.6h molecule]

3-(1-(Furan-2-yl)-3-phenylprop-2-yn-1-yl)-1-methyl-1H-indole (3.6h). The coupling of
3.1h, 3.2a, and 3.8b was performed on 0.206 mmol scale with a total reaction time of 11h. Purification by flash chromatography eluting with hexanes/CH$_2$Cl$_2$ (3:1) provided 44 mg (68%) of 3.6h as a dark yellow oil. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.73 (d, $J = 8.0$ Hz, 1 H), 7.52-7.50 (m, 2 H), 7.39 (t, $J = 1.5$ Hz, 1 H), 7.34-7.31 (m, 4 H), 7.29-7.25 (m, 1 H), 7.16-7.13 (m, 2 H), 6.36-6.34 (m, 2 H), 5.58 (s, 1 H), 3.78 (s, 3 H); $^{13}$C NMR (125 MHz) $\delta$ 154.0, 142.0, 137.5, 132.0, 128.4, 128.2, 127.4, 126.6, 123.6, 122.0, 119.8, 119.4, 112.3, 110.5, 109.6, 106.4, 88.0, 82.6, 33.0, 29.8; IR (neat) 3116, 3053, 2930, 2879, 2824, 1598, 1614, 1488, 1010; HRMS (ESI) m/z 312.1355 [C$_{22}$H$_{17}$N$_2$O (M+1) requires 312.1383].

1-Methyl-3-(3-phenyl-1-(thiophen-2-yl)prop-2-yn-1-yl)-1H-indole (3.6i). The coupling of 3.1i, 3.2a, and 3.8b was performed on 0.206 mmol scale with a total reaction time of 11 h. Purification by flash chromatography eluting with hexanes/CH$_2$Cl$_2$ (2:1) provided 48 mg (71%) of 3.6i as a yellow solid. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.68-7.66 (m, 1 H), 7.48-7.46 (m, 2 H), 7.30-7.28 (m, 4 H), 7.22 (dt, $J = 6.0$, 1.0 Hz, 1 H), 7.16 (dd, $J = 5.0$, 1.5 Hz, 1 H), 7.11-7.08 (m, 3 H), 6.92 (dd, $J = 5.0$, 3.5 Hz, 1 H), 5.71 (s, 1 H), 3.75 (s, 3 H); $^{13}$C NMR (125 MHz) $\delta$ 146.1, 137.6, 131.9, 128.4, 128.2, 127.3, 126.7, 126.4, 125.1, 124.5, 123.6, 122.1, 119.8, 119.4, 115.0, 109.6, 90.1, 83.0, 33.0, 31.0; IR (neat) 3054, 2932, 2824, 1698, 1614, 1579, 1488, 1472; m.p. = 118-121 °C (decomposed).
**tert-Butyl 3-(1-(4-methoxyphenyl)-3-phenylprop-2-yn-1-yl)-1H-indole-1-carboxylate (3.6j).** The coupling of 3.1a, 3.2a, and 3.8c was performed on 0.206 mmol scale with a total reaction time of 11 h. Purification by flash chromatography eluting with hexanes/EtOAc (12:1) provided 57 mg (63%) of 3.6j as a clear oil. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.61 (s, 1 H), 7.53 (d, $J$ = 8.0 Hz, 1 H), 7.47-7.44 (m, 4 H), 7.31-7.29 (m, 4 H), 7.19-7.16 (m, 1 H), 6.90-6.87 (m, 2 H), 5.35 (s, 1 H), 3.81 (s, 3 H), 1.69 (s, 9 H); $^{13}$C NMR (125 MHz) $\delta$ 158.8, 132.2, 131.9, 129.1, 128.4, 128.2, 124.6, 124.0, 123.6, 122.7, 121.6, 120.2, 115.5, 114.2, 89.7, 84.0, 55.5, 34.8, 28.4; IR (neat) 3053, 2980, 2933, 2837, 1733, 1603, 1509, 1451, 1371, 1264, 1155.

**3-(1-(4-Methoxyphenyl)-3-phenylprop-2-yn-1-yl)-1,2-dimethyl-1H-indole (3.6k).** The coupling of 3.1a, 3.2a, and 3.8d was performed on 0.206 mmol scale with a total reaction time of 11 h. Purification by flash chromatography eluting with hexanes/CH$_2$Cl$_2$ (2:1) provided 60 mg (80%) of 3.6k as a dark yellow oil. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.67 (d, $J$ = 8.0 Hz, 1 H), 7.46-7.41 (m, 4 H), 7.28-7.22 (m, 4 H), 7.15-7.11 (m, 1 H), 7.05-7.02 (m, 1 H), 6.81-6.78 (m, 2 H), 5.50 (s, 1 H), 3.72 (s, 3 H), 3.60 (s, 3 H), 2.42 (s, 3 H); $^{13}$C
NMR (125 MHz) δ 158.3, 136.8, 133.9, 133.4, 131.8, 128.5, 128.4, 127.9, 126.6, 124.0, 120.9, 119.2, 119.1, 113.8, 111.0, 108.9, 90.9, 83.4, 55.4, 33.3, 29.7, 10.8; IR (neat) 3051, 2999, 2933, 2834, 1609, 1508, 1489, 1249, 1175, 1034.

4-(1-(4-Methoxyphenyl)-3-phenylprop-2-yn-1-yl)-N,N-dimethylaniline (3.6l). The coupling of 3.1a, 3.2a, and 3.8e was performed on 0.206 mmol scale with a total reaction time of 11 h. Purification by flash chromatography eluting with hexanes/CH₂Cl₂ (1:2) provided 57 mg (81%) of 3.6l as a clear, orange oil. ¹H NMR (500 MHz, CDCl₃) δ 7.47-7.44 (m, 2 H), 7.35-7.33 (m, 2 H), 7.29-7.25 (m, 5 H), 6.85-6.82 (m, 2 H), 6.70-6.67 (m, 2 H), 5.08 (s, 1 H), 3.75 (s, 3 H), 2.89 (s, 6 H); ¹³C NMR (125 MHz) δ 158.6, 149.8, 135.0, 132.0, 130.4, 129.1, 128.8, 128.5, 128.1, 124.1, 114.2, 113.1, 91.6, 84.5, 55.6, 42.3, 41.0; IR (neat) 3051, 2933, 2836, 2805, 1603, 1509, 1443, 1352, 1034; HRMS (ESI) m/z 342.1858 [C₂₄H₂₃NO (M+1) requires 342.1852].

N,N-dimethyl-4-(3-phenyl-1-(1-tosyl-1H-indol-3-yl)prop-2-yn-1-yl)aniline (3.6m). The coupling of 3.1g, 3.2a, and 3.8e was performed on 0.206 mmol scale with a total reaction time of 11 h. Purification by flash chromatography eluting with hexanes/CH₂Cl₂
(1:1) provided 71 mg (68%) of **3.6m** as a clear, orange oil. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.96-7.94 (m, 1 H), 7.75 (dd, \(J = 8.0, 2.0\) Hz, 2 H), 7.51-7.49 (m, 2 H), 7.44-7.42 (m, 2 H), 7.30-7.24 (m, 5 H), 7.20 (dd, \(J = 8.5, 1.0\) Hz, 2 H), 7.16-7.13 (m, 2 H), 6.67 (d, 8.5 Hz, 2 H), 5.23 (s, 1 H), 2.92 (s, 6 H), 2.33 (s, 3 H); \(^{13}\)C NMR (125 MHz) \(\delta\) 150.0, 145.1, 136.0, 135.5, 132.0, 130.1, 129.8, 128.8, 128.5, 128.2, 127.4, 127.1, 124.9, 124.4, 124.3, 123.7, 123.4, 120.8, 114.0, 112.9, 89.8, 83.9, 53.7, 40.9, 34.7.

![Image of molecule](image)

**3-(1,3-Bis(4-methoxyphenyl)prop-2-yn-1-yl)-1-methyl-1H-indole (3.6n).** The coupling of **3.1a**, **3.2b**, and **3.8b** was performed on 0.206 mmol scale with a total reaction time of 11 h. Purification by flash chromatography eluting with hexanes/CH\(_2\)Cl\(_2\) (1:1) provided 66 mg (83%) of **3.6n** as a yellow solid. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.69 (d, \(J = 8.0\) Hz, 1 H), 7.54-7.51 (m, 2 H), 7.49-7.46 (m, 2 H), 7.35 (d, \(J = 8.5\) Hz, 1 H), 7.30-7.27 (m, 1 H), 7.16-7.13 (m, 1 H), 7.03 (s, 1 H), 6.95-6.92 (m, 2 H), 6.90-6.87 (m, 2 H), 5.48 (s, 1 H), 3.85 (s, 3 H), 3.85 (s, 3 H), 3.78 (s, 3 H); \(^{13}\)C NMR (125 MHz) \(\delta\) 159.4, 158.5, 137.6, 134.0, 133.2, 129.0, 127.3, 126.6, 121.9, 119.9, 119.2, 116.1, 116.0, 114.0, 113.9, 109.5, 89.6, 82.9, 55.4, 34.8, 32.8 (one signal not observed); IR (neat) 3052, 2957, 2837, 2304, 1607, 1508, 1247, 1034; HRMS (ESI) \(m/z\) 404.1652 [C\(_{26}\)H\(_{23}\)NO\(_2\) (M+Na) requires 404.1621].

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3-(3-(4-Chlorophenyl)-1-(4-methoxyphenyl)prop-2-yn-1-yl)-1-methyl-1H-indole (3.6o).

The coupling of 3.1a, 3.2d, and 3.8b was performed on 0.206 mmol scale with a total reaction time of 11 h. Purification by flash chromatography eluting with hexanes/CH₂Cl₂ (2:1) provided 50 mg (83%) of 3.6o as an orange solid. ¹H NMR (500 MHz, CDCl₃) δ 7.63-7.61 (m, 1 H), 7.47-7.44 (m, 2 H), 7.41-7.38 (m, 2 H), 7.32-7.22 (m, 4 H), 7.09 (dt, J = 13.0, 1.0 Hz, 1 H), 6.95 (s, 1H), 6.91-6.88 (m, 2H), 5.43 (s, 1 H), 3.81 (s, 3 H), 3.80 (s, 3 H); ¹³C NMR (125 MHz) δ 158.7, 137.6, 133.9, 133.5, 133.1, 129.0, 128.7, 127.3, 126.6, 122.5, 122.0, 119.8, 115.5, 114.1, 109.6, 92.2, 82.1, 55.5, 34.8, 32.9; IR (neat) 2932, 2357, 1633, 1549, 1250, 1090; m.p. = 121-126 °C.

