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Redox and Lewis Acid Relay Catalysis: A Titanocene/Zinc Catalytic Platform in the Development of Multicomponent Coupling Reactions

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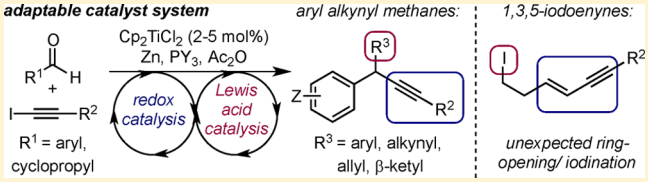
Supporting Information

ABSTRACT: A titanocene-catalyzed multicomponent coupling is described herein. Using catalytic titanocene, phosphine, and zinc dust, zinc acetylides 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 acetylides, allyl silanes, electron-rich aromatics, silyl enol ethers, and silyl ketene acetals. Additionally, employing cyclopropane carboxaldehydes led to ring-opened products resulting from iodine incorporation. Taken together, these results form the basis for a new mode of three-component coupling reactions, which allows for rapid access to value added products in a single synthetic operation.



INTRODUCTION

The all-carbon tertiary center is a ubiquitous motif found throughout pharmaceutically and biologically important compounds (Figure 1).[1] While a number of stepwise methods exist for the synthesis of tertiary carbon centers, a catalytic, three-component assembly of all-carbon tertiary centers remains a formidable challenge to the synthetic chemist.[2] Surprisingly, there are few reported protocols for the unsymmetrical, geminal substitution of two distinct coupling partners to a 2-carbon acceptor functionality.[3] This type of synthetic assembly is generally limited to Friedel–Crafts type bisalkylations catalyzed by Lewis and Brønsted acids, which typically only provide achiral tertiary centers.[4] Van Vranken, Wang, and others have recently reported an elegant approach to this challenge in tertiary carbon construction by employing either a copper- or palladium-catalyzed carbene formation followed by *in situ* sequential cross-coupling events.[5] A key migratory insertion of the metal-stabilized carbene efficiently incorporates the third alkyl substituent. While undoubtedly a *tour de force* in transition-metal-catalyzed cross-couplings, the light and heat sensitivity of diazo compounds[6] and at times indiscriminate reactivity of metal-stabilized carbenes[7] are limiting factors.

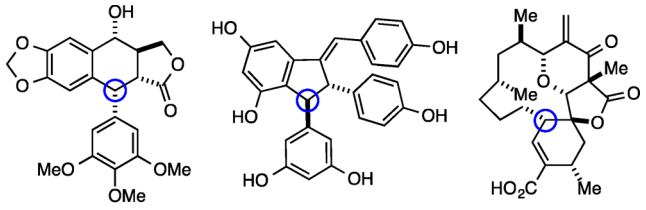


Figure 1. Representative biologically active natural products.

In an effort to streamline tertiary carbon construction, we sought to develop a three-component coupling of readily available feedstock materials under exceptionally mild conditions that would enable the assembly of architecturally diverse frameworks. Speculating that aromatic aldehydes could serve as the acceptor of two distinct nucleophilic components in a dielectrophilic fashion,[8] we focused on the identification of a mixed metal catalyst system to perform multiple mechanistically distinct synthetic transformations in a one-pot fashion. Specifically, the addition of an acetylide anion to an electron deficient aldehyde results in an activated propargylic alkoxide intermediate that under Lewis acidic conditions would undergo an S_N2-like displacement in the presence of a second carbon nucleophile.[9] To achieve this design, we required a catalyst system that would facilitate the metalation and subsequent carbonyl addition to aldehyde **4** via the C–X activation of alkynyl iodide **5**, and then mediate the C–O activation of the resulting alkoxide to form a second C–C bond (Figure 2). The incorporation of a third component **6** ultimately provides the desired coupling adduct **8** bearing the targeted tertiary carbon assemblage.

The well-established redox and Lewis acidic properties of titanocene and zinc complexes[10] led us to initially evaluate these inexpensive metals as catalysts to facilitate these mechanistically disparate reaction pathways. Titanocene(III) chloride (Nugent's reagent) has garnered substantial interest in

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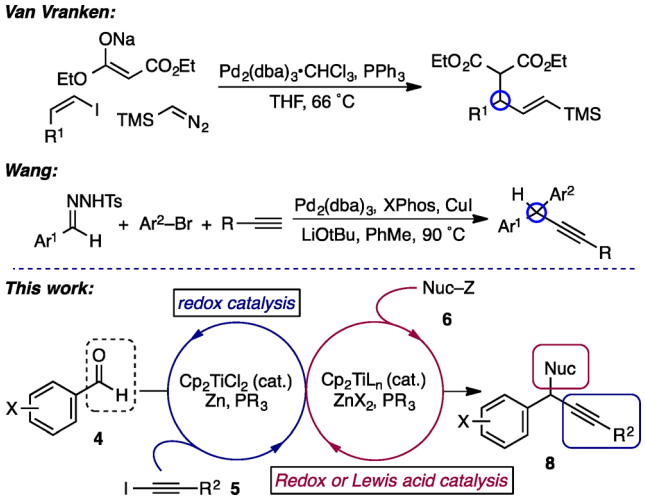
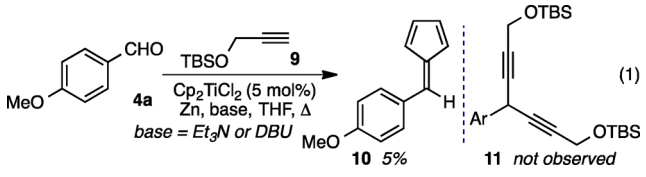


Figure 2. Recent approaches toward 3° carbon construction.

the synthetic community as a single electron transfer (SET) catalyst in recent years. Its ability to mildly and chemoselectively affect SET processes has allowed for a wide range of transformations, including pinacol couplings,[11] Reformatsky reactions,[12] Barbier reactions,[12a,13] and reductive epoxide openings.[14] Furthermore, the ability of titanocene to affect multiple carbon–carbon bond formations has been elegantly demonstrated by Gansäuer, Oltra, and Cuerva in radical-cascade reactions, which have been applied to several natural products and interesting chemotypes.[15] In our own lab, we investigated the catalytic Barbier reaction catalyzed by titanocene and phosphine. We discovered that the combination of Cp_2TiCl_2 and phosphine, in the presence of a reducing metal, had a synergistic effect on the generation of organometallic reagents from allylic and benzylic halides.[13a,b,d] In light of our previous work and those of others, we hypothesized that a combination of Cp_2TiCl_2, phosphine, and zinc dust would result in the mild generation of a metal-acetylide. Upon addition to an electrophilic aldehyde, the combination of Ti^{IV} and *in situ* generated Zn^{II} would initiate activation of the propargylic alkoxide intermediate for attack by either a second acetylide equivalent,[16] arene,[17] allyl silane,[18] or silyl enol ether[19] to form the second C–C bond. Herein we describe our efforts and observations toward the development of a convergent and flexible multicomponent coupling method for the assembly of these versatile molecular frameworks.

RESULTS AND DISCUSSION

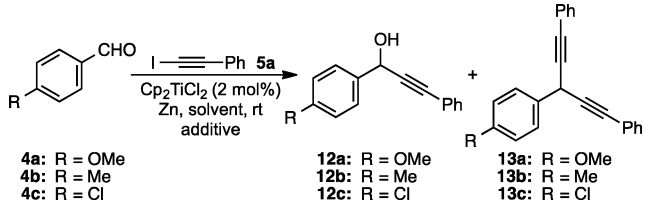
We began our study by examining a functionalized alkyne as both the first and second nucleophiles in this three-component coupling reaction. Recognizing that the initial challenge was going to be the catalytic metalation and addition of an acetylide to an aldehyde,[20] we focused on the coupling of two equivalents of alkyne **9** to aldehyde **4a** (eq 1). While Periasamy



and co-workers demonstrated that titanium(IV) acetylides could be generated from terminal acetylenes upon treatment with $TiCl_4$ and Et_3N,[21] these conditions yielded only recovered starting materials. Expanding on our previous work in the area of Cp_2TiCl_2-catalyzed organozinc formations, we next explored the metalation of **9** and its subsequent addition of aldehyde **4a** using a combination of Cp_2TiCl_2 (5 mol %), Zn dust, and a non-nucleophilic amine base.[13a] Unfortunately, neither diyne **11** or the intermediate propargylic alcohol (not shown) were observed, but rather migratory insertion of a Cp ligand from Cp_2TiCl_2 gave fulvene **10** in ≤5% yield and recovered **4a**.[22]

Given the inefficient metalation of terminal alkyne **9**, we next attempted acetylide formation from halo-acetylenes utilizing a metal–halogen exchange process. While Srihari and co-workers showed that the metalation of iodoacetylenes could be effected with zinc dust in THF, refluxing conditions were required, which limited the iodoalkyne and aldehyde functional group compatibility.[23] To establish a milder and general protocol, we examined the use of Cp_2TiCl_2 as a Barbier-type redox metalation catalyst under milder conditions. Gratifyingly, the addition of iodoacetylene **5a** to aldehyde **4a** in the presence of Cp_2TiCl_2 (2 mol %) and Zn dust in THF afforded propargyl alcohol **12a** in 50% yield along with only trace amounts of the desired 1,4-diyne **13a** (Table 1, entry 1). Speculating that the

Table 1. Titanocene-Catalyzed Acetylide Addition[a]



entry	4	additive	solvent	yield of **12** (%)	yield of **13** (%)
1	**4a**		THF	50	≤5
2[b]	**4a**	TMSCl	THF	69	≤5
3[b]	**4a**	TMSCl	CH_2Cl_2	55	12
4[c]	**4a**	Ac_2O	CH_2Cl_2	≤5	65
5	**4b**		CH_2Cl_2	10	≤5
6[d]	**4b**		CH_2Cl_2/THF	55	≤5
7[c]	**4b**	Ac_2O	CH_2Cl_2	≤5	5
8	**4c**		CH_2Cl_2	10	≤5
9	**4c**	Ac_2O	CH_2Cl_2	≤5	11
10	**4c**	P^tBu_3	CH_2Cl_2	66	≤5
11	**4c**	Ac_2O $P(4\text{-}MeOC_6H_4)_3$	CH_2Cl_2	0	33