3-(1-(4-Methoxyphenyl)-3-(4-(trifluoromethyl)phenyl)prop-2-yn-1-yl)-1-methyl-1H-indole (3.6p). The coupling of 3.1a, 3.2c, and 3.8b was performed on 0.206 mmol scale with a total reaction time of 11 h. Purification by flash chromatography eluting with hexanes/CH₂Cl₂ (2:1) provided 69 mg (80%) of 3.6p as a light brown solid. ¹H NMR (500 MHz, CDCl₃) δ 7.60 (d, J = 8.0 Hz, 1 H) 7.52 (br s, 4 H), 7.43-7.42 (m, 2 H), 7.29-7.28 (m, 1
H), 7.23-7.20 (m, 1 H), 7.08-7.05 (m, 1 H), 6.91 (s, 1 H), 6.88-6.85 (m, 2 H), 5.42 (s, 1 H), 3.77 (s, 3 H), 3.72 (s, 3 H); $^{13}$C NMR (125 MHz) δ 158.7, 137.7, 133.2, 132.1, 129.1, 127.8, 127.3, 126.6, 125.3, 125.33, 125.27, 125.24, 122.1, 119.8, 119.4, 115.3, 114.1, 109.6, 93.9, 82.0, 55.5, 34.8, 32.9; IR (neat) 3054, 2998, 2936, 2835, 2219, 1611, 1508, 1324; HRMS (ESI) m/z 420.1542 [C$_{26}$H$_{20}$NOF$_3$ (M+1) requires 420.1570]; m.p = 135-137 °C.

3-(1-(4-Methoxyphenyl)hept-2-yln-yl)-1-methyl-1H-indole (3.6q). The coupling of 3.1a, 3.2e, and 3.8b was performed on 0.206 mmol scale with a total reaction time of 11 h. Purification by flash chromatography eluting with hexanes/CH$_2$Cl$_2$ (2:1) provided 54 mg (80%) of 3.6q as a clear, yellow oil. $^1$H NMR (500 MHz, CDCl$_3$) δ 7.54 (dt, J = 8.0, 0.5 Hz, 1 H), 7.38-7.35 (m, 2 H), 7.26-7.24 (m, 1 H), 7.20-7.16 (m, 1 H), 7.04-7.01 (m, 1 H), 6.87 (d, J = 1.0 Hz, 1 H) 6.84-6.81 (m, 2 H), 5.16 (s, 1 H), 3.76 (s, 3 H), 3.70 (s, 3 H), 2.25 (dt, J = 7.0, 2.5, 2 H), 1.56-1.50 (m, 2 H), 1.46-1.39 (m, 2 H), 0.91 (t, 7.0 Hz, 3 H); $^{13}$C NMR (125 MHz) δ 158.4, 137.6, 134.6, 128.9, 127.2, 126.7, 121.8, 120.0, 119.0, 116.6, 113.9, 109.4, 83.2, 81.3, 55.4, 34.2, 32.9, 31.4, 22.3, 18.9, 13.9; IR (neat) 3052, 2959, 2934, 2873, 2305, 1609, 1509, 1265, 1033; HRMS (ESI) m/z 332.2012 [C$_{23}$H$_{26}$NO (M+1) requires 332.2009].
3-(4-(Benzyloxy)-1-(4-methoxyphenyl)but-2-yn-1-yl)-1-methyl-1H-indole (3.6r). The coupling of 3.1a, 3.2f, and 3.8b was performed on 0.206 mmol scale with a total reaction time of 11 h. Purification by flash chromatography eluting with hexanes/CH₂Cl₂ (1:1) provided 43 mg (53%) of 3.6r as a yellow oil. ¹H NMR (500 MHz, CDCl₃) δ 7.55-7.53 (m, 1H), 7.40-7.38 (m, 2H), 7.34-7.26 (m, 6H), 7.23-7.19 (m, 1H), 7.07-7.03 (m, 1H), 6.92 (s, 1H), 6.87-6.84 (m, 2H), 5.27 (br s, 1H), 4.61 (s, 2H), 4.28 (d, J = 2.0 Hz, 2H), 3.79 (s, 3H), 3.74 (s, 3H); ¹³C NMR (125 MHz) δ 158.6, 137.8, 137.7, 133.6, 129.0, 128.6, 128.4, 128.0, 127.4, 126.5, 122.0, 119.8, 115.6, 114.0, 109.5, 88.2, 78.8, 71.5, 58.0, 55.5, 34.3, 32.9; IR (neat) 3057, 3029, 2932, 2851, 1610, 1509, 1469, 1249; HRMS (ESI) m/z 418.1789 [C₂₇H₂₅NO₂ (M+Na) requires 418.1778].

3-(1-(4-Methoxyphenyl)-3-(triisopropylsilyl)prop-2-yn-1-yl)-1-methyl-1H-indole (3.6s). The coupling of 3.1a, 3.2g, and 3.8b was performed on 0.206 mmol scale with a total reaction time of 11 h. Purification by flash chromatography eluting with hexanes/EtOAc (8:1) provided 59 mg (67%) of 3.6s as a pale, yellow oil. ¹H NMR (500 MHz, CDCl₃) δ 7.58 (d, J = 8.0 Hz, 1H), 7.40-7.37 (m, 2H), 7.26-7.23 (m, 1H), 7.19-7.16 (m, 1H), 7.04-7.01 (m, 1H), 6.90 (s, 1H), 6.83-6.80 (m, 2H), 5.24 (s, 1H), 3.76 (s, 3H), 3.71 (s, 3H), 1.06 (d, J
= 8.5 Hz, 18 H), 1.00-0.98 (m, 3 H); \( ^{13} \text{C} \) NMR (125 MHz) \( \delta \) 158.4, 137.6, 134.0, 129.0, 127.3, 126.6, 121.8, 120.0, 119.0, 116.0, 113.8, 109.4, 109.4, 83.1, 55.4, 35.3, 32.9, 18.9, 11.6; IR (neat) 3051, 2941, 2863, 2167, 1610, 1509, 1464, 1250.

\[ \text{1-cyclohexyl-3-phenylprop-2-yn-1-yl acetate (3.9)} \]

Propargyl acetate 3.9 was recovered from the coupling of cyclohexane carboxaldehyde 3.1j, 3.2a and 3.8b performed on 0.206 mmol scale, with a total reaction time of 11 h. Purification by flash chromatography eluting with hexanes/EtOAc (4:1) provided 50 mg (94%) of 3.9 as a pale yellow oil. The \(^1\)H NMR data for 3.9 was found to be consistent with literature reported values.\(^{129}\)

\[ \text{3,3'-(4-methoxyphenyl)methylene)bis(1-methyl-1H-indole) (3.10).} \]

Triarylmethane 3.10 was recovered from the coupling of 3.1a, 3.2h and 3.8b performed on 0.206 mmol scale, with a total reaction time of 11 h. Purification by flash chromatography eluting with hexanes/EtOAc (4:1) provided 53 mg (67%) of 3.10 as a red solid. The \(^1\)H NMR data for 3.10 was found to be consistent with literature reported values.\(^{130}\)

\[ \text{5-(1-methyl-1H-indol-3-yl)-1-phenylpent-1-yn-3-yl acetate (3.11).} \]

Propargyl acetate
3.11 was recovered from the coupling of 3.1k and 3.2a performed on 0.206 mmol scale, with a total reaction time of 11 h. Purification by flash chromatography eluting with hexanes/EtOAc (4:1) provided 67 mg (98%) of 3.11 as a pale, yellow oil. \(^{1}\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.60 (d, \(J = 7.5\) Hz, 1H), 7.46-7.44 (m, 2 H), 7.32-7.27 (m, 3 H), 7.22 (dt, \(J = 8.5, 1\) Hz, 1 H), 7.10 (dt, \(J = 7, 1\) Hz, 1 H), 6.87 (s, 1 H), 5.65 (t, \(J = 7\) Hz, 1 H), 3.72 (s, 3 H), 3.03-2.92 (m, 2 H), 2.32-2.13 (m, 2 H), 2.11 (s, 3 H) \(\delta\) 137.3, 132.1, 128.8, 128.4, 127.9, 126.5, 122.5, 121.8, 119.0, 118.9, 113.5, 109.4, 86.7, 85.7, 64.5, 35.6, 32.8, 21.3, 20.9; IR (neat) 3056, 2933, 2230, 1738, 1677, 1613, 1489, 1225. HRMS (ESI) \(m/z\) 354.1461 [C\(_{22}\)H\(_{21}\)NO\(_2\) (M+Na) requires 354.1465].

5-(3-Phenyl-1-(o-tolyl)prop-2-yn-1-yl)furan-2(5H)-one (3.6t). A two-dram screw cap vial, equipped with a magnetic stir bar, was charged with Cp\(_2\)TiCl\(_2\) (2.6 mg, 10.3 \(\mu\)mol) and zinc dust (40.0 mg, 0.165 mmol) then purged with argon for 5 min. Dry, degassed CH\(_2\)Cl\(_2\) (0.50 mL) was added and the suspension stirred at room temperature until a blue/green color persisted. A solution of \(^{1}\)Bu\(_3\)P (16.0 mg, 0.082 mmol) in CH\(_2\)Cl\(_2\) (0.25 mL) was then added dropwise, and the mixture stirred for an additional 10 min. A solution of 3.1f (25 mg, 0.206 mmol), 3.2a (141 mg, 0.618 mmol) and 3.8f (64 mg, 0.418 mmol) in CH\(_2\)Cl\(_2\) (0.75 mL) was then added and the reaction stirred at room temperature until full consumption of o-tolualdehyde was observed by TLC analysis (~1 h). A solution of Ac\(_2\)O (46 mg, 0.453 mmol, 43 \(\mu\)L) in CH\(_2\)Cl\(_2\) (0.5 mL) was then added slowly over 11 h
via syringe pump. The reaction was then diluted with CH₂Cl₂ (2 mL), filtered through a short plug of silica gel eluting with CH₂Cl₂ (50 mL), and the filtrate concentrated under reduced pressure. Purification by flash chromatography eluting with hexanes/EtOAc (2:1) provided 39 mg (66%) of 3.6t in a 1:1 mixture of diastereomers as a yellow oil.

1H NMR (500 MHz, CDCl₃) Isomer A: δ 7.61-7.59 (m, 1 H), 7.56-7.54 (m, 1 H), 7.50-7.47 (m, 1 H), 7.45-7.40 (comp, 2 H), 7.32-7.16 (comp, 5 H), 6.27 (dd, J = 6.0, 2.0 Hz, 1 H), 5.36 (ddd, J = 5.5, 2.0, 2.0 Hz, 1 H), 4.61 (d, J = 6.5 Hz), 2.44 (s, 3 H) Isomer B: δ 7.61-7.59 (m, 1 H), 7.56-7.54 (m, 1 H), 7.50-7.47 (m, 1 H), 7.45-7.40 (comp, 2 H), 7.32-7.16 (comp, 5 H), 6.13 (dd, J = 6.0, 2.0 Hz, 1 H), 5.19 (ddd, J = 6.5, 1.5, 1.5 Hz, 1 H), 4.56 (d, J = 5.5 Hz), 2.41 (s, 3 H); 13C NMR (125 MHz) Isomer A: δ 172.6, 154.0, 136.0, 134.2, 131.9, 131.0, 128.6, 128.5, 128.3, 128.1, 126.7, 123.4, 122.8, 86.5, 85.5, 84.6, 39.3, 20.0 Isomer B: 172.5, 153.9, 136.0, 133.8, 131.9, 131.1, 128.6, 128.5, 128.2, 127.0, 126.5, 1234, 122.7, 85.9, 85.5, 84.6, 38.4, 19.7; IR (neat) 3103, 3020, 2938, 2877, 2877, 2230, 1788, 1659, 1588, 1490, 1275, 1152, 1032; HRMS (ESI) m/z 311.1017 [C₂₀H₁₆O₂ (M+Na) requires 311.1043].

![3-oxo-3-phenyl-1-(o-tolyl)propyl acetate (3.18)](image)

3-oxo-3-phenyl-1-(o-tolyl)propyl acetate (3.18): A two-dram screw cap vial, equipped with a magnetic stir bar, was charged with Cp₂TiCl₂ (2.6 mg, 10.3 μmol) and zinc dust (27.0 mg, 0.412 mmol) then purged with argon for 5 min. Dry, degassed THF (0.25 mL) was added and the suspension stirred at room temperature until a green color persisted. To this suspension was added a solution of 3.1f (24.0 μL, 0.206 mmol), 2-bromo-1-phenylethanone 3.17 (94.0 mg, 0.412 mmol), and acetic anhydride (57 μL,
0.412 mmol) in THF (0.75 mL), dropwise. The reaction was stirred for 4 h at room temperature. The reaction was then diluted with Et₂O (2 mL), filtered through a short plug of silica gel eluting with Et₂O (50 mL), and the filtrate concentrated under reduced pressure. Purification by flash chromatography eluting with hexanes/EtOAc (8:1) provided 32 mg (55%) of **3.18** as a colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 7.96 (d, J = 7.2 Hz, 2 H), 7.59 (t, J = 8.6 Hz, 1 H), 7.48 (t, J = 7.8 Hz, 2 H), 7.41-7.39 (m, 1 H), 7.23-7.16 (m, 3 H), 6.60 (dd, J = 8.8, 4.3 Hz), 3.70 (dd, J = 16.9, 8.8 Hz, 1 H), 3.26 (dd, J = 16.9, 4.3 Hz, 1 H), 2.48 (s, 3 H), 2.02 (s, 3 H); ¹³C NMR (125 MHz) δ 196.4, 170.0, 138.7, 136.9, 135.5, 133.6, 130.9, 128.9, 128.4, 128.2, 126.5, 125.9, 69.0, 44.6, 21.2, 19.4; HRMS (ESI) m/z 305.1141 [C₁₈H₁₈O₃ (M+Na) requires 305.1148].

![Chemical Structure](image_url)

**3.19**

**(E)-1-phenyl-3-(o-tolyl)prop-2-en-1-one (3.19)**. A two-dram screw cap vial, equipped with a magnetic stir bar, was charged with Cp₂TiCl₂ (2.6 mg, 10.3 µmol) and zinc dust (27.0 mg, 0.412 mmol) then purged with argon for 5 min. Dry, degassed THF (0.25 mL) was added and the suspension stirred at room temperature until a green color persisted. To this suspension was added a solution of Et₃N (57.0 µL, 0.412 mmol), **3.1f** (24.0 µL, 0.206 mmol), 2-bromo-1-phenylethaneone **3.17** (94.0 mg, 0.412 mmol), and acetic anhydride (57 µL, 0.412 mmol) in THF (0.75 mL), dropwise. The reaction was stirred for four hours at room temperature. The reaction was then diluted with Et₂O (2 mL), filtered through a short plug of silica gel eluting with Et₂O (50 mL), and the filtrate concentrated under reduced pressure. Purification by flash chromatography eluting with
hexanes/EtOAc (8:1) provided 32 mg (70%) of 3.19 as a colorless oil. The $^1$H NMR and $^{13}$C NMR data for 3.19 were found to be consistent with literature reported values.$^{131}$

1-(4-methoxyphenyl)-4-phenyl-2-(p-tolyl)but-3-yn-1-ol (3.16): A two-dram screw cap vial, equipped with a magnetic stir bar, was charged with Cp$_2$TiCl$_2$ (10 mg, 0.04 mmol) and zinc dust (28.0 mg, 0.44 mmol) then purged with argon for 5 min. Dry, degassed CH$_2$Cl$_2$ (0.50 mL) was added and the suspension stirred at room temperature until a green color persisted. To this mixture was added a solution of 3-phenyl-1-(p-tolyl)prop-2-yn-1-yl acetate 3.15 (53 mg, 0.20 mmol) and p-anisaldehyde 3.1a (27 mg, 0.20 mmol) in CH$_2$Cl$_2$ (1.0 mL). The resulting solution was stirred 4 h at room temperature. The reaction was then diluted with Et$_2$O (2 mL), filtered through a short plug of silica gel eluting with Et$_2$O (50 mL), and the filtrate concentrated under reduced pressure. Purification by flash chromatography eluting with hexanes/EtOAc (4:1) provided 23 mg (34%) of 3.16 in a 1:1 mixture of diastereomers as a yellow oil. $^1$H NMR (500 MHz, CDCl$_3$). Isomer A: $\delta$ 7.47-7.44 (m, 1 H), 7.33-7.26 (comp, 6 H), 7.19-7.13 (comp, 3 H), 7.08 (d, $J$ = 8.0 Hz, 1 H), 6.88-6.86 (m, 1 H), 6.83-6.81 (m, 1 H), 4.86-4.81 (comp, 1 H), 4.08 (d, $J$ = 7.6 Hz, 1 H), 3.82 (s, 3 H), 2.36 (s, 3 H), Isomer B: $\delta$ 7.47-7.44 (m, 1 H), 7.33-7.26 (comp, 6 H), 7.19-7.13 (comp, 3 H), 7.08 (d, $J$ = 8.0 Hz, 1 H), 6.88-6.86 (m, 1 H), 6.83-6.81 (m, 1 H), 4.86-4.81 (comp, 1 H), 4.10 (d, $J$ = 6.4 Hz, 1 H), 3.80 (s, 3 H), 2.32 (s, 3 H); $^{13}$C NMR (100 MHz) Isomer A: $\delta$ 159.44, 137.15, 135.07, 133.40, 131.80, 130.38, 129.49,
129.27, 128.94, 128.70, 128.49, 128.39, 128.36, 128.15, 128.10, 123.41, 114.09, 113.54, 88.48, 85.34, 78.08, 55.48, 47.81, 21.29, Isomer B: δ 159.56, 137.46, 135.22, 133.61, 131.96, 130.38, 129.49, 129.27, 128.94, 128.70, 128.49, 128.39, 128.36, 128.15, 128.10, 123.62, 114.56, 113.59, 89.04, 85.94, 78.10, 55.50, 48.23, 21.32; IR (neat) 3587 2990 2873 2285 1968 1383 1142 845; HRMS (ESI) m/z 365.1526 \([C_{24}H_{22}O_2(M+Na)] requires 365.1512\).

**General procedure for the indium-catalyzed synthesis of diarylethynylmethanes:** A two-dram screw cap vial, equipped with a magnetic stir bar, was charged with InBr₃ (29 mg, 0.082 mmol) and diisopropylethylamine (36 µL, 0.21 mmol) under an argon atmosphere. Phenylacetylene (90 µL, 0.82 mmol) was added dropwise, via syringe, followed by the addition of aldehyde (0.41 mmol) in one portion. The mixture was stirred until consumption of the aldehyde was judged to be complete by TLC (5-10 h). A solution of 1,3,5-trimethoxy benzene (69 mg, 0.41 mmol) and (±)-camphorsulfonic acid (20 mg, 0.082 mmol) in CH₂Cl₂ (0.50 mL) was added, and stirred at 25 °C until full consumption of the intermediate alcohol was observed by TLC (1-4 hours). The reaction was then partitioned between CH₂Cl₂ (2.0 mL) and water (2.0 mL), and the aqueous layer was extracted with CH₂Cl₂ (3 x 2.0 mL). The combined organic extracts were dried over MgSO₄. The resulting solution was filtered and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography eluting with the indicated solvent mixture to give the corresponding diarylethynyl methane **3.6**.
1,3-diphenylprop-2-yn-1-ol (3.3d). Compound 3.3d was recovered from the coupling of 1.63, 3.20 and 3.8g, performed on a 0.412 mmol scale using 0.412 mmol InBr₃ and 0.824 mmol DIPEA, with a total reaction time of 5 h. Purification by flash chromatography eluting with hexanes/EtOAc (3:1) provided 81 mg (94%) of 3.3d as a yellow oil. The $^1$H-NMR data for 3.3d was consistent with literature reported data.¹³²

(3-(2,4,6-trimethoxyphenyl)prop-1-yn-1,3-diyl)dibenzene (3.6u). The coupling of 1.63, 3.20 and 3.8g was performed on 0.412 mmol scale with a total reaction time of 28 h. Purification by flash chromatography eluting with hexanes/EtOAc (8:1) provided 111 mg (75%) of 3.6u as an orange oil. The $^1$H NMR and $^{13}$C NMR data for 3.6u were found to be consistent with literature reported values.¹³³

2-(1-(4-chlorophenyl)-3-phenylprop-2-yn-1-yl)-1,3,5-trimethoxybenzene (3.6v). The coupling of 3.1b, 3.20, and 3.8g was performed on a 0.412 mmol scale with a total
reaction time of 28 h. Purification by flash chromatography eluting with hexanes/EtOAc (8:1) provided 137 mg (85%) of 3.6v as a yellow oil. The 1H NMR and 13C NMR data for 3.6v were found to be consistent with literature reported values.8

5.2 Synthetic Procedures From Chapter 4

5.2.1 General

The following compounds were prepared following previously reported literature procedures: 4.7,134 4.8,135 4.11a,109 4.11b,136 4.11h,137 4.12,138 4.14,139 4.17,140 and 4.23141. Zinc dust was rinsed with 1M HCl, filtered and washed thoroughly with water, acetone and ether and dried under vacuum.