[a]Reaction conditions: **4** (0.50 mmol), **5a** (0.75 mmol), Cp_2TiCl_2 (5 mol %), and Zn (1.1 mmol) at 0.25 M for 2 h at rt. [b]TMSCl (0.75 mmol) was added to the reaction. [c]Ac_2O (0.75 mmol) was added to the reaction. [d]CH_2Cl_2/THF was used in a 1:1 ratio.

reaction conditions were not sufficiently Lewis acidic to enable C–O bond activation of the intermediate propargylic alkoxide, the *in situ* functionalization to a better leaving group should alleviate this issue. Thus, the addition of TMSCl, which is known to promote catalyst turnover in Cp_2TiCl_2-catalyzed reactions,[11a–d,f,g,12,13,13c–f,14] gave **12a** in 69% yield but with no diyne formation (entry 2). However, utilizing CH_2Cl_2 in place of THF with the addition of TMSCl gave us our first glimpse of 1,4-diyne **13a** albeit in 12% yield along with alcohol **12a** (entry 3). Employing Ac_2O in place of TMSCl significantly improved the yield of **13a** to 65% while enabling ≥95% conversion of the intermediate propargylic alcohol **12a** (entry 4). We quickly

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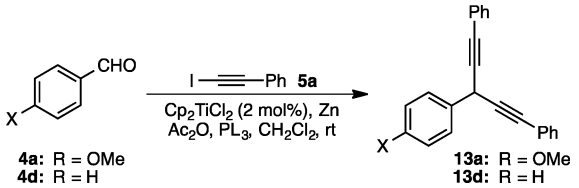
learned that the electronic nature of the aldehyde played a critical role in product distribution. For example, treatment of 4-methylbenzaldehyde (**4b**) in CH_2Cl_2 or a mixed solvent system of CH_2Cl_2/THF (1:1) provided only alcohol **12b** to 10 and 55%, respectively (entries 5 and 6). Again, the addition of Ac_2O led to formation of 1,4-diyne **13b** albeit in a mere 5% yield (entry 7).

A close inspection of the conversion of **4a** to **13a** from the experiment in entry 4 revealed a significant quantity of unreacted iodo alkyne **5a**, leading us to conclude that acetylide formation was a problematic step in this multicomponent coupling. Employing aldehyde **4c** bearing an electron withdrawing group failed to provide significant quantities of alcohol **12c** or diyne **13c**, even in the presence of Ac_2O (entries 8 and 9). Previously, we had shown that the addition of phosphines had a marked impact on the titanocene-catalyzed metalation of allylic halides.[13a] On the basis of this work, we initially examined what effect phosphine additives would have on the formation of 1,4-diynes. Attempting the alkynylation of aldehyde **4c** with **5a** in CH_2Cl_2 with the addition of P^tBu_3 (40 mol %) improved the yield of **12c** to 66% yield (entry 10). Interestingly, the combination of Ac_2O and the electron-rich triaryl phosphine P(4-MeO-C_6H_4)$_3$ enabled full conversion of the intermediate alcohol to 1,4-diyne **13c** in 33% yield (entry 11). While the role of phosphine in the metalation of **5a** and subsequent addition to aldehyde **4c** is unclear at present, it is conceivable that ligation to either zinc or low-valent titanocene may attenuate the reactivity of either metal en route to product formation.[24] Further attempts at optimization by varying the time, temperature, and solvent failed to improve the yield of **13c**. However, with these results in hand, we turned our attention toward examining the phosphine in this three-component coupling.

While halogenated solvents and the addition of Ac_2O aided in conversion of the intermediate propargylic alcohol to 1,4-diyne, these conditions appeared to inhibit metalation of the iodoalkyne, except when in the presence of phosphine. Therefore, we next surveyed a series of phosphorus reagents in an effort to optimize conversion of both the starting aldehyde and intermediate propargylic alcohol to the desired 1,4-diyne (Table 2). In general, the reaction appeared sensitive to both the electronic and steric properties of the added phosphines. Treatment of aldehyde **4a** with the more electron-rich triaryl phosphine, P(4-MeO-C_6H_4)$_3$, increased the yield of 1,4-diyne **13a** to 83% (entry 1). Should the reaction proceed through a propargylic cation, the *p*-MeO substituent of **4a** would likely assist in this conversion that may mask the generality of these reaction conditions. Thus, we chose to evaluate benzaldehyde (**4d**) and discovered that, although in the absence of phosphine, 1,4-diyne **13d** was formed, the addition of P(4-MeO-C_6H_4)$_3$ increased the yield from 20% to 66% (entries 2 and 3). Trialkyl phosphines and phosphites effectively inhibited 1,4-diyne formation, whereas P(2-furyl)$_3$ gave **13d** in 26% yield (entries 4−7). The addition of P(2,4,6-MeO-C_6H_4)$_3$ improved the yield to 34% but remained inferior to P(4-MeO-C_6H_4)$_3$ (entries 3 and 8). While using less P(4-MeO-C_6H_4)$_3$ led to a similar decrease in yield, employing 40 mol % provided **13d** in 80% yield (entries 9 and 10). The addition of more than 40 mol % phosphine inhibited formation of **14d**, leading to decreased yields.

To gain further insight into the mechanism of this three-component coupling, and to obtain a better understanding of its strengths and limitations, a few key control experiments are

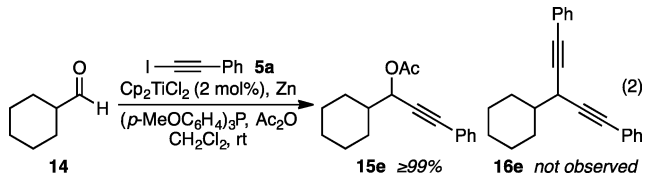
Table 2. Role of Phosphine in 1,4-Diyne Generation[a]



entry	4	PL_3 (mol %)	yield of **13** (%)
1	**4a**	P(4-MeO-C_6H_4)$_3$ (20)	83
2	**4d**	–	20
3	**4d**	P(4-MeO-C_6H_4)$_3$ (20)	66
4	**4d**	P^nBu_3 (20)	0
5	**4d**	$P(PhO)_3$ (20)	<5
6	**4d**	$P(MeO)_3$ (20)	<5
7	**4d**	P(2-furyl)$_3$ (20)	26
8	**4d**	P(2,4,6-MeO-C_6H_4)$_3$ (20)	34
9	**4d**	P(4-MeO-C_6H_4)$_3$ (10)	58
10	**4d**	P(4-MeO-C_6H_4)$_3$ (40)	80

[a]Reaction conditions: **4** (0.50 mmol), **5a** (0.75 mmol), Cp_2TiCl_2 (5 mol %), Zn (1.1 mmol), and Ac_2O (0.75 mmol) at 0.25 M for 2 h at rt.

worth noting. The presence of both Cp_2TiCl_2 and Zn dust were crucial to 1,4-diyne formation, as the absence of either component in the coupling of aldehyde **4a** and phenyl iodoacetylene **5a** led to quantitative recovery of both of the starting materials. While earlier work has shown the compatibility of Mn powder and Mg turnings as stoichiometric reductants in the presence of Cp_2TiCl_2,[11−14] substituting Zn dust for either of these metals failed to provide the corresponding 1,4-diyne. Additionally, the aromatic nature of aldehyde itself proved important for 1,4-diyne formation. When cyclohexane carboxaldehyde (**14**) was subjected to our optimized conditions, acetate **15** was obtained in quantitative yield without subsequent conversion to 1,4-diyne **16** (eq 2). Additionally, the initial acetylide addition proved chemoselective for aldehydes, as both acetophenone and benzophenone were recovered unreacted.



Although our optimized conditions depicted in Table 2 proved effective for the assembly of symmetrical 1,4-diynes, employing two different iodoalkynes yielded a nearly statistical mixture of symmetrical and unsymmetrical adducts. For example, the addition of iodoalkynes **5a** and **5b** to aldehyde **4a** led to 1,4-diynes **13a**, **13e**, and **13g** in a 3.3:1.4:1.0 ratio and 57% overall yield (eq 3). Speculating that a sequential addition of the iodoacetylene components would minimize formation of the symmetrical adducts, and in an effort to slow down the rate of the second C−C bond formation, we examined the addition of **5a** to electron deficient aldehyde **4c** followed by addition of the slower metalating iodo alkyne **5c** (eq 4). Interestingly, the major product from this experiment was determined to be the symmetrical 1,5-diyne **17a**. The formation of this 1,5-diyne is likely due to the propensity of propargylic acetates to undergo metalation by Cp_2TiCl_2 in the presence of Zn, which in the

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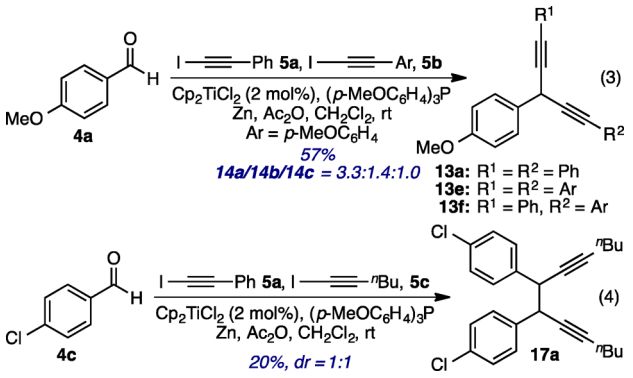
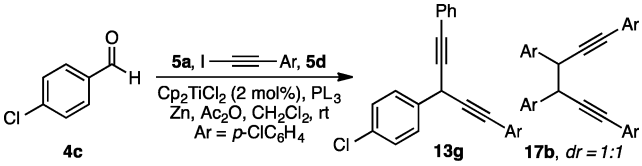


absence of a second iodoalkyne or suitable electrophile would then couple to give the observed major product.[25]

Ding and co-workers previously reported this homodimerization of activated propargylic acetates in the presence of Cp_2TiCl_2.[26] Whether these 1,5-diynes result from a free-radical combination or polar substitution mechanism, we hypothesized that minimizing the effective concentration of the intermediate propargylic acetate would be key to unsymmetrical 1,4-diyne formation. Thus, we examined the syringe pump addition of acetic anhydride upon alkoxide formation while in the presence of the second acetylene equivalent (Table 3). Treatment of

Table 3. Optimization of Unsymmetrical 1,4-Diynes[a]