5.2.2 Synthesis of Substrates and Reagents

*tert*-butyl(4-(6-iodo-3-((triethylsilyl)oxy)hex-5-yn-1-yl)phenoxy)dimethylsilane (4.10):

A solution of BF3•OEt2 (423 µL, 3.34 mmol) in CH2Cl2 (15 mL) was added, dropwise, to a solution of aldehyde 4.7 (589 mg, 2.23 mmol) and stannane 4.8 (1.10 g, 3.34 mmol) in CH2Cl2 (6.0 mL) at −78 °C. After 30 min, the reaction was quenched with a saturated NaHCO3(aq) solution (5.0 mL), and extracted (3 x 10 mL) with Et2O. The combined organic extracts were dried (MgSO4), filtered, concentrated in vacuo, and taken on without further purification. 1H NMR (500 MHz, CDCl3) δ 7.03 (d, J = 8.5 Hz, 2 H), 6.76 (d, J = 8.5 Hz, 2 H), 3.86-3.82 (m, 1 H), 2.69-2.40 (comp, 4 H), 1.92-1.75 (m, 2 H), 1.00-0.96 (comp,
18 H), 0.64-0.59 (comp, 12 H); $^{13}$C NMR (125 MHz) $\delta$ 153.8, 134.9, 129.4, 120.1, 92.0, 70.8, 39.0, 30.9, 29.9, 25.9, 7.13, 5.24, −4.4, −5.1; IR (neat) 2953, 2930, 2876, 2858, 2320, 1609, 1509, 1251, 1098, 914; HRMS (ESI) $m/z$ 567.1564 [C$_{24}$H$_{41}$I$_2$Si$_2$ (M+Na) requires 567.1582].

**(S)-((1-(4-(Benzyloxy)phenyl)-6-iodohex-5-yn-3-yl)oxy)triethylsilane (4.16).** To a solution of TiCl$_4$ (0.24 g, 1.27 mmol, 0.14 mL) in CH$_2$Cl$_2$ (25.0 mL) was added Ti(OPr)$_4$ (1.06 g, 3.81 mmol, 1.10 mL) dropwise at 0 °C and stirred for 1 h. Ag$_2$O (589 mg, 2.54 mmol) was then added in one portion and the reaction vessel wrapped in aluminum foil to exclude ambient light. The resulting mixture was stirred for 5 h then (R)-BINOL (1.40 g, 5.08 mmol) was added portionwise, the reaction warmed to room temperature by removal of the ice water cooling bath, and stirring continued for 2 h. The reaction was cooled to –20 °C, then aldehyde 18 (3.06 g, 12.73 mmol) and allenyltributyltin (IV) (12.60 g, 38.2 mmol) were added sequentially. After continued stirring for 24 h at –20 °C, saturated aqueous NaHCO$_3$ (25.0 mL) was added, and the resulting mixture was allowed to warm to room temperature by removal of the cooling bath. The biphasic mixture was filtered through celite eluting with Et$_2$O (100 mL), and the layers separated. The aqueous phase was extracted with Et$_2$O (3 x 15 mL), and the combined organic extracts were dried (Na$_2$SO$_4$) and concentrated under reduced pressure. The resulting crude mixture was purified by flash chromatography eluting with hexanes/EtOAc (3:1) to provide 3.1 g (85%, 83% ee) of the target alcohol as a colorless oil. Enantiometric excess
was determined by HPLC analysis using a Chiral-Dex OD column (96:4 hexanes/PrOH) \( t_r = 26.48 \) min; \( t_r = 31.15 \) min \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta 7.48-7.46 \) (m, 2 H), \( 7.43-7.40 \) (m, 2 H), \( 7.37-7.34 \) (m, 1 H), \( 7.18-7.15 \) (m, 2 H), \( 6.96-6.94 \) (m, 2 H), \( 5.07 \) (s, 2 H), \( 3.82-3.79 \) (m, 1 H), \( 2.81-2.76 \) (m, 1 H), \( 2.71-2.65 \) (m, 1 H), \( 2.49-2.35 \) (m, 2 H), \( 2.11-2.10 \) (m, 1 H) 1.89-1.85 (m, 2 H); \(^{13}\)C NMR (125 MHz) \( \delta 157.2, 137.3, 134.1, 129.5, 128.7, 128.1, 127.6, 115.0, 80.9, 71.2, 70.2, 69.2, 38.1, 31.1, 27.6; \) IR (neat) 3285, 3030, 2926, 2247, 1610, 1510, 1237; [\( \alpha \)]\( _D \) = –11.10° (c = 1.0, CHCl\(_3\)); HRMS (ESI) \( m/z \) 281.1524 [C\(_{19}\)H\(_{20}\)O\(_2\) (M+1) requires 281.1536].

Imidazole (2.6 g, 38.19 mmol) and TESCl (4.27 mL, 25.5 mmol) were added sequentially to a solution of the starting alcohol (3.10 g, 10.88 mmol) in DMF (25 mL) at room temperature and stirred for 10 min. The mixture was then diluted with water (20 mL) and Et\(_2\)O (50 mL), the layers separated, and the organic phase washed with water (2 x 10 mL). The resulting organic layer was dried (Na\(_2\)SO\(_4\)) and concentrated under reduced pressure. The crude mixture was dissolved in THF (20 mL) and cooled to –78 °C. \(^{n}\)BuLi (1.7 M in hexanes, 7.46 mmol, 4.39 mL) was added dropwise, the mixture stirred for 30 min, then a solution of I\(_2\) (2.1 g, 8.15 mmol) in THF (5.0 mL) was added. The reaction mixture was allowed to warm to room temperature by removal of the cooling bath, diluted with saturated aqueous Na\(_2\)S\(_2\)O\(_3\), and the layers separated. The aqueous phase was extracted with Et\(_2\)O (3 x 10 mL) and the combined organic extracts were dried (Na\(_2\)SO\(_4\)) and concentrated under reduced pressure. The resulting crude mixture was purified by flash chromatography eluting with hexanes/CH\(_2\)Cl\(_2\) (1:1) to provide 3.11 g (55%) of 15 as a pale yellow oil. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta 7.47-7.46 \) (m, 2 H), 7.43-
7.39 (m, 2 H), 7.36-7.33 (m, 1 H), 7.15-7.13 (m, 2 H), 6.95-6.93 (m, 2 H), 5.07 (s, 2 H),
3.91-3.86 (m, 1 H), 2.74-2.56 (m, 4 H), 1.96-1.89 (m, 1 H), 1.86-1.79 (m, 1 H), 1.01 (t, \( J = 
8.0 \text{ Hz}, 9 \text{ H})
 ), 0.65 (q, \( J = 7.5 \text{ Hz}, 6 \text{ H})
).

\( ^{13} \text{C} \) NMR (125 MHz) \( \delta 157.2, 137.4, 134.7, 129.6, 129.4, 128.8, 128.1, 127.7, 
115.0, 91.9, 70.8, 70.2, 39.1, 30.8, 29.9, 7.1, 5.2; \) IR (neat)
3063, 3031, 2952, 2910, 2875, 2247, 1611, 1583, 1510, 1455, 1379, 1239, 1102, 1016, 
909; HRMS (ESI) \( m/z \) 521.1348 [C\(_{25}\)H\(_{33}\)O\(_2\)Si (M+1) requires 521.1367]; \([\alpha]_D = -11.30^\circ \) (c = 
1.0, CHCl\(_3\)).

**General Procedure for the ortho-Deprotection of Phenols.** A clean, oven dried 2 dram 
screw cap vial was charged with ZnCl\(_2\) (26 mg, 0.19 mmol) and Et\(_2\)O (1.0 mL). A solution of ortho-protected phenol (0.18 mmol) in Et\(_2\)O (0.9 mL) was added via syringe and the reaction stirred at the indicated temperature until starting material was consumed as determined by TLC analysis. The reaction was then diluted with saturated aqueous NH\(_4\)Cl (2.0 mL), the layers were separated, and the aqueous phase was extracted with diethyl ether (3 x 2.0 mL). The combined organic fractions were dried over MgSO\(_4\), and concentrated under reduced pressure. The resulting crude material was purified by flash chromatography eluting with the indicated solvent to give the ortho-deprotected phenol.

![Image](4.13c)

**4-((benzyloxy)methoxy)-2-hydroxybenzaldehyde** (4.13c). The deprotection of 4.11c was performed at 0 °C, with a total reaction time of 2 h. Purification by flash
chromatography eluting with hexanes/EtOAc (4:1) provided 34 mg (71%) of 4.13c as a white solid. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 11.37 (s, 1 H), 9.74 (s, 1 H), 7.46 (d, \(J = 8.5\) Hz, 1 H), 7.37 – 7.29 (m, 5 H), 6.69 (dd, \(J = 8.5, 2.0\) Hz, 1 H), 6.65 (d, \(J = 2.0\) Hz, 1 H), 5.33 (s, 2 H), 4.71 (s, 2 H); \(^1\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 194.9, 164.6, 164.3, 136.9, 135.6, 128.7, 128.3, 128.2, 116.2, 109.3, 103.7, 92.1, 70.8; IR (neat) 3437, 3330, 3272, 3084, 3064, 3032, 2916, 2871, 1680, 1652, 1629, 1602, 1579, 1497, 1454, 1439, 1384, 1250, 1216, 1179, 1157, 1076, 999, 811 cm\(^{-1}\); HRMS (ESI) \(m/z = 259.0979\) [C\(_{15}\)H\(_{15}\)O\(_4\) (M+1) requires 259.0965].

4-((2-ethyloxy)methoxy)-2-hydroxybenzaldehyde (4.13d). The deprotection of 4.11d was performed at 0 °C, with a total reaction time of 2 h. Purification by flash chromatography eluting with hexanes/EtOAc (4:1) provided 20 mg (55%) of 4.13d as a colorless oil. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 11.38 (s, 1 H), 9.74 (d, \(J = 1.0\) Hz, 1 H), 7.45 (d, \(J = 8.5\) Hz, 1 H), 6.66 (dd, \(J = 8.5, 2.5\) Hz, 1 H), 6.61 (d, \(J = 2.5\) Hz, 1 H), 5.27 (s, 2 H), 3.73 (q, \(J = 2.0\) Hz, 2 H), 1.23 (t, \(J = 2.0\) Hz, 3 H); \(^1\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 194.8, 164.7, 164.3, 135.6, 116.0, 109.3, 103.6, 93.0, 65.1, 15.3; IR (neat) 3377, 2975, 2894, 1655, 1631, 1445, 1381, 1333, 1230, 1089, 1049, 994, 881 cm\(^{-1}\); HRMS (ESI) \(m/z = 197.0819\) [C\(_{10}\)H\(_{13}\)O\(_4\) (M+1) requires 197.0808].

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1-(2-(tert-butyldimethylsilyl)oxy)-6-hydroxyphenyl)ethanone (4.13e). The deprotection of 4.11e was performed at 0 °C, with a total reaction time of 2 h. Purification by flash chromatography eluting with hexanes/EtOAc (4:1) provided 18 mg (86%) of 10 as a colorless solid. 1H NMR (300 MHz, CDCl3) δ 7.24 (t, J = 8.4 Hz, 1 H), 6.55 (dd, J = 8.4, 1.2 Hz, 1 H), 6.35 (dd, J = 8.4, 0.9, 1 H), 1.00 (s, 9 H), 0.34 (s, 6 H).

(((3S)-1,7-Bis(4-(benzyl)oxy)phenyl)-7-(2,4,6-trimethoxyphenyl)hept-5-yn-3-yl)oxy)triethylsilane (4.18): A 25 mL round bottom flask, equipped with a magnetic stir bar, was charged with Cp2TiCl2 (14 mg, 0.059 mmol) and zinc dust (154 mg, 2.36 mmol) then purged with argon for 5 min. Dry, degassed DCE (2.0 mL) was added and the suspension stirred at room temperature until a blue/green color persisted. A solution of tBu3P (95 mg, 0.472 mmol) in DCE (1.0 mL) was then added dropwise, and the reaction stirred for an additional 10 min. A solution of 4.17 (250 mg, 1.18 mmol), 4.16 (1.23 g, 2.36 mmol), and 3.8g (397 mg, 2.36 mmol) in DCE (2.0 mL) was then added, and the reaction stirred for 1 h. Cs2CO3 (384 mg, 1.18 mmol) was added in one portion followed by the slow addition of Ac2O (0.265 mg, 2.60 mmol, 0.245 mL) in DCE (5.0 mL) over 11 h
via syringe pump. After the addition was complete, the reaction was diluted with CH₂Cl₂ (10 mL), filtered through a plug of silica gel eluting with CH₂Cl₂ (250 mL), and the filtrate concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with hexanes/CH₂Cl₂ (3:1 → 0:1) to provide 893 mg (>99%) of 4.18 in a 1:1 mixture of diastereomers as a clear, yellow oil. ¹H NMR (500 MHz, CDCl₃) Isomer A: δ 7.47-7.32 (m, 12 H), 7.11 (d, J = 8.5 Hz, 2 H), 6.92-6.87 (comp, 4 H), 6.15 (br s, 2 H), 5.65 (br s, 1 H), 5.07 (br s, 2 H), 5.05 (br s, 2 H), 3.97-3.89 (m, 1 H), 3.82 (s, 3 H), 3.72 (s, 6 H), 2.80-2.74 (m, 2 H), 2.55-2.44 (comp, 2 H), 2.12-2.05 (m, 2 H), 1.01 (t, J = 8 Hz, 9 H), 0.66 (q, J = 8.0 Hz, 6 H); Isomer B: δ 7.47-7.32 (m, 12 H), 7.11 (d, J = 8.5 Hz, 2 H), 6.92-6.87 (comp, 4 H), 6.14 (br s, 2 H), 5.65 (br s, 1 H), 5.07 (br s, 2 H), 5.05 (br s, 2 H), 3.97-3.89 (m, 1 H), 3.82 (s, 3 H), 3.71 (s, 6 H), 2.66-2.60 (m, 2 H), 2.55-2.44 (comp, 2 H), 1.96-1.88 (m, 2 H), 1.01 (t, J = 8.0 Hz, 9 H), 0.65 (q, J = 8.0 Hz, 6 H); ¹³C NMR (125 MHz) δ 160.3, 158.6, 157.0, 157.0, 137.5, 137.4, 135.2, 134.7, 129.5, 128.7, 128.5, 128.4, 128.0, 127.7, 127.1, 126.0, 114.9, 114.2, 114.2, 112.0, 91.6, 91.5, 82.8, 71.3, 71.2, 70.2, 56.1, 56.0, 55.4, 38.7, 38.6, 30.7, 30.3, 30.2, 28.2, 7.1, 5.2; IR (neat) 3063, 3033, 2954, 2932, 2877, 2859, 1641, 1609, 1512, 1254, 1175; HRMS (ESI) m/z 779.3736 [C₄₈H₅₆O₆Si (M+Na) requires 779.3738].

![Chemical Structure](image)

(3S)-1,7-bis(4-(benzyloxy)phenyl)-7-(2,4,6-trimethoxyphenyl)hept-5-yn-3-ol (4.19). A solution of TBAF·3H₂O (0.08 g, 0.30 mmol) in THF (1.0 mL) was added to a solution of
4.18 (0.22 g, 0.30 mmol) in THF (1.0 mL) at 0 °C. The resulting solution was stirred for 4 h at room temperature then diluted with a saturated aqueous NH₄Cl (2.0 mL). The layers were separated and aqueous phase extracted with Et₂O (3 x 1.0 mL). The combined organic extracts were dried (MgSO₄), and concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with hexanes/EtOAc (2:1) to provide 160 mg (83%) of 4.19 as a yellow oil. ¹H NMR (500 MHz, CDCl₃) Isomer A: δ 7.46-7.31 (m, 12 H), 7.15-7.10 (m, 2 H), 6.94-6.90 (m, 2 H), 6.89-6.85 (m, 2 H), 6.16 (s, 2 H), 5.66 (s, 1 H), 5.06 (s, 2 H), 5.04 (s, 2 H), 3.81, (s, 3 H), 3.75 (br s, 8 H), 2.81-2.62 (m, 2 H), 2.56-2.48 (m, 1 H), 2.43-2.33 (s, 1 H), 1.97-1.74 (m, 2 H) Isomer B: δ 7.46-7.31 (m, 12 H), 7.15-7.10 (m, 2 H), 6.94-6.90 (m, 2 H), 6.89-6.85 (m, 2 H), 6.16 (s, 2 H), 5.66 (s, 1 H), 5.06 (s, 2 H), 5.04 (s, 2 H), 3.80, (s, 3 H), 3.75 (br s, 8 H), 2.81-2.62 (m, 2 H), 2.56-2.48 (m, 1 H), 2.43-2.33 (s, 1 H), 1.97-1.74 (m, 2 H); ¹³C NMR (125 MHz) Isomer A: δ 160.4, 158.4, 157.2, 137.4, 137.4, 134.6, 134.3, 129.6, 129.6, 128.7, 128.4, 128.1, 127.7, 114.9, 114.9, 114.3, 112.0, 91.8, 85.0, 77.5, 77.2, 77.0, 70.2, 69.5, 66.1, 56.2, 55.5, 38.3, 31.3, 30.1, 28.3 Isomer B: 160.4, 158.4, 157.2, 137.4, 137.4, 134.6, 134.3, 129.6, 129.6, 128.7, 128.4, 128.1, 127.7, 114.9, 114.9, 114.3, 112.0, 91.8, 84.9, 77.5, 77.2, 77.0, 70.2, 69.3, 66.1, 56.2, 55.5, 38.2, 31.3, 30.1, 28.3; IR (neat) 3054, 2960, 2937, 2836, 2303, 1671, 1597, 1489, 1443, 1265; HRMS (ESI) m/z 643.3054 [C₄₂H₄₃O₆ (M+1) requires 643.3025].
(6S)-6-(4-(benzyloxy)phenethyl)-3-((4-methoxyphenyl)(2,4,6-trimethoxyphenyl)methyl)-2,2- dimethyl-5,6-dihydro-2H-1,2-oxasiline (4.20). A 10 mL round bottom flask was charged with 4.19 (0.32 g, 0.5 mmol), and tetramethyldisilazane (0.20 g, 1.5 mmol). The neat mixture was heated to 50°C and stirred for 5 h. The flask was allowed to cool to room temperature by removal of the oil bath then placed under vacuum (~1 mmHg) for 45 min to remove excess tetramethyldisilazane. The flask was purged with Ar, and the residue dissolved in CH₂Cl₂ (1.0 mL). The resulting solution was cooled to 0 °C, and Cp*Ru(MeCN)₃PF₆ (0.015 g, 0.03 mmol) was added in one portion. The cooling bath was removed and the reaction stirred for 1 h while warming to room temperature, and the mixture filtered through a short plug of silica eluting with Et₂O (40 mL). The crude residue was purified by flash chromatography eluting with hexanes/EtOAc (4:1) to provide 150 mg (43%) of 4.20 as a yellow oil. ¹H NMR (500 MHz, CDCl₃) Isomer A: δ 7.46-7.31 (m, 10 H), 7.20-7.17 (m, 2 H), 7.12 (d, J = 8.5 Hz, 2 H), 6.92-6.90 (m, 2 H), 6.87-6.84 (m, 2 H), 6.12 (s, 2 H), 6.10-6.08 (m, 1 H), 5.30 (s, 1 H), 5.06 (s, 2 H), 5.03 (s, 2 H), 3.85-3.80 (comp, 4 H), 3.68 (s, 6 H), 2.78-2.71 (m, 1 H), 2.66-2.58 (m, 1 H), 2.23-2.07 (m, 2 H), 1.91-1.83 (m, 1 H), 1.73-1.65 (m, 1 H), 0.03 (s, 3 H), −0.13 (s, 3 H) Isomer B: δ 7.46-7.31 (m, 10 H), 7.20-7.17 (m, 2 H), 7.12 (d, J = 8.5 Hz, 2 H), 6.92-6.90 (m, 2 H), 6.87-6.84 (m, 2 H), 6.12 (s, 2 H), 6.06-6.04 (m, 1 H), 5.30 (s, 1 H), 5.05 (s, 2 H),
5.03 (s, 2 H), 3.85-3.80 (comp, 4 H), 3.68 (s, 6 H), 2.78-2.71 (m, 1 H), 2.66-2.58 (m, 1 H), 2.23-2.07 (m, 2 H), 1.91-1.83 (m, 1 H), 1.73-1.65 (m, 1 H), 0.06 (s, 3 H), −0.17 (s, 3 H); $^{13}$C NMR (125 MHz) Isomer A: δ 160.5, 159.4, 157.1, 156.9, 141.1, 139.2, 138.5, 137.6, 135.5, 135.0, 130.8, 129.7, 128.8, 128.1, 127.7, 127.7, 114.8, 114.0, 112.6, 91.4, 70.6, 70.3, 70.2, 70.1, 55.7, 55.6, 55.4, 43.7, 39.7, 36.5, 31.1, −0.4, −0.7 Isomer B: δ 160.5, 159.4, 157.1, 156.9, 141.1, 139.2, 138.5, 137.6, 135.5, 135.0, 130.8, 129.7, 128.7, 128.0, 127.7, 127.7, 114.8, 114.0, 112.5, 91.3, 70.6, 70.3, 70.2, 70.1, 55.7, 55.6, 55.4, 43.6, 39.7, 36.4, 31.0, −0.4, −0.5.