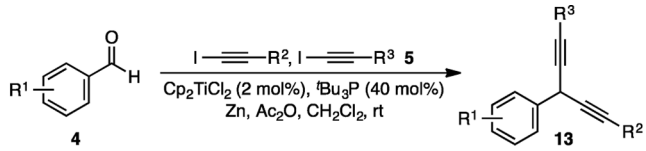
entry	PL_3	Ac_2O addition (h)	yield of **13g**[b] (%)	yield of **17b**[b] (%)
1	$P(4\text{-MeO-}C_6H_4)_3$	0	8	11
2	P^tBu_3	0	17	10
3	P^tBu_3	5	35	16
4	P^tBu_3	11	60	7

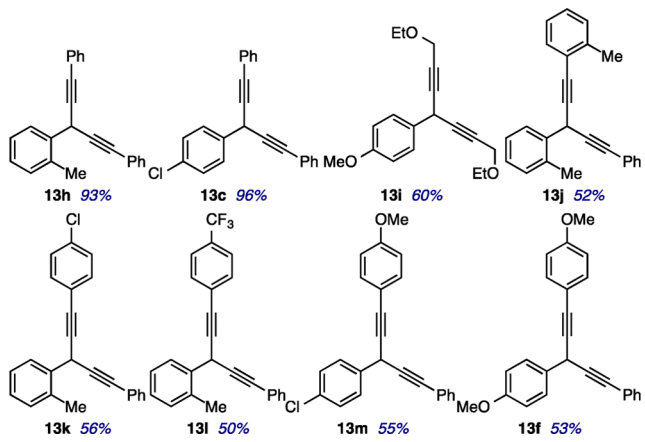
[a]Reaction conditions: **4c** (0.50 mmol), **5a** (0.75 mmol), Cp_2TiCl_2 (5 mol %), Zn (1.1 mmol), and Ac_2O (0.75 mmol) at 0.25 M for 2 h at rt. [b]Yields determined by 500 MHz ^1H NMR.

aldehyde **4c** with iodide **5a** with Cp_2TiCl_2 (2 mol %), (4-MeO-C_6H_4)$_3$P (40 mol %), and Zn dust led to the expected propargylic alkoxide, as observed by TLC analysis. Then iodide **5d** and Ac_2O were added sequentially to give 1,5-diyne **17b** as the major product (entry 1). Switching to the more Lewis basic $^tBu_3P$ led to an increase in 1,4-diyne formation, and the addition of Ac_2O via a syringe pump over 5 h further improved the yield of **13g** to 17% (entries 2 and 3). The ratio of **13g** to **17b** could be further improved by the addition of Ac_2O over 11 h, whereas longer addition times led to intractable mixtures of unidentified side products.

With a set of optimized conditions in hand, we turned our focus toward evaluating the scope of 1,4-diyne construction (Table 4). In general, modest yields of the desired adducts were obtained with various aldehydes and iodo alkynes. Aryl aldehydes bearing both electron donating and electron withdrawing substituents performed admirably to provide the corresponding symmetrical 1,4-diynes **13c**, **13h**, and **13i**. Also, alkyl substituted acetylenes proved to be viable coupling partners, as illustrated by the formation of diyne **13i**. The

Table 4. Synthesis of 1,4-Diynes[a]

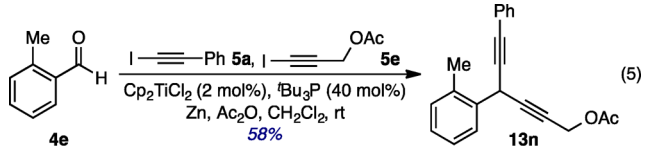




[a]Reaction conditions: **4** (0.21 mmol), **13**[1] (0.25 mmol), **13**[2] (0.25 mmol), Cp_2TiCl_2 (2 mol %), Zn (0.50 mmol), $^tBu_3P$ (0.084 mmol), and Ac_2O (0.50 mmol) at 0.10 M.

iodoalkyne component proved equally tolerable to electronic differences, as illustrated by the formation of diynes **13j–m** and **13f**. Importantly, the aldehyde component showed good steric and electronic tolerance. Substitution at the *ortho* position did not hinder the carbonyl addition or benzylic substitution events (**13j–l**).

A distinct advantage to transition-metal-catalyzed couplings is the exceptional chemoselectivity that these catalysts exhibit for specific functional groups.[27] Similarly, our titanocene-catalyzed three-component coupling proved chemoselective for the aryl-propargylic acetate in the second C–C bond formation. To illustrate, the coupling of aldehyde **4e** with iodide **5a** and the iodoalkyne **5e** gave unsymmetrical 1,4-diyne **13n** in 58% yield without formation of adducts resulting from displacement of the primary propargylic acetate (eq 5).



A major driving force behind the design concept depicted in Figure 2 is the mechanistic flexibility of the Ti^{IV}/Zn catalyst system to permit the incorporation of components bearing different modes of reactivity. To further probe the mechanistic flexibility of this catalyst system, we chose to examine the addition of nucleophilic silicon reagents (Table 5).[18] Our hypothesis was that the addition of either an allyl silane or silyl enol ether would prompt the catalyst system to proceed down a Lewis-acid-mediated C–C bond formation for incorporation of the third component. Thus, treatment of aldehydes **4** with iodo alkyne **5** and various allyl silanes **18** (Z = CHR) provided the corresponding 1,5-enynes **19a–f** in good to excellent yields. Aromatic, silyl, and alkynyl iodoalkynes were effectively

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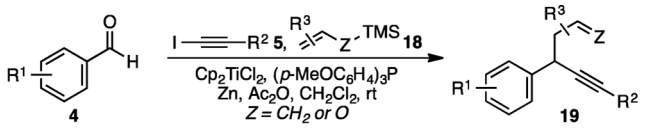
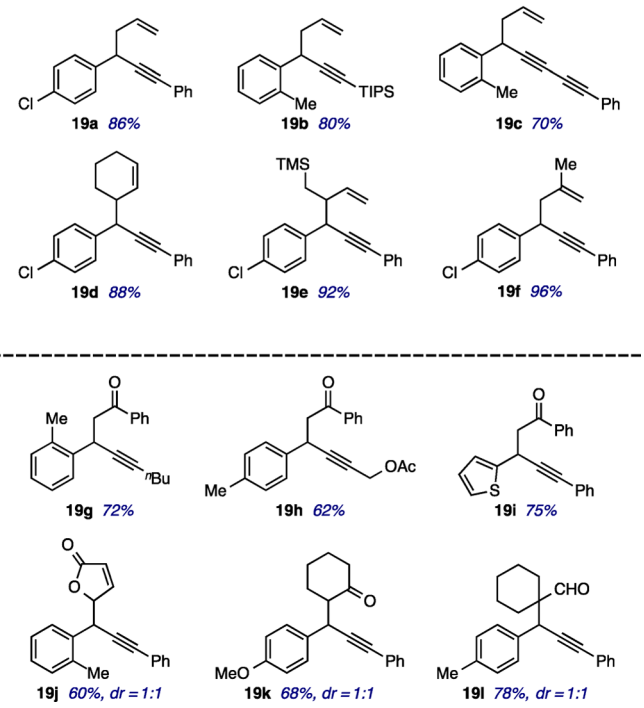
Table 5. 1,5-Enynes and β-Alkynyl Carbonyls[a]



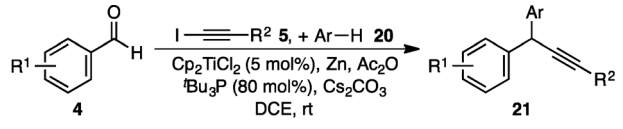


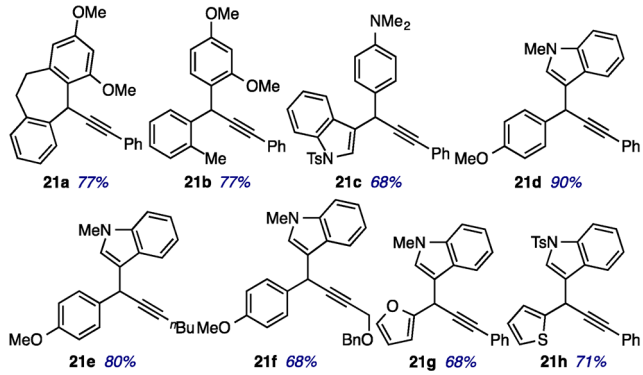
[a]Reaction conditions: **6** (0.40 mmol), **13** (0.80 mmol), **17** (0.80 mmol), Cp_2TiCl_2 (2 mol %), Zn (0.80 mmol), $(4\text{-}MeOC_6H_4)_3P$ (0.16 mmol), and Ac_2O (0.48 mmol) at 0.10 M.

integrated in the assembly of **19a** and **19b**, as well as substituted C1−C3 substituted allyl silanes (**19d−f**). A variety of silyl enol ether derivatives proved competent nucleophilic components under the reaction conditions, including those derived from acetophenone (**19g−i**), siloxy furan (**19j**), cyclohexanone (**19k**), and cyclohexane carboxaldehyde (**19l**) derivatives.

The reactivity observed in the incorporation of allyl and carbonyl components was also applicable to electron-rich arenes as the second nucleophile to provide diarylethynyl methanes (Table 6).[17] Anticipating a Friedel−Crafts-like arylation of the intermediate propargylic acetate, we supplemented our optimized conditions with Cs_2CO_3 and found that P^tBu_3 (80 mol %) 1,2-dichloroethane (DCE) provided better yields of the diarylethynyl methanes. Initially, we examined the acetylide addition to an aryl aldehyde bearing a pendant arene nucleophile and discovered that the intramolecular arylation proved quite facile to give the tricyclic adduct **21a** in 77% yield. The intermolecular reaction likewise provided a good yield of **21b**, as did the utilization of *N*,*N*-dimethyl aniline in the formation of **21c**. Additionally, heteroaromatics, in particular *N*-protected indole, were excellent nucleophiles in the formation of **21d−h**. Heteroaromatic aldehydes also proved effective substrates, producing heteroaryl methanes **21c**, **21g**, and **23h**. In contrast to the optimized procedures for the formation of unsymmetrical 1,4-diynes, 1,5-enynes, and β-alkynyl carbonyls, the electron-rich arene was added simultaneously with the iodoalkyne and aldehyde, without formation of the undesired symmetrical 1,4-diynes or 1,5-diyne dimers previously observed.