(E)-3-(4-(Benzyloxy)phenyl)-1-(3-((5S)-1,7-bis(4-(benzyloxy)phenyl)-5-hydroxyhept-2-yn-1-yl)-2,4,6-trimethoxyphenyl)prop-2-en-1-one (4.24). N-Bromosuccinimide (38 mg, 0.215 mmol) was added in one portion to a solution of 4.18 (163 mg, 0.215 mmol) in THF (7 mL) at room temperature and stirred for 30 min. Solid NaHCO$_3$ (200 mg, 2.38 mmol) was then added and stirring continued for an additional 30 min. The resulting suspension was filtered and concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with hexanes/EtOAc (4:1) to provide 166 mg (92%) of the target aryl bromide (4.22) as a pale yellow oil. $^1$H NMR (500 MHz, CDCl$_3$) Isomer A: δ 7.47-7.33 (m, 12 H), 7.10-7.08 (m, 2 H), 6.92-6.88 (comp, 4 H), 6.31 (s, 1 H), 5.59 (s, 1 H), 5.07 (br s, 2 H), 5.05 (br s, 2 H), 3.90 (comp, 1 H), 3.89 (s, 3 H), 3.78 (s, 3 H), 2.23-2.07 (m, 2 H), 1.91-1.83 (m, 1 H), 1.73-1.65 (m, 1 H), 0.06 (s, 3 H), −0.17 (s, 3 H); $^{13}$C NMR (125 MHz) Isomer A: δ 160.5, 159.4, 157.1, 156.9, 141.1, 139.2, 138.5, 137.6, 135.5, 135.0, 130.8, 129.7, 128.8, 128.1, 127.7, 127.7, 114.8, 114.0, 112.6, 91.4, 70.6, 70.3, 70.2, 70.1, 55.7, 55.6, 55.4, 43.7, 39.7, 36.5, 31.1, −0.4, −0.7 Isomer B: δ 160.5, 159.4, 157.1, 156.9, 141.1, 139.2, 138.5, 137.6, 135.5, 135.0, 130.8, 129.7, 128.7, 128.0, 127.7, 127.7, 114.8, 114.0, 112.5, 91.3, 70.6, 70.3, 70.2, 70.1, 55.7, 55.6, 55.4, 43.6, 39.7, 36.4, 31.0, −0.4, −0.5.
3.68 (s, 3 H), 2.77-2.70 (m, 2 H), 2.51-2.45 (comp, 2 H), 2.09-2.00 (m, 2 H), 1.00 (t, J = 8.0 Hz, 9 H), 0.64 (q, J = 8.0 Hz, 6 H). Isomer B: δ 7.47-7.33 (m, 12 H), 7.10-7.08 (m, 2 H), 6.92-6.88 (comp, 4 H), 6.30 (s, 1 H), 5.59 (s, 1 H), 5.07 (br s, 2 H), 5.05 (br s, 2 H), 3.90 (comp, 1 H), 3.89 (s, 3 H), 3.76 (s, 3 H), 3.66 (s, 3 H), 2.65-2.58 (m, 2 H), 2.51-2.45 (comp, 2 H), 1.93-1.85 (m, 2 H), 1.00 (t, J = 8.0 Hz, 9 H), 0.64 (q, J = 8.0 Hz, 6 H); 13C NMR (125 MHz) δ 157.2, 157.0, 157.0, 157.0, 137.4, 137.4, 135.0, 133.9, 129.4, 128.7, 128.7, 128.5, 128.3, 128.0, 127.7, 127.6, 127.6, 127.1, 126.0, 119.1, 119.1, 114.9, 114.9, 114.3, 82.2, 78.8, 71.0, 70.2, 56.5, 56.1, 38.7, 31.7, 30.7, 28.1, 7.1, 5.2; IR (neat) 3031, 2936, 2874, 1588, 1509, 1454, 1239, 1105, 1016; HRMS (ESI) m/z 859.2769 [C_{48}H_{55}O_{6}BrSi (M+Na) requires 859.2827].

Phenyl lithium (1.4 M in ²Bu₂O, 0.14 mmol, 0.18 mL) was added to a solution of aryl bromide (108 mg, 0.13 mmol) in THF (1.0 mL) at −78 °C and stirred for 10 min. A solution of aldehyde 4.23 (61 mg, 0.26 mmol) in THF (0.5 mL) was then added dropwise, and the mixture stirred for an additional 2 h. The reaction was diluted with pH 7 phosphate buffer (2.0 mL) and the layers separated. The aqueous phase was extracted with Et₂O (3 x 2.0 mL), and the organic fraction dried (Na₂SO₄) and concentrated under reduced pressure. The crude mixture of diastereomeric alcohols was dissolved in 1,4-dioxane (3.0 mL) then added to a stirred solution of DDQ (29 mg, 0.13 mmol) and K₂CO₃ (45 mg, 0.32 mmol) in 1,4-dioxane (1.0 mL) at room temperature and stirred for 10 min. The reaction was then passed through a short plug of silica gel eluting with Et₂O (25 mL), and the filtrate concentrated under reduced pressure. The crude mixture was dissolved in THF (1.5 mL), cooled to 0 °C, and a solution of TBAF•3H₂O (30 mg, 0.087 mmol) in THF
(1.5 mL) was added. The mixture was stirred for 3 h, then diluted with water (1.0 mL), and allowed to warm to room temperature by removal of the cooling bath. The layers were separated and the aqueous phase extracted with Et₂O (5 x 3.0 mL). The combined organic fractions were dried (Na₂SO₄) and concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with hexanes/EtOAc (2:1) to provide 44 mg (39%) of 4.24 as a clear, yellow oil. Isomer A: δ 7.51-7.49 (m, 1 H), 7.43-7.31 (comp, 20 H), 7.10-7.08 (m, 2 H), 6.97-6.93 (comp, 3 H), 6.91-6.88 (comp, 5 H), 6.33 (s, 1 H), 5.59 (s, 1 H), 5.06 (s, 2 H), 5.04 (s, 2 H), 5.01 (s, 2 H), 3.81 (s, 3 H), 3.79 (s, 3 H), 3.72-3.70 (m, 1 H), 3.49 (s, 3 H), 2.75-2.68 (m, 1 H), 2.65-2.60 (m, 1 H), 2.55-2.47 (m, 1 H), 2.43-2.35 (m, 1 H), 1.86-1.75 (m, 2 H). Isomer B: δ 7.51-7.49 (m, 1 H), 7.43-7.31 (comp, 20 H), 7.10-7.08 (m, 2 H), 6.97-6.93 (comp, 3 H), 6.91-6.88 (comp, 5 H), 6.32 (s, 1 H), 5.59 (s, 1 H), 5.05 (s, 2 H), 5.04 (s, 2 H), 5.01 (s, 2 H), 3.81 (s, 3 H), 3.79 (s, 3 H), 3.72-3.70 (m, 1 H), 3.45 (s, 3 H), 2.75-2.68 (m, 1 H), 2.65-2.60 (m, 1 H), 2.55-2.47 (m, 1 H), 2.43-2.35 (m, 1 H), 1.86-1.75 (m, 2 H). ¹³C NMR (125 MHz) δ 194.2, 171.4, 160.9, 159.4, 159.3, 158.9, 157.7, 157.3, 157.2, 157.1, 145.1, 145.0, 137.3, 137.3, 136.6, 134.5, 133.7, 130.6, 130.5, 130.3, 129.5, 128.8, 128.7, 128.4, 128.3, 128.1, 128.0, 127.8, 127.7, 127.6, 126.5, 117.3, 117.0, 115.3, 114.9, 114.5, 92.4, 84.2, 84.1, 78.2, 70.2, 69.6, 64.5, 63.1, 56.3, 56.2, 38.3, 31.3, 31.2, 30.8, 30.7, 28.3; IR (neat) 3425, 2932, 1660, 1597, 1509, 1389, 1242, 1104.
(E)-3-(4-(Benzyloxy)phenyl)-1-(3-((5S,E)-1,7-bis(4-(benzyloxy)phenyl)-5-hydroxyhept-2-en-1-yl)-2,4,6-trimethoxyphenyl)prop-2-en-1-one (4.25). To a solution of alcohol 4.24 (17 mg, 0.019 mmol) in CH$_2$Cl$_2$ (0.10 mL) was added Et$_3$N (3.8 mg, 0.038 mmol, 5.0 µL) followed by Me$_2$HSiCl (2.0 mg, 0.021 mmol, 2.5 µL) at 0 ºC and the resulting solution stirred for 1 h. The reaction was allowed to warm to room temperature by removal of the ice water bath, diluted with water (0.1 mL), and the layers separated. The aqueous phase was extracted with CH$_2$Cl$_2$ (5 x 0.5 mL), dried (Na$_2$SO$_4$), and concentrated under reduced pressure. The crude silane was dissolved in CH$_2$Cl$_2$ (0.10 mL) and Cp*Ru(CH$_3$CN)$_3$PF$_6$ (0.5 mg, 0.95 µmol) was added in one portion at room temperature. The mixture was stirred for 1 h then filtered through a short plug of silica gel eluting with EtOAc (25 mL), and the filtrate was concentrated under reduced pressure. The crude mixture was dissolved in DMF (0.10 mL), heated to 120 ºC, and stirred for 15 min. The reaction was allowed to cool to room temperature by removal of the oil bath, diluted with water (0.1 mL), and the layers separated. The aqueous phase was extracted with Et$_2$O (5 x 0.5 mL), and the combined organic fractions dried (Na$_2$SO$_4$) and concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with hexanes/EtOAc (2:1) to provide 10 mg (29% over 3 steps) of 4.25 as a colorless oil. Isomer A: δ 7.48 (d, $J = 8.4$ Hz, 2 H), 7.45 (d, $J = 8.4$ Hz, 2 H),
Isomer A: δ 7.45-7.31 (comp, 15 H), 7.12-7.08 (m, 3 H), 6.96 (d, J = 8.4 Hz, 2 H), 6.92-6.89 (m, 3 H), 6.87-6.84 (m, 2 H), 6.32-6.20 (comp, 2 H), 5.58-5.51 (m, 1 H), 5.18-4.98 (comp, 9 H), 3.80 (s, 3 H), 3.74 (s, 3 H), 3.67 (m, 1 H), 3.47 (s, 3 H), 2.74-2.73 (m, 2 H), 2.36-2.32 (m, 2 H).

Isomer B: δ 7.48 (d, J = 8.4 Hz, 2 H), 7.45 (d, J = 8.4 Hz, 2 H), 7.45-7.31 (comp, 15 H), 7.12-7.08 (m, 3 H), 6.96 (d, J = 8.4 Hz, 2 H), 6.92-6.89 (m, 3 H), 6.87-6.84 (m, 2 H), 6.32-6.20 (comp, 2 H), 5.58-5.51 (m, 1 H), 5.18-4.98 (comp, 9 H), 3.80 (s, 3 H), 3.74 (s, 3 H), 3.67 (m, 1 H), 3.47 (s, 3 H), 2.66-2.62 (m, 2 H), 2.32-2.19 (m, 2 H). 13C NMR (125 MHz) δ 194.6, 160.9, 160.0, 159.9, 157.3, 157.2, 157.0, 145.0, 144.9, 137.4, 136.7, 136.6, 136.2, 135.9, 135.9, 134.8, 134.7, 132.4, 130.5, 129.5, 128.9, 128.8, 128.7, 128.6, 128.4, 128.1, 127.9, 127.7, 127.7, 127.2, 126.7, 126.3, 118.7, 118.6, 117.1, 115.4, 115.0, 114.5, 114.4, 92.5, 70.3, 70.3, 70.2, 63.1, 56.2. 56.0, 43.0, 42.7, 41.0, 38.9, 31.4, 31.3; IR (neat) 3385, 3067, 3034, 2930, 2875, 2856, 1666, 1595, 1455, 1239, 1104, 1018; HRMS (ESI) m/z 903.3879 [C₅₈H₅₆O₈ (M+Na) requires 903.3867].

2-formyl-5-methoxy-1,3-phenylene dibenzenesulfonate (4.11g): Aldehyde 4.11g was provided by C. Campos. 1H NMR (500 MHz, CDCl₃) δ 9.59 (s, 1 H), 7.89-7.87 (m, 4 H), 7.23-7.69 (m, 2 H), 7.58-7.55 (m, 4 H), 6.79 (s, 2 H), 3.85 (s, 3 H); 13C NMR (125 MHz) δ 183.6, 164.2, 151.4, 135.1, 129.6, 128.8, 116.6, 109.1, 56.5; IR (neat) 3099, 3070, 3031, 2942, 2907, 2814, 1694, 1610, 1569, 1381, 1293, 1186. HRMS (ESI) m/z 471.0148 [C₂₀H₁₆O₈S₂ (M+Na) requires 471.0179].
((4-((SS)-1,7-bis(4-(benzyloxy)phenyl)-5-((triethyloxyl)silyl)oxy)hept-2-yn-1-yl)-5-methoxy-1,3-phenylene)bis(oxy))bis(triethylsilane) (4.18): A 2 dram vial, equipped with a magnetic stir bar, was charged with Cp₂TiCl₂ (1.4 mg, 0.006 mmol) and zinc dust (22 mg, 0.333 mmol) then purged with argon for 5 min. Dry, degassed DCE (0.25 mL) was added and the suspension stirred at room temperature until a blue/green color persisted. A solution of t-Bu₃P (9.0 mg, 0.044 mmol) in DCE (0.25 mL) was then added dropwise, and the reaction stirred for an additional 10 min. A solution of 4.17 (24.0 mg, 0.111 mmol), 4.16 (173 mg, 0.333 mmol), and 4.27 (82 mg, 0.222 mmol) in DCE (0.50 mL) was then added, and the reaction stirred for 1 h. Cs₂CO₃ (36 mg, 0.111 mmol) was added in one portion followed by the slow addition of Ac₂O (26.0 µL, 0.25 mmol) in DCE (0.5 mL) over 11 h via syringe pump. After the addition was complete, the reaction was diluted with CH₂Cl₂ (2.0 mL), filtered through a plug of silica gel eluting with CH₂Cl₂ (100 mL), and the filtrate concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with hexanes/CH₂Cl₂ (1:1) to provide 84 mg (79%) of 4.18 in a 1:1 mixture of diastereomers as a clear, yellow oil. ¹H NMR (500 MHz, CDCl₃) Isomer A: δ 7.45-7.31 (m, 12 H), 7.10-7.08 (m, 2 H), 6.91-6.89 (m, 2 H), 6.85-6.83 (m, 2 H), 6.06 (br s, 1 H), 6.01 (br s, 1 H), 5.56 (br s, 1 H), 5.05 (s, 2 H), 5.04, (s, 2 H), 3.92-3.90 (m, 1 H), 3.63 (s, 3 H), 2.77-2.71 (m, 1 H), 2.63-2.57 (m, 1 H), 2.25-2.38 (m, 2 H), 1.89-1.82 (m, 2 H), 1.03 (t, J = 8 Hz, 9 H), 0.99 (t, J = 8 Hz, 9 H), 0.93, (t, J = 8 Hz, 9 H),
0.78-0.68 (m, 12 H), 0.66-0.61 (m, 6 H). Isomer B: 7.45-7.31 (m, 12 H), 7.10-7.08 (m, 2 H), 6.91-6.89 (m, 2 H), 6.85-6.83 (m, 2 H), 6.06 (br s, 1 H), 6.01 (br s, 1 H), 5.56 (br s, 1 H), 5.05 (s, 2 H), 5.04, (s, 2 H), 3.92-3.90 (m, 1 H), 3.62 (s, 3 H), 2.77-2.71 (m, 2 H), 2.63-2.57 (m, 2 H), 2.25-2.38 (m, 2 H), 1.89-1.82 (m, 2 H), 1.03 (t, J = 8 Hz, 9 H), 0.99 (t, J = 8 Hz, 9 H), 0.93, (t, J = 8 Hz, 9 H), 0.78-0.68 (m, 12 H), 0.66-0.61 (m, 6 H)\(^{13}\)C NMR (125 MHz) \(\delta\) 156.9, 155.4, 137.4, 137.3, 135.0, 134.6, 134.5, 129.3, 129.3, 128.5, 128.5, 128.3, 128.2, 127.8, 127.8, 127.5, 127.4, 126.0, 114.7, 114.0, 102.9, 102.8, 82.7, 77.4, 71.2, 71.1, 70.1, 55.7, 38.6, 30.6, 30.6, 30.5, 28.2, 14.0, 6.9, 6.6, 6.6, 5.2, 5.0, 5.0; IR (neat) 3059, 2953, 2875, 2363, 1607, 1584, 1508, 1455, 1417, 1237, 1106; HRMS (ESI) \(m/z\) 957.5313 \([\text{C}_{88}\text{H}_{81}\text{O}_{6}\text{Si}_{3}] (\text{M}+1)\) requires 957.5335.

\begin{center}
\[\text{OME} \quad \text{OTES} \quad \text{OTES}\]
\end{center}

\((5\text{-methoxy-1,3-phenylene})\text{bis(oxy))bis(triethylsilane)} \quad (4.27): \) Trimethyloxonium tetrafluoroborate (92 mg, 0.62 mmol) was added to a solution of 3,5-bis((triethylsilyl)oxy)phenol\(^{142}\) (220 mg, 0.56 mmol) and proton sponge (265 mg, 1.2 mmol) in \(\text{CH}_2\text{Cl}_2\) (10 mL). The resulting heterogenous solution was stirred 45 min at room temperature, and partitioned between \(\text{CH}_2\text{Cl}_2\) (25 mL) and water (25 mL). The aqueous layer was extracted with \(\text{CH}_2\text{Cl}_2\) (3 x 10 mL), and the combined organic extracts were dried over \(\text{MgSO}_4\), filtered, and concentrated under reduced pressure. The resulting crude material was purified by flash chromatography eluting with hexanes/EtOAc (8:1) to give 131 mg (63%) of 4.27 as a colorless oil. \(^1\)H NMR (500 MHz, \(\text{CDCl}_3\) \(\delta\) 6.07 (d, \(J = 2.1\) Hz, 2 H), 6.01 (t, \(J = 2.1\) Hz, 1 H), 3.74 (s, 3 H), 1.00 (t, \(J = 8.1\) Hz,
18 H), 0.74 (q, J = 8.0 Hz); 13C NMR (125 MHz) δ 161.3, 157.3, 104.8, 99.9, 55.4, 6.8, 5.2; IR (neat) 2955, 2925, 2912, 2877, 1589, 1456, 1430, 1238, 1151, 1003; HRMS (ESI) m/z 369.2246 [C_{19}H_{36}O_{3}Si_{2} (M+H) requires 369.2276].