Table 6. Synthesis of Diarylethynyl Methanes[a]

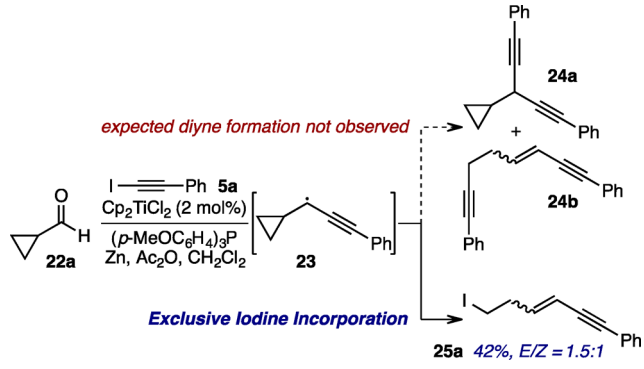




[a]Reaction conditions: **6** (0.21 mmol), **13** (0.63 mmol), **18** (0.42 mmol), Cp_2TiCl_2 (5 mol %), Zn (0.63 mmol), $^tBu_3P$ (0.17 mmol), and Ac_2O (0.50 mmol) at 0.10 M.

The formation of 1,5-diynes in our optimization of unsymmetrical 1,4-diyne construction was certainly intriguing, and prompted us to further probe the potential synthetic utility of intermediates arising from the SET reduction of propargylic acetates. Given the propensity of cyclopropylcarbinyl radicals to undergo ring expansion,[28] we speculated that addition of the acetylide derived from **5a** to cyclopropyl carboxaldehyde (**22**) in the presence of Cp_2TiCl_2, Zn dust, and $P(4\text{-}MeOC_6H_4)_3$ would provide either 1,4-diyne **24a** following direct acetate substitution or 1,3-enyne **24b** upon ring expansion (Scheme 1).

Scheme 1. Iodine Incorporation in Cyclopropane Ring Openings



Surprisingly, neither **24a** nor **24b** was obtained, but rather iodine reincorporation to give iodo enyne **25** as the sole product in a 1.5:1 ratio of *E*/*Z* isomers was observed. This rather intriguing conversion amounts to the formal insertion of a homoallyl fragment into the C−I bond of **5a**.

The synthetic utility of 1,3-enynes in transition-metal-catalyzed processes is well established,[29] and this architectural motif is quite prevalent in many biologically active com-

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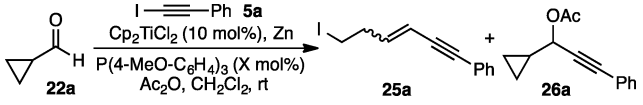
pounds.[30] Therefore, we sought to identify the optimal set of reaction conditions for the formation of **25a** (Table 7). While

Table 7. Effect of Phosphine on Iodoenyne Formation[a]



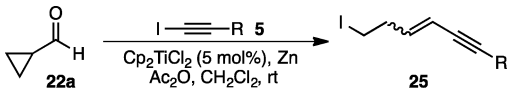
entry	mol % of phosphine	yield of **25a**[b] (%)	yield of **26a**[b] (%)
1[c]	100	27	63
2[c]	60	57	11
3	40	52	0
4	0	69	0
5[d]	0	71	0

[a]Reaction conditions: **28a** (0.50 mmol), **13b** (0.75 mmol), Cp_2TiCl_2 (10 mol %), Zn (1.1 mmol), and Ac_2O (0.75 mmol) at 0.25 M for 2 h at rt. [b]Product obtained as a 1.4:1 mixture of *E*/*Z* isomers. [c]Yields determined by 500 MHz ^{1}H NMR. [d]5 mol % Cp_2TiCl_2 employed.

the yield of **25a** showed a modest improvement with 5 mol % Cp_2TiCl_2, a more dramatic effect was observed with the amount of P(4-MeOC_6H_4)$_3$ employed. In contrast to our three-component couplings described *vide supra*, the yield of **25a** was *inversely* proportional to the amount of phosphine added. The addition of 100 mol % P(4-MeOC_6H_4)$_3$ produced a mixture of enyne **25a** and propargylic acetate **26a** in 27 and 63% yield, respectively (entry 1). Decreasing the amount of phosphine to 60 mol % gave a 57% yield of **25a** and 11% of recovered **26a** (entry 2). The acetate underwent complete conversion with 40 mol % phosphine, and the yield of **25a** was improved to 69% by omitting P(4-MeOC_6H_4)$_3$ altogether (entries 3 and 4).

The formation of enyne **25** showed comparable tolerance to structural variability on the iodoalkyne component in the ring-opening iodination reaction, as was observed in the synthesis of unsymmetrical 1,4-diynes (Table 8). Aryl iodoalkynes provided

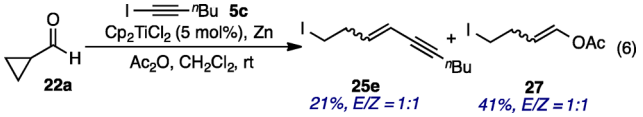
Table 8. Functional Diversity of Iodoalkynes[a]



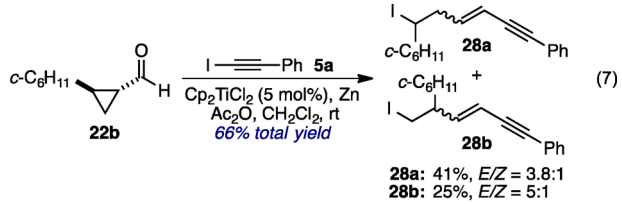
entry	R	product	yield[b] (%)	*E*/*Z*[c]
1	2-Me-C_6H_4	**25b**	81	1:1
2	4-Cl-C_6H_4	**25c**	43	1.3:1
3	4-CF_3-C_6H_4	**25d**	69	1.5:1

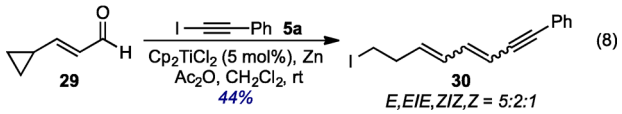
[a]Reaction conditions: **22a** (0.50 mmol), **5** (0.75 mmol), Cp_2TiCl_2 (5 mol %), Zn (1.1 mmol), and Ac_2O (0.75 mmol) at 0.25 M for 2 h at rt. [b]Isolated yields. [c]Ratios determined by 500 MHz ^{1}H NMR.

iodoenynes **25** in moderate to good yields with 2-methyl phenyl substituted alkyne giving the corresponding enyne in 81% yield (entries 2−4). In contrast, aliphatic iodoalkyne **5c** furnished enyne **25e** in 21% yield along with enol acetate **27** (eq 6). It should be noted that, for each combination of aldehyde and iodoalkyne we have examined thus far, only a modest preference for the *E*-alkene isomer was observed.



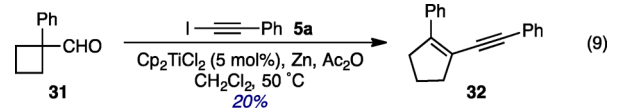
The addition to substituted cyclopropyl carboxaldehydes presents regioselectivity issues in the iodine incorporation step. Treatment of cyclohexane substituted cyclopropyl carboxaldehyde **22b** and iodoalkyne **5a** to the optimized reaction conditions led to *E*/*Z* mixtures of both regioisomers **28a** and **28b** in 66% total yield (eq 7). As we saw previously, there was a





modest preference in each case for the *E*-alkene and a 1.7:1 ratio of regioisomers favoring incorporation of iodine at the more substituted cyclopropyl carbon. This result is consistent with a radical−radical annihilation wherein cyclopropane ring opening occurs to yield the more stable carbon-centered radical.[28] However, a carbocation intermediate that is quenched by iodide, a β-carbon elimination pathway, or a reductive coupling from an organotitanocene complex cannot be ruled out at this stage.[31] Furthermore, the presence of the alkene in α,β-unsaturated aldehyde **29** led to the expected, fully conjugated dienyne **30** in 44% yield and a 5:2:1 mixture of olefin isomers (eq 7). The formation of enynes **25** and **28** and dienyne **30** supports a mechanism involving a reduction of an intermediate propargylic acetate or alkoxide followed by strain-driven ring expansion and subsequent iodine incorporation either through a radical, carbocation, or titanocene-bound intermediate.[32] This rather unusual reactivity allows for the rapid assembly of an extended carbon chain bearing multiple functional handles, including a primary iodide, from readily accessible starting materials.

Seeking to expand on this ring opening approach toward 1,3-enynes, we next focused our attention on the addition of the metal acetylide derived from **5a** to cyclobutyl carboxaldehyde **31** (eq 9). While the reactivity of **31** was certainly less than



when compared to the cyclopropyl analogues, a ring expansion followed by β-elimination provided 1,2-disubstituted cyclopentene **32**, albeit in only 20% yield (eq 9). Unfortunately, attempts to improve the yield of **32** proved problematic, and an intractable mixture of unidentifiable side product was the most common result. However, this initial proof of concept demonstrates the various mechanistic pathways that the intermediate propargylic acetate may proceed down in the presence of low-valent titanocene.

The varied reactivity of each starting component and reagents, different oxidation states, and possible ligand complexes lead to an unusually high number of potential mechanistic permutations en route to each product illustrated herein. However, on the basis of our findings, and those presented in the literature, our working mechanistic hypothesis

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involves initial metal acetylide generation that is catalyzed by $Cp_2Ti^{III}Cl$ arising from the *in situ* reduction of $Cp_2Ti^{IV}Cl_2$ and Zn dust. The resulting acetylide undergoes addition to the starting aldehyde, which may be enhanced by phosphine ligation, to provide an initial alkoxide, which is acylated by Ac_2O. At this stage, either Lewis-acid-mediated ionization or SET reduction of the activated acetate precedes the second C−C bond formation step, the nature of which is highly dependent on the nucleophile employed.

CONCLUSION

In summary, this study serves to highlight the utility of titanocene catalysts to enable production of various structurally interesting carbon-based subunits from relatively simple starting materials. The ability of titanocene to mildly and effectively generate a range of organometallic intermediates can serve as an initial starting point for the development of a diverse array of sequential cross-coupling events. The ability of a mixed metal system comprised of Cp_2TiCl_2 and Zn dust to behave in a redox or Lewis acidic fashion provides the adaptable reactivity necessary to assemble components of varying structure to access diverse libraries important to pharmaceutical drug design. This catalyst system effectively streamlines molecular assembly, and continued research in this area of reaction development will likely continue to unveil new applications for many years to come.