1,3,5-tris((triethylsilyl)oxy)benzene (4.28): A 50 mL round bottom flask, equipped with a magnetic stir bar, was charged with phloroglucinol (0.50 g, 4.0 mmol) and imidazole (1.10 g, 15.8 mmol), followed by DMF (12.0 mL) and the mixture was stirred at room temperature. To the solution was added TESCl (2.10 mL, 12.3 mmol), dropwise. The reaction was stirred 24 h, then partitioned between Et₂O (25 mL) and H₂O (25 mL). The aqueous layer was extracted (2x 10 mL), and the combined organic extracts were dried over MgSO₄ and concentrated under vacuum. The crude residue was purified by flash chromatography eluting with hexanes/CH₂Cl₂ (1:1) to provide 1.8 g (97%) of 4.28 as a colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 6.04 (s, 3 H), 1.00 (t, J = 7.8 Hz, 27 H), 0.73 (q, J = 7.8 Hz, 18 H); ¹³C NMR (125 MHz) δ 157.0, 106.0, 6.7, 5.1; IR (neat) 2955, 2938, 2912, 2877, 1695, 1587, 1442, 1156, 1003. HRMS (ESI) m/z 469.2949 [C_{24}H_{48}O_{3}Si_{3} (M+H) requires 469.2984].

4-((5S)-1,7-bis(4-(benzyloxy)phenyl)-5-((triethylsilyl)oxy)hept-2-yn-1-yl)-3,5-
bis((triethylsilyl)oxy)phenol (4.30): A 25 mL round bottom flask, equipped with a magnetic stir bar, was charged with Cp₂TiCl₂ (9.0 mg, 0.036 mmol) and zinc dust (287 mg, 1.42 mmol) then purged with argon for 5 min. Dry, degassed DCE (1.0 mL) was added and the suspension stirred at room temperature until a blue/green color persisted. A solution of tBu₃P (57 mg, 0.248 mmol) in DCE (1.0 mL) was then added dropwise, and the reaction stirred for an additional 10 min. A solution of aldehyde 4.17 (151 mg, 0.710 mmol), iodoalkyne 4.16 (922 mg, 1.77 mmol), and arene 4.28 (665 mg, 1.42 mmol) in DCE (2.0 mL) was then added, and the reaction stirred for 1 h. Cs₂CO₃ (231 mg, 0.710 mmol) was added in one portion followed by the slow addition of Ac₂O (0.148 mL, 1.56 mmol) in DCE (5.0 mL) over 11 h via syringe pump. After the addition was complete, the reaction was diluted with CH₂Cl₂ (10 mL), filtered through a plug of silica gel eluting with CH₂Cl₂ (250 mL), and the filtrate concentrated under reduced pressure and taken on without further purification. The resulting crude material was transferred to a 250 mL round bottom flask, and taken up in 50 mL THF. To this solution was added 40 mL AcOH/H₂O (1:1) slowly over 4 h at ambient temperature, at which point the reaction was judged to be complete by TLC. To quench the reaction, saturated aqueous Na₂CO₃ was added slowly until bubbling ceased. The organic layer was then extracted with Et₂O (3 x 20 mL) and the combined organic extracts were dried (MgSO₄) and concentrated under reduced pressure. The resulting crude mixture was purified by flash chromatography eluting with hexanes/EtOAc (8:1) to give 502 mg (75% over two steps) of 4.30 in a 1:1 mixture of diastereomers as a colorless oil. ¹H NMR (500 MHz, CDCl₃)

Isomer A: δ 7.47-7.28 (m, 10 H), 7.14-7.11 (m, 2 H), 6.93-6.91 (m, 4 H), 6.85 (d, J = 8.5
Hz, 2 H), 6.03 (s, 2 H), 5.55 (br s, 1 H), 5.06 (s, 4 H), 3.75-3.74 (m, 1 H), 2.78-2.73 (m, 1 H), 2.55-2.52 (m, 1 H), 2.42-2.40 (m, 1 H), 2.39-2.38 (m, 1 H), 1.88-1.78 (m, 2 H), 1.03 (t, J = 7.5 Hz, 9 H), 0.93-0.89 (m, 18 H), 0.78-0.74 (m, 6 H), 0.69-0.65 (m, 12 H). Isomer B: δ 7.47-7.28 (m, 10 H), 7.14-7.11 (m, 2 H), 6.93-6.91 (m, 4 H), 6.85 (d, J = 8.5 Hz, 2 H), 6.03 (s, 2 H), 5.55 (br s, 1 H), 5.06 (s, 4 H), 3.75-3.74 (m, 1 H), 2.69-2.62 (m, 1 H), 2.51-2.50 (m, 1 H), 2.40-2.39 (m, 1 H), 2.37-2.36 (m, 1 H), 1.88-1.78 (m, 2 H), 1.03 (t, J = 7.5 Hz, 9 H), 0.93-0.89 (m, 18 H), 0.78-0.74 (m, 6 H), 0.69-0.65 (m, 12 H). 13C NMR (125 MHz)

Isomer A: δ 157.2, 157.1, 155.2, 137.6, 137.5, 135.6, 134.2, 129.6, 128.8, 128.7, 128.3, 128.1, 128.0, 127.7, 127.5, 116.8, 115.1, 115.0, 114.4, 104.1, 84.5, 70.3, 69.6, 38.3, 31.3, 31.0, 29.9, 28.5, 6.8, 6.8, 5.4, 5.2; Isomer B: δ 157.2, 157.1, 155.2, 137.6, 137.5, 134.6, 134.2, 129.6, 128.8, 128.7, 128.3, 128.1, 128.0, 127.7, 127.5, 116.6, 115.1, 115.0, 114.4, 104.0, 84.4, 70.3, 69.5, 38.3, 31.3, 31.0, 29.9, 28.5, 6.8, 6.8, 5.4, 5.2;

IR (neat) 3437, 3065, 2967, 2945, 2875, 1595, 1578, 1423, 1234, 1173, 1082, 1026, 768, 730. HRMS (ESI) m/z 965.5029 [C57H78O6Si3 (M+Na) requires 965.4998].

$$\text{(2-((5S)-1,7-bis(4-(benzyloxy)phenyl)-5-((triethylsilyl)oxy)hept-2-yn-1-yl)-5-methoxy-1,3-phenylene)bis(oxy))bis(triethylsilane)} \ (4.31):$$  
To a solution of 4.30 (99 mg, 0.11 mmol) in CH₂Cl₂ (2.0 mL), was added proton sponge (47 mg, 0.22 mmol) followed by trimethylloxonium tetrafluoroborate (23 mg, 0.16 mmol) in one portion. After 3 h, the
resulting heterogeneous solution was filtered through Celite eluting with CH₂Cl₂ (30 mL), and concentrated under reduced pressure. The resulting crude material was purified using flash chromatography eluting with hexanes/EtOAc (4:1) to give 50 mg (50%) 4.31 in a 1:1 mixture of diastereomers as a colorless oil. ¹H NMR (500 MHz, CDCl₃) Isomer A: δ 7.45-7.32 (m, 10 H), 7.09 (d, J = 9 Hz, 2 H), 6.92-6.87 (m, 4 H), 5.96 (s, 2 H), 5.56 (s, 1 H), 5.04 (s, 2 H), 5.01 (s, 2 H), 3.40 (s, 3 H), 3.39-3.36 (m, 1 H), 2.72-2.58 (m, 2 H), 2.56-2.53 (m, 2 H), 1.96-1.88 (m, 2 H), 1.01 (t, J = 8 Hz, 9 H), 0.97 (t, J = 8 Hz, 18 H), 0.64 (q, J = 8 Hz, 6 H), 0.56 (q, J = 8 Hz, 12 H). Isomer B: δ 7.45-7.32 (m, 10 H), 7.09 (d, J = 9 Hz, 2 H), 6.92-6.87 (m, 4 H), 5.96 (s, 2 H), 5.56 (s, 1 H), 5.04 (s, 2 H), 5.00 (s, 2 H), 3.40 (s, 3 H), 3.39-3.36 (m, 1 H), 2.72-2.58 (m, 2 H), 2.56-2.53 (m, 2 H), 1.96-1.88 (m, 2 H), 1.01 (t, J = 8 Hz, 9 H), 0.97 (t, J = 8 Hz, 18 H), 0.64 (q, J = 8 Hz, 6 H), 0.56 (q, J = 8 Hz, 12 H); ¹³C NMR (125 MHz) δ 157.9, 157.2, 156.3, 155.6, 137.4, 137.3, 134.4, 134.4, 133.0, 133.0, 129.6, 128.8, 128.4, 128.1, 127.8, 127.8, 115.1, 107.4, 107.3, 82.5, 82.1, 78.8, 70.4, 70.3, 57.1, 35.7, 30.7, 30.5, 29.9, 23.7, 23.6, 7.1, 6.9, 6.7, 6.0; IR (neat) 3065, 3032, 2954, 2929, 2875, 1608, 1540, 1508, 1457, 1239, 1037; HRMS (ESI) m/z 979.5185 [C₅₈H₈₀O₆Si₃ (M+Na) requires 979.5155].

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APPENDIX A:

$^1$H and $^{13}$C-NMR SPECTRA
MeO

3.6e

Me

Ph

N

Phenyl

3.6e

N

Phenyl
Qgd

Me

Ph

Cl

3.6f
Ph$_3$N

Roc

MeO

Boc

3.6j

1H NMR spectrum
Ph\[3.6l\]

\[\text{Me}_2N\]

\[\text{MeO}\]
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