EXPERIMENTAL SECTION

Solvents and reagents were ACS reagent grade and used without further purification unless noted below. Dimethylformamide (DMF), tetrahydrofuran (THF), dichloromethane (CH_2Cl_2), and diethyl ether (Et_2O) were passed through a column of molecular sieves and stored under argon. 1,2-Dichloroethane (DCE) was distilled, stored over 4 Å molecular sieves, and degassed prior to use. Acetic anhydride (Ac_2O) was distilled over CaH, and zinc dust was washed sequentially with 1.0 M aq. HCl, water, and Et_2O prior to use. All reactions were carried out in flame-dried glassware under an argon atmosphere unless otherwise specified. Aldehydes **4a**−**e** and **22a** were purchased and used without further purification. Alkynyl iodides **5a**−**e**,[33] alkyne **9**,[34] and aldehydes **22b**,[35] **29**,[36] and **31**[37] were prepared according to literature procedures.

^{1}H Nuclear magnetic resonance (NMR) spectra were obtained at either 300 or 500 MHz, and $^{13}C\{^1H\}$ NMR spectra, at 100, 125, or 150 MHz. Chemical shifts are reported in parts per million (ppm, δ), and referenced to residual solvent 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 an FT-IR instrument 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 TOF mass spectrometer. Analytical thin layer chromatography (TLC) was performed using 250 μm 60 F_{254} silica gel plates, visualized with UV light and stained with a *p*-anisaldehyde solution. Flash column chromatography was performed according to Still's procedure[35b] using 40−63 μm 60 Å silica gel.

Representative Acetylide Addition Procedure. A two-dram screw cap vial, equipped with a magnetic stir bar, was charged with Cp_2TiCl_2 (2.5 mg, 0.01 mmol) and zinc dust (72 mg, 1.1 mmol) and then purged with argon for 5 min. Dry, degassed solvent (0.50 mL) was added and the suspension stirred at room temperature until a blue/green color persisted. A solution of aldehyde **4** (0.50 mmol) and iodophenylacetylene **13a** (171 mg, 0.75 mmol) in the indicated solvent (1.5 mL) was then added and the reaction stirred at room temperature until full consumption of aldehyde **6** was observed by TLC (~1 h). The reaction was then diluted with CH_2Cl_2 (2 mL), filtered through a short plug of silica gel eluting with CH_2Cl_2 (50 mL), and the filtrate concentrated under reduced pressure. The crude mixture was purified directly by flash chromatography eluting with the indicated solvent mixture to give the corresponding propargyl alcohol **12**.

1-(4-Methoxyphenyl)-3-phenylprop-2-yn-1-ol (***12a***). Purification by flash chromatography eluting with hexanes/EtOAc (2:1) provided 82 mg (69%) of **12a** as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (d, J = 8.5 Hz, 2 H), 7.46−7.44 (m, 2 H), 7.30−7.29 (m, 3 H), 6.91 (d, J = 8.8 Hz, 2 H), 5.62 (s, 1 H), 3.80 (s, 3 H). $^{13}C\{^1H\}$ NMR (125 MHz) δ 133.2, 132.0, 128.8, 128.5, 128.4, 128.4, 122.7, 114.2, 89.1, 86.7, 65.0, 55.6. IR (neat) 3388, 3064, 2999, 2955, 2836, 2250, 1607, 1510, 1491, 1438, 1253, 1171. HRMS (ESI) Calcd for $C_{16}H_{14}O_2Na$, 261.0886; Found, 261.0918.

3-Phenyl-1-(p-tolyl)prop-2-yn-1-ol (***12b***). Purification by flash chromatography eluting with hexanes/EtOAc (3:1) provided 61 mg (55%) of **12b** as a yellow oil. Spectral data (^{1}H NMR and $^{13}C\{^1H\}$ NMR) were consistent with literature values.[38]

1-(4-Chlorophenyl)-3-phenylprop-2-yn-1-ol (***12c***). Purification by flash chromatography eluting with hexanes/EtOAc (3:1) provided 80 mg (66%) of **12c** as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (d, J = 8.3 Hz, 2 H), 7.47−7.46 (m, 2 H), 7.37 (d, J = 8.5 Hz, 2 H), 7.34−7.32 (m, 3 H), 5.67 (s, 1 H). $^{13}C\{^1H\}$ NMR (125 MHz) δ 139.3, 134.5, 132.0, 129.2, 129.2, 128.5, 128.3, 122.4, 88.4, 87.2, 64.6. IR (neat) 3312, 3056, 2926, 2857, 2228, 1599, 1520, 1488, 1408, 1266, 1192, 1092. HRMS (ESI) Calcd for $C_{15}H_{11}ClONa$, 265.0391; Found, 265.0430.

Representative 1,4-Diyne Procedure. 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 CH_2Cl_2 (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 CH_2Cl_2 (0.25 mL) was added slowly, followed by the dropwise addition of a solution of aldehyde **4** (0.37 mmol) and the first alkynyl iodide **5** (0.37 mmol) in CH_2Cl_2 (0.50 mL). The resulting mixture was stirred at 25 °C until TLC indicated full consumption of the starting aldehyde (3−4 h), at which time the second alkynyl iodide **5** (0.55 mmol) was added neat and in one portion via syringe. A solution of Ac_2O (80 μL, 0.84 mmol) in CH_2Cl_2 (0.80 mL) was then added at the indicated temperature over 11 h via a syringe pump. Once the addition of Ac_2O was complete, the resulting crude mixture was diluted with CH_2Cl_2 (2.0 mL) and filtered through a plug of silica gel eluting with 100% Et_2O. The filtrate was concentrated under reduced pressure and purified by flash column chromatography eluting with the indicated solvent system to yield the desired 1,4-diyne **13**.

(3-(4-Methoxyphenyl)penta-1,4-diyne-1,5-diyl)dibenzene (***13a***). 1,4-Diyne **13a** was obtained in 83% yield (0.26 mmol scale, 69 mg) after 2 h at 25 °C, eluting with 1:1 hexanes/CH_2Cl_2, as a clear, yellow oil. Spectral data (^{1}H NMR and $^{13}C\{^1H\}$ NMR) were consistent with literature values.[39]

(3-(p-Tolyl)penta-1,4-diyne-1,5-diyl)dibenzene (***13b***). 1,4-Diyne **13b** was obtained in 5% yield (0.26 mmol scale, 4 mg) after 2 h at 25 °C, eluting with 1:1 hexanes/CH_2Cl_2, as a clear, yellow oil. Spectral data (^{1}H NMR and $^{13}C\{^1H\}$ NMR) were consistent with literature values.[39]

(3-(4-Chlorophenyl)penta-1,4-diyne-1,5-diyl)dibenzene (***13c***). 1,4-Diyne **13c** was obtained in 96% yield (0.37 mmol scale, 120 mg) after 2 h at 25 °C, eluting with 10:1 hexanes/CH_2Cl_2, as a clear yellow oil. ^{1}H NMR (500 MHz) δ 5.17 (s, 1 H), 7.30−7.33 (comp, 6 H), 7.36−7.38 (m, 2 H), 7.46−7.49 (comp, 4 H), 760−7.62 (m, 2 H). $^{13}C\{^1H\}$ (125 MHz) δ 29.8, 83.3, 86.2, 122.9, 128.5, 128.6, 128.9, 129.1, 132.0, 133.6, 136.6. IR (neat) 3081, 3057, 3033, 1598, 1488, 1442, 1404, 1293, 1092, 1016. HRMS (ESI) Calcd for $C_{23}H_{16}Cl$, 327.0935; Found, 327.0948.

Penta-1,4-diyne-1,3,5-triyltribenzene (***13d***). 1,4-Diyne **13d** was obtained in 80% yield (0.26 mmol scale, 60 mg) after 2 h at 25 °C, eluting with 3:1 hexanes/CH_2Cl_2, as a clear, yellow oil. Spectral data

(^{1}H NMR and ^{13}C{^{1}H} NMR) were consistent with literature values.[37]

*4,4′,4″-(Penta-1,4-diyne-1,3,5-triyl)tris(methoxybenzene) (**13e**).* 1,4-Diyne **13e** was obtained in 58% yield (0.37 mmol scale, 57 mg) after 8 h at 50 °C, eluting with 1:1 hexanes/CH_2Cl_2 to 4:1 CH_2Cl_2/hexanes, as a clear, orange oil. ^{1}H NMR (500 MHz) δ 3.82 (s, 6 H), 3.83 (s, 3 H), 5.15 (s, 1 H), 6.83−6.86 (m, 4 H), 6.93−6.95 (m, 2 H), 7.42−7.44 (m, 4 H), 7.59−7.60 (m, 2 H). ^{13}C{^{1}H} (125 MHz) δ 29.5, 55.4, 55.5, 82.5, 85.8, 114.0, 114.2, 115.4, 128.6, 130.7, 133.4, 159.1, 159.7. IR (neat) 3052, 3005, 2959, 2935, 2838, 1606, 1571, 1463, 1442, 1249, 1173, 1034. HRMS (ESI) Calcd for $C_{26}H_{23}O_3$, 383.1642; Found, 383.1677.

*4,4′-(5-Phenylpenta-1,4-diyne-1,3-diyl)bis(methoxybenzene) (**13f**).* 1,4-Diyne **13f** was obtained in 53% yield (0.37 mmol scale, 69 mg) after 14 h at 25 °C, eluting with 4:1 hexanes/CH_2Cl_2, as a clear, orange oil. ^{1}H NMR (500 MHz) δ 3.82 (s, 3 H), 3.84 (s, 3 H), 5.16 (s, 1 H), 6.84−6.85 (m, 2 H), 6.93−6.95 (m, 2 H), 7.30−7.31 (comp, 3 H), 7.42−7.44 (m, 2 H), 7.47−7.49 (comp, 2 H), 7.59−7.60 (m, 2 H). ^{13}C{^{1}H} (125 MHz) δ 29.5, 55.5, 55.6, 82.6, 82.7, 85.6, 87.3, 114.0, 114.3, 115.3, 123.3, 128.38, 128.41, 128.6, 130.5, 132.0, 133.4, 159.1, 159.7. IR (thin film) 3055, 3004, 2958, 2935, 2837, 1602, 1509, 1462, 1291, 1250, 1174, 1071, 1032. HRMS (ESI) Calcd for $C_{25}H_{21}O_2$, 353.1536; Found, 353.1535.

*4,4′-(5-Phenylpenta-1,4-diyne-1,3-diyl)bis(chlorobenzene) (**13g**).* 1,4-Diyne **13g** was obtained in 50% yield (0.37 mmol scale, 66 mg) after 14 h at 25 °C, eluting with 20:1 hexanes/CH_2Cl_2, as a clear, yellow oil. ^{1}H NMR (500 MHz) δ 5.16 (s, 1 H), 7.28−7.32 (comp, 5 H), 7.36−7.41 (m, 4 H), 7.47−7.49 (comp, 2 H), 7.58−7.60 (m, 2 H). ^{13}C{^{1}H} (125 MHz) δ 29.8, 82.2, 83.5, 85.9, 87.3, 121.4, 122.8, 128.5, 128.7, 128.8, 128.9, 129.1, 132.0, 133.3, 133.7, 134.7, 136.5. IR (neat) 3057, 2925, 2852, 1594, 1487, 1443, 1401, 1373, 1294, 1243, 1092, 1046, 1015. HRMS (ESI) Calcd for $C_{23}H_{15}Cl_2O$, 377.0494; Found, 377.0466.

*(3-(o-Tolyl)penta-1,4-diyne-1,5-diyl)dibenzene (**13h**).* 1,4-Diyne **13h** was obtained in 93% yield (0.37 mmol scale, 104 mg) after 2 h at 25 °C, eluting with 100% hexanes, as a clear, yellow oil. Spectral data (^{1}H NMR and ^{13}C{^{1}H} NMR) were consistent with literature values.[39]

*1-(1,7-Diethoxyhepta-2,5-diyn-4-yl)-4-methoxybenzene (**13i**).* 1,4-Diyne **13i** was obtained in 60% yield (0.37 mmol scale, 64 mg) after 3 h at 25 °C, eluting with 100% CH_2Cl_2, as a clear, colorless oil. ^{1}H NMR (300 MHz) δ 1.22 (t, J = 7.0 Hz, 6 H), 3.56 (q, J = 7.0 Hz, 4 H), 3.80 (s, 3 H), 4.18 (d, J = 2.0 Hz, 4 H), 4.78 (m, 1 H), 6.88 (d, J = 9.0 Hz, 2 H), δ 7.42 (d, J = 9.0 Hz, 2 H). ^{13}C{^{1}H} NMR (75 MHz) δ 15.0, 28.2, 55.3, 58.2, 65.4, 78.5, 83.4, 114.0, 128.2, 129.6, 158.9. IR (neat) 2974, 2934, 2245, 2198, 1510, 1250, 1177, 1105. HRMS (ESI) Calcd for $C_{18}H_{22}O_3Na$, 309.1461; Found, 309.1483.

*2,2′-(5-Phenylpenta-1,4-diyne-1,3-diyl)bis(methylbenzene) (**13j**).* 1,4-Diyne **13j** was obtained in 52% yield (0.37 mmol scale, 72 mg) after 14 h at 25 °C, eluting with 20:1 hexanes/CH_2Cl_2, as a clear yellow oil. Product was isolated as a mixture of **13j** and the corresponding symmetrical diynes. The combined yield of the minor symmetrical adducts (11%) was determined by integration of their benzylic protons at 5.30 and 5.22 ppm in the ^{1}H NMR spectrum of the mixture. ^{1}H NMR (500 MHz) δ 2.43 (s, 3 H), 2.56 (s, 3 H), 5.26 (s, 1 H), 7.09−7.12 (comp, 1 H), 7.16−7.30 (comp, 8 H), 7.41−7.47 (comp, 3 H), 7.78−7.80 (m, 1 H). ^{13}C{^{1}H} (125 MHz) δ 19.6, 20.9, 28.5, 81.8, 82.5, 86.7, 90.5, 123.0, 123.3, 126.7, 125.6, 127.8, 127.9, 128.37, 128.39, 128.4, 129.6, 131.0, 131.9, 132.2, 136.0, 136.5, 140.6. IR (neat) 3057, 2923, 2853, 1655, 1592, 1489, 1443, 1399, 1293, 1176, 1092, 1015. HRMS (ESI) Calcd for $C_{25}H_{21}$, 321.1638; Found, 321.1625.

*1-(1-(4-Chlorophenyl)-5-phenylpenta-1,4-diyn-3-yl)-2-methylbenzene (**13k**).* The reaction was performed in 1,2-dichloroethane. The mixture was stirred at 25 °C for 3 h and heated to 45 °C upon addition of Ac_2O for 11 h. 1,4-Diyne **13k** was obtained in 56% yield (0.37 mmol scale, 70 mg), eluting with 15:1 hexanes/CH_2Cl_2, as a clear, orange oil. ^{1}H NMR (500 MHz) δ 2.54 (s, 3 H), 5.21 (s, 1 H), 7.20−7.31 (comp, 8 H), 7.37−7.39 (m, 2 H), 7.45−7.47 (comp, 2 H), 7.74−7.75 (m, 1 H). ^{13}C{^{1}H} (125 MHz) δ 19.5, 28.4, 81.50, 82.8, 86.2, 87.5, 121.7, 123.1, 126.7, 127.8, 128.0, 128.4, 128.5, 128.7, 131.0, 132.0, 133.2, 134.4, 136.0, 136.1. IR (neat) 3063, 3022, 2926, 1596, 1488, 1462, 1443, 1398, 1380, 1265, 1176, 1091, 1014. HRMS (ESI) Calcd for $C_{24}H_{18}Cl$, 341.1092; Found, 341.1072.

*1-Methyl-2-(1-phenyl-5-(4-(trifluoromethyl)phenyl)penta-1,4-diyn-3-yl)benzene (**13l**).* The reaction was performed in 1,2-dichloroethane. The mixture was stirred at 25 °C for 3 h and then heated to 45 °C upon addition of Ac_2O over 11 h. 1,4-Diyne **13l** was obtained in 50% yield (0.37 mmol scale, 68 mg), eluting with 15:1 hexanes/CH_2Cl_2, as a clear orange oil. ^{1}H NMR (500 MHz) δ 2.55 (s, 3 H), 5.24 (s, 1 H), 7.22−7.31 (comp, 6 H), 7.46−7.48 (m, 2 H), 7.55 (s, 4 H), 7.75 (d, J = 7, 1 H). ^{13}C{^{1}H} (125 MHz) δ 19.6, 28.4, 81.3, 83.0, 85.9, 89.2, 123.0, 125.3 (q, J = 3.6 Hz), 126.8, 127.8, 128.1, 218.4, 128.5, 131.1, 132.0, 132.2, 135.9, 136.0. IR (neat) 3062, 3023, 2928, 1735, 1677, 1615, 1490, 1461, 1323, 1265, 1168, 1129, 1068, 1017. HRMS (ESI) Calcd for $C_{25}H_{18}F_3$, 375.1355; Found, 375.1361.

*1-Chloro-4-(1-(4-methoxyphenyl)-5-phenylpenta-1,4-diyn-3-yl)-benzene (**13m**).* 1,4-Diyne **13m** was obtained in 55% yield (0.37 mmol scale, 72 mg) after 2 h at 50 °C, eluting with 4:1 hexanes/CH_2Cl_2, as an orange solid. ^{1}H NMR (500 MHz) δ 3.81 (s, 3 H), 5.16 (s, 1 H), 6.83−6.85 (m, 2 H), 7.30−7.32 (comp, 3 H), 7.36−7.37 (m, 2 H), 7.40−7.42 (m, 2 H), 7.47−7.49 (comp, 2 H), 7.60−7.62 (m, 2 H). ^{13}C{^{1}H} (125 MHz) δ 29.8, 55.5, 83.19, 83.22, 86.5, 96.1, 114.1, 115.0, 123.0, 128.5, 128.6, 128.9, 129.0, 132.0, 133.4, 136.9, 159.9. IR (thin film) 3055, 2957, 2933, 2836, 1605, 1509, 1488, 1289, 1249, 1173, 1070, 1033, 1015. HRMS (ESI) Calcd for $C_{24}H_{18}ClO$, 357.1041; Found, 357.1031.

*6-Phenyl-4-(o-tolyl)hexa-2,5-diyn-1-yl acetate (**13n**).* 1,4-Diyne **13n** was obtained in 58% yield (0.37 mmol scale, 65 mg) after 14 h at 25 °C, eluting with 3:1 hexanes/CH_2Cl_2, as a clear yellow oil. ^{1}H NMR (500 MHz) δ 2.08 (s, 3 H), 2.48 (s, 3 H), 4.73 (d, J = 2.5, Hz, 1 H), 5.05 (t, J = 2.0, Hz, 1 H), 7.18−7.33 (comp, 6 H), 7.41−7.45 (m, 2 H), 7.67−7.68 (m, 1 H). ^{13}C{^{1}H} (125 MHz) δ 19.5, 20.9, 27.8, 52.7, 76.4, 82.8, 83.9, 85.9, 123.0, 126.7, 127.8, 128.0, 128.4, 128.5, 131.0, 131.9, 135.7, 136.0, 170.4. IR (neat) 3067, 2942, 1747, 1597, 1489, 1450, 1376, 1271, 1226, 1051, 1028. HRMS (ESI) Calcd for $C_{21}H_{18}O_2Na$, 325.1199; Found, 325.1212.

(±)-4,4′-Tetradeca-5,9-diyne-7,8-diyl)bis(chlorobenzene) (meso and dl). 1,5-Diyne **17a** was obtained as a 1:1 mixture in 20% yield (0.18 mmol scale, 15 mg) after 12 h at 25 °C, eluting with 12:1 hexanes/CH_2Cl_2, as a yellow solid. ^{1}H NMR (500 MHz) δ 0.90 (t, J = 7, 6 H), 0.92 (t, J = 7, 6 H), 1.32−1.52 (m, 16 H), 2.17 (t, J = 7, 4 H), 2.21 (t, J = 7, 4 H), 3.86 (s, 2 H), 3.90 (s, 2 H), 7.08−7.10 (m, 4 H), 7.15−7.18 (m, 4 H), 7.19−7.23 (comp, 8 H). ^{13}C{^{1}H} (125 MHz) δ 13.9, 18.6, 18.7, 22.0, 22.1, 31.0, 31.1, 45.3, 45.4, 78.6, 79.2, 86.0, 86.3, 128.1, 130.2, 130.3, 133.1, 137.9, 138.0. IR (neat) 3051, 2959, 2932, 2872, 1594, 1490, 1464, 1407, 1378, 1329, 1265, 1091, 1015. HRMS (ESI) Calcd for $C_{26}H_{28}Cl_2$, 410.1568; Found, 410.1579.

General Procedure for the Synthesis of 1,5-Enynes. An 8 mL screw cap vial, equipped with a magnetic stir bar, was charged with Cp_2TiCl_2 (2.0 mg, 8.0 μmol) and zinc dust (52.3 mg, 0.8 mmol) and then purged with argon for 10 min. The mixture was taken up in CH_2Cl_2 (0.25 mL) and the resulting suspension stirred at room temperature until a blue/green color persisted. Tris(4-methoxyphenyl)phosphine (28.2 mg, 0.08 mmol) was then added in one portion and the mixture stirred for an additional 5 min. A solution of **4** (0.4 mmol) and **5** (0.8 mmol) in CH_2Cl_2 (1.0 mL) was added dropwise and stirred at room temperature until full consumption of **4** was observed by TLC (~2 h). The reaction was then cooled to 0 °C, and a solution of **18** (0.8 mmol) in CH_2Cl_2 (0.75 mL) was added followed by Ac_2O (45.0 mg, 0.44 mmol) in one portion. After consumption of the propargyl acetate intermediate was observed by TLC (~6 h), the reaction was diluted with hexanes (4 mL), filtered through a short plug of neutral alumina gel eluting with hexanes/CH_2Cl_2 4:1 (15 mL), and the filtrate concentrated under reduced pressure. The resulting crude mixture was purified by flash chromatography eluting with the indicated solvent system to give the target 1,5-enyne **19**.

*1-Chloro-4-(1-phenylhex-5-en-1-yn-3-yl)benzene (**19a**).* The multicomponent coupling was performed on a 0.4 mmol scale. Purification

by filtration on neutral alumina gel eluting with hexane/CH_2Cl_2 (4:1) provided 92 mg (86%) of **19a** as a pale, yellow oil. ^1H NMR and $^{13}C\{^1H\}$ NMR spectra were consistent with literature reported values.[40]

*Triisopropyl(3-(o-tolyl)hex-5-en-1-yn-1-yl)silane (**19b**).* The multicomponent coupling was performed on a 0.4 mmol scale. Purification by flash chromatography eluting with hexanes/CH_2Cl_2 (20:1) provided 105 mg (80%) of **19b** as a white paste. ^1H NMR (500 MHz, $CDCl_3$) δ 7.61 (m, 1 H), 7.25−7.20 (m, 1 H), 7.17−7.13 (m, 2 H) 6.01−5.93 (m, 1 H), 5.14−5.08 (m, 2 H), 2.50−2.45 (m, 2 H), 2.38 (s, 3 H), 1.12 (s, 9 H). $^{13}C\{^1H\}$ NMR (125 MHz) δ 139.9, 136.0, 135.0, 130.6, 128.0, 126.9, 126.4, 117.1, 110.0, 83.4, 41.9, 35.9, 18.9, 18.9, 11.6. IR (neat) 3075, 3018, 2941, 2863, 2168. HRMS (ESI) Calcd for $C_{22}H_{34}Si$, 349.2322; Found, 349.2354.

*1-Methyl-2-(8-phenylocta-1-en-5,7-diyn-4-yl)benzene (**19c**).* The multicomponent coupling was performed on a 0.4 mmol scale. Purification by flash chromatography eluting with hexanes/CH_2Cl_2 (10:1) provided 81 mg (70%) of **19c** as a pale yellow oil. ^1H NMR (500 MHz, $CDCl_3$) δ 7.53−7.50 (comp, 3 H), 7.38−7.31 (comp, 3 H), 7.27−7.24 (m, 1 H), 7.22−7.17 (m, 2 H), 5.94 (ddt, J = 17, 10, 7 Hz, 1 H), 5.19−5.13 (m, 2 H), 4.08−4.05 (m, 1 H) 2.63−2.51 (m, 2 H), 2.39 (s, 3 H). $^{13}C\{^1H\}$ NMR (125 MHz) δ 138.54, 135.20, 135.05, 132.70, 130.77, 129.12, 128.55, 127.73, 127.28, 126.65, 122.14, 117.67, 85.47, 76.26, 74.44, 67.57, 40.92, 35.36, 19.50. IR (neat) 3052, 2980, 2304, 2244. HRMS (ESI) Calcd for $C_{21}H_{18}$, 270.1409; Found, 270.1403.

*1-Chloro-4-(1-(cyclohex-2-en-1-yl)-3-phenylprop-2-yn-1-yl)-benzene (**19d**).* The multicomponent coupling was performed on a 0.4 mmol scale. Purification by flash chromatography eluting with hexanes/CH_2Cl_2 (20:1) provided 108 mg (88%) of **19d** (1:1 dr) as a pale, yellow oil. ^1H NMR (500 MHz, $CDCl_3$): Diastereomer A: δ 7.44−7.42 (m, 2 H), 7.35−7.29 (m, 7 H), 5.87 (d, J = 10.5, 1 H), 5.83−5.75 (m, 1 H), 3.77 (d, J = 7, 1 H), 2.54−2.50 (m, 1 H), 2.00−1.99 (comp, 2 H), 1.82−1.72 (comp, 2 H), 1.65−1.49 (comp, 2 H). Diastereomer B: 7.44−7.42 (m, 2 H), 7.35−7.29 (m, 7 H), 5.83−5.75 (m, 1 H), 5.50 (dd, J = 10.5, 2, 1 H), 3.77 (d, J = 7, 1 H), 2.54−2.50 (m, 1 H), 2.00−1.99 (comp, 2 H), 1.82−1.72 (comp, 2 H), 1.65−1.49 (comp, 2 H). $^{13}C\{^1H\}$ NMR (125 MHz): Diastereomer A: 139.3, 132.8, 132.6, 129.9, 129.5, 129.1, 128.7, 128.4, 128.1, 123.8, 90.5, 84.5, 43.8, 42.7, 27.9, 25.5, 21.8. Diastereomer B: δ 139.2, 132.7, 131.9, 129.8, 129.3, 129.0, 128.7, 128.6, 128.4, 123.8, 90.3, 84.5, 43.8, 42.5, 26.5, 25.4, 21.6. IR (neat) 2932, 2198. HRMS (ESI) Calcd for $C_{21}H_{19}Cl$, 306.1144; Found, 306.1175.

*(3-(4-Chlorophenyl)-5-phenyl-2-vinylpent-4-yn-1-yl)-trimethylsilane (**19e**).* The multicomponent coupling was performed on a 0.4 mmol scale. Purification by flash chromatography eluting with hexanes/CH_2Cl_2 (20:1) provided 130 mg of **19e** (1:1 dr, 92%) as a pale, yellow oil. ^1H NMR (500 MHz, $CDCl_3$): Diastereomer A: δ 7.47−7.45 (m, 2 H), 7.31−7.30 (comp, 6 H), 7.28 (s, 1 H), 5.72−5.63 (m, 1 H), 5.03−4.99 (comp, 1 H), 4.95 (dd, J = 10.5, 2.0 Hz, 1 H), 3.87 (d, J = 4.5 Hz, 1 H), 2.57−2.49 (comp, 1 H), 0.98−0.84 (m, 2 H) 0.02 (s, 9 H). Diastereomer B: δ 7.47−7.45 (m, 2 H), 7.31−7.30 (comp, 6 H), 7.28 (s, 1 H), 5.72−5.63 (m, 1 H), 5.03−4.99 (comp, 1 H), 4.77 (dd, J = 17.5, 1.5 Hz, 1 H), 3.83 (d, J = 5.5 Hz, 1 H), 2.57−2.49 (comp, 1 H), 0.80−0.73 (m, 2 H), −0.06 (s, 9 H). $^{13}C\{^1H\}$ NMR (125 MHz): Diastereomer A: δ 142.0, 139.0, 132.7, 131.9, 130.1, 128.5, 128.3, 126.0, 116.3, 89.8, 85.3, 47.7, 46.6, 21.3, −0.5. Diastereomer B: δ 140.4, 138.8, 132.6, 131.9, 130.0, 128.4, 128.3, 128.1, 123.8, 115.9, 89.4, 85.2, 47.7, 46.3, 18.4, −0.5. IR (neat) 3078, 2952, 2924. HRMS (ESI) Calcd for $C_{22}H_{25}ClSi$, 352.1429; Found, 352.1414.

*1-Chloro-4-(5-methyl-1-phenylhex-5-en-1-yn-3-yl)benzene (**19f**).* The multicomponent coupling was performed on a 0.4 mmol scale. Purification by filtration on neutral alumina gel eluting with hexane/CH_2Cl_2 (4:1) provided 108 mg (96%) of **19f** as a pale yellow oil. ^1H NMR and $^{13}C\{^1H\}$ NMR spectra were consistent with literature reported values.[40]

General Procedures for the Synthesis of β-Alkynyl Ketones. A vial, equipped with a magnetic stir bar, was charged with Cp_2TiCl_2 (2.0 mg, 8.0 μmol) and zinc dust (55 mg, 0.84 mmol) and then purged with nitrogen for 5 min. Dry, degassed CH_2Cl_2 (0.25 mL) was added, and the resulting gray slurry was stirred vigorously at room temperature until it took on a blue/green color. Tris(4-methoxyphenyl)phosphine (56 mg, 0.16 mmol) was then added in one portion followed by the dropwise addition of a solution of aldehyde **4** (0.40 mmol) and alkynyl iodide **5** (0.48 mmol) in CH_2Cl_2 (1.0 mL). The resulting mixture was stirred at room temperature until TLC indicated full consumption of the starting aldehyde (∼2−4 h); then, silyl enol ether **18** (0.48 mmol) was added in one portion via a syringe followed by a solution of Ac_2O (40 μL, 0.44 mmol) in CH_2Cl_2 (0.75 mL) over 11 h via a syringe pump. Once the addition of Ac_2O was complete, the resulting crude mixture was stirred at room temperature for 2 h, diluted with CH_2Cl_2 (2 mL), and then filtered through a short plug of silica gel eluting with 100% Et_2O (55 mL). The filtrate was concentrated under reduced pressure and purified by flash column chromatography eluting with the indicated solvent system to yield β-alkynyl ketone **19**.

1-Phenyl-3-(o-tolyl)non-4-yn-1-one. Ketone **19g** was isolated as a clear, yellow oil in 72% yield (0.5 mmol scale, 110 mg) after 14 h at room temperature, eluting with 20:1 hexanes/EtOAc to EtOAc. ^1H NMR (500 MHz, $CDCl_3$) δ 7.95−7.97 (m, 2 H), 7.53−7.58 (m, 2 H), 7.43−7.46 (m, 2 H), 7.13−7.22 (m, 3 H), 4.55 (ddt, J = 2, 4.5, 9.3 Hz, 1 H), 3.53 (dd, J = 9.5, 16.5 Hz, 1 H), 3.15 (dd, J = 4.5, 16.3 Hz, 1 H), 2.41 (s, 3 H), 2.12 (td, J = 2, 7 Hz Hz, 2 H), 1.27−1.42 (m, 4 H), 0.83 (s, 3 H). $^{13}C\{^1H\}$ NMR (125 MHz) δ 197.8, 140.2, 137.2, 135.2, 133.3, 130.8, 128.7, 128.4, 127.5, 127.0, 126.5, 83.2, 81.2, 46.1, 31.1, 30.1, 22.1, 19.4, 18.6, 13.8. IR (neat) 3066, 2956, 2930, 2871, 2363, 1688, 1597, 1458, 1449, 1350, 1253, 1202, 1038. HRMS (ESI) Calcd for $C_{22}H_{25}O$, 305.1900; Found, 305.1914.

6-Oxo-6-phenyl-4-(p-tolyl)hex-2-yn-1-yl acetate. Ketone **19h** was isolated as a pale, yellow liquid in 62% yield (0.5 mmol scale, 99 mg) after 14 h at room temperature, eluting with 3:1 hexanes/CH_2Cl_2 to CH_2Cl_2. ^1H NMR (500 MHz, $CDCl_3$) δ 7.91−7.93 (m, 2 H), 7.53−7.57 (m, 1 H), 7.42−7.46 (m, 2H), 7.30−7.32 (m, 2 H), 7.13 (app d, J = 8 Hz, 2 H), 4.66 (d, J = 2 Hz, 2 H), 4.41−4.45 (m, 1 H), 3.55 (dd, J = 7.5, 17 Hz, 1 H), 3.34 (dd, J = 6.5, 17 Hz, 1 H), 2.32 (s, 3 H), 2.05 (s, 3 H). $^{13}C\{^1H\}$ NMR (125 MHz) δ 197.0, 170.5, 137.8, 137.0, 136.8, 133.4, 129.6, 128.8, 128.3, 127.6, 88.6, 76.7, 52.9, 47.1, 32.7, 21.2, 21.0. IR (neat) 3055, 3024, 2922, 1747, 1691, 1596, 1512, 1448, 1358, 1225, 1147, 1024, 976. HRMS (ESI) Calcd for $C_{21}H_{21}O_3$, 321.1485; Found, 321.1472.

1,5-Diphenyl-3-(thiophen-2-yl)pent-4-yn-1-one. Ketone **19i** was isolated as an orange oil in 75% yield (0.4 mmol scale, 93 mg) after 14 h at room temperature, eluting with 20:1 hexanes/EtOAc. ^1H NMR (500 MHz, $CDCl_3$) δ 8.99−8.01 (m, 2 H), 7.57−7.60 (m, 1 H), 7.46 (app t, J = 8 Hz, 2 H), 7.39−7.42 (m, 2 H), 7.28−7.30 (m, 3 H), 7.21 (dd, J = 1.5, 5.3 Hz, 1 H), 7.13 (app dt, J = 1, 3.5 Hz, 1 H), 6.96 (dd, J = 3, 5 Hz, 1 H), 4.98 (app t, J = 7 Hz, 1 H), 3.72 (dd, J = 7, 16.8 Hz, 1 H), 3.57 (dd, J = 7, 17 Hz, 1 H). $^{13}C\{^1H\}$ NMR (125 MHz) δ 196.8, 144.8, 136.8, 133.6, 131.8, 128.8, 128.4, 128.3, 128.2, 127.0, 125.1, 124.4, 123.2, 90.3, 83.1, 47.6, 29.1. IR (neat) 3061, 2904, 1767, 1680, 1596, 1580, 1489, 1446, 1404, 1350, 1219, 1180, 1070, 1003. HRMS (ESI) Calcd for $C_{21}H_{17}OS$, 317.0995; Found, 317.0999.

*5-(3-Phenyl-1-(o-tolyl)prop-2-yn-1-yl)furan-2(5H)-one (**19j**).* A two-dram screw cap vial, equipped with a magnetic stir bar, was charged with Cp_2TiCl_2 (2.6 mg, 10.3 μmol) and zinc dust (40.0 mg, 0.165 mmol) and then purged with argon for 5 min. Dry, degassed CH_2Cl_2 (0.50 mL) was added and the suspension stirred at room temperature until a blue/green color persisted. A solution of $^tBu_3P$ (16.0 mg, 0.082 mmol) in CH_2Cl_2 (0.25 mL) was then added dropwise and the mixture stirred for an additional 10 min. A solution of *o*-tolualdehyde (25 mg, 0.206 mmol), phenyliodoacetylene **5a** (141 mg, 0.618 mmol), and (furan-2-yloxy)trimethylsilane (64 mg, 0.418 mmol) in CH_2Cl_2 (0.75 mL) was then added, and the reaction was stirred at room temperature until full consumption of *o*-tolualdehyde was observed by TLC (∼1 h). A solution of Ac_2O (46 mg, 0.453 mmol, 43 μL) in CH_2Cl_2 (0.5 mL) was then added slowly over 11 h via a syringe pump. The reaction was then diluted with CH_2Cl_2 (2 mL) and filtered through a short plug of silica gel eluting with CH_2Cl_2 (50 mL), and the filtrate was concentrated under reduced pressure.

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Purification by flash chromatography eluting with hexanes/EtOAc (2:1) provided 39 mg (66%) of **19j** in a 1:1 mixture of diastereomers as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): 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). ^{13}C{^{1}H} 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, 2230, 1788, 1659, 1588, 1490, 1275, 1152, 1032. HRMS (ESI) Calcd for $C_{20}H_{16}O_2Na$, 311.1043; Found, 311.1017.

2-(1-(4-Methoxyphenyl)hept-2-yn-1-yl)cyclohexanone. Ketone **19k** was prepared as a 1:1 mixture of diastereomers according to the general procedure to provide the product as a clear colorless liquid in 68% yield (0.4 mmol scale, 81 mg) after 14 h at room temperature, eluting with 1:1 hexanes/CH_2Cl_2. ^{1}H NMR (500 MHz, $CDCl_3$): Isomer A: δ 7.25−7.29 (comp, 2 H), 6.81−6.88 (comp, 2 H), 4.35 (ddd, J = 2.3, 2.3, 4.5 Hz, 1 H), 3.78 (s, 3 H), 2.66−2.71 (m, 1 H), 2.40−2.47 (comp, 2 H), 2.21 (td, J = 1, 7 Hz, 2 H), 1.20−2.07 (comp, 10 H), 0.91 (t, J = 7 Hz, 3 H). Isomer B: δ 7.25−7.29 (comp, 2 H), 6.81−6.88 (comp, 2 H), 4.09 (ddd, J = 2.3, 2.3, 7 Hz, 1 H), 3.78 (s, 3 H), 2.40−2.47 (comp, 1 H), 2.19−2.35 (comp, 2 H), 2.17 (td, J = 1, 7 Hz, 2 H), 1.20−2.07 (comp, 10 H), 0.89 (t, J = 7 Hz, 3 H). ^{13}C{^{1}H} NMR (125 MHz): Isomer A: δ 158.5, 133.4, 129.9, 113.8, 84.8, 81.7, 57.8, 55.4, 42.2, 35.9, 31.3, 30.8, 27.9, 24.9, 22.2, 18.7, 13.8. Isomer B: δ 158.4, 132.0, 129.1, 113.6, 82.7, 79.4, 57.2, 55.3, 42.1, 35.9, 31.2, 29.0, 27.4, 24.6, 22.1, 18.6, 13.8. IR (neat) 2935, 2868, 1712, 1602, 1512, 1462, 1301, 1252, 1176, 1124, 1032. HRMS (ESI) Calcd for $C_{20}H_{27}O_2$, 299.2006; Found, 299.2017.

1-(3-Phenyl-1-(p-tolyl)prop-2-yn-1-yl)cyclohexanecarbaldehyde. Ketone **19l** was prepared according to the general procedure with the addition of Ac_2O performed at 0 °C to provide the product as a clear colorless oil in 78% yield (0.5 mmol scale, 124 mg) as a 1:1 mixture of diastereomers after 14 h at room temperature, eluting with 3:1 hexanes/CH_2Cl_2 to CH_2Cl_2. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.68 (s, 1 H), 7.43−7.45 (m, 2 H), 7.29−7.31 (m, 3 H), 7.17−7.19 (m, 2 H), 7.11−7.13 (m, 2 H), 3.89 (s, 1 H), 2.33 (s, 3 H), 2.12−2.18 (m, 1 H), 2.04−2.07 (m, 1 H), 1.45−1.68 (comp, H), 1.07−1.30 (comp, H). ^{13}C{^{1}H} NMR (125 MHz) δ 207.3, 137.4, 133.7, 131.9, 129.5, 129.1, 128.5, 128.3, 123.5, 88.4, 85.6, 53.2, 46.0, 29.8, 29.8, 25.6, 23.0, 22.9, 21.3. IR (neat) 2933, 2857, 1698, 1602, 1512, 1490, 1451, 1415, 1285, 1242, 1178, 1023. HRMS (ESI) Calcd for $C_{23}H_{24}ONa$, 339.1719; Found, 339.1740.

General Procedure for the Synthesis of Diarylethynylmethanes. A two-dram screw cap vial, equipped with a magnetic stir bar, was charged with Cp_2TiCl_2 (2.6 mg, 10.3 μmol) and zinc dust (40.0 mg, 0.165 mmol) and then purged with argon for 5 min. Dry, degassed DCE (0.50 mL) was added and the suspension stirred at room temperature until a blue/green color persisted. A solution of ^{t}Bu$_3$P (33.0 mg, 0.165 mmol) in DCE (0.25 mL) was then added dropwise, and the mixture was stirred for an additional 10 min. A solution of aldehyde (0.206 mmol), iodoacetylene **5** (0.618 mmol), and arene **20** (0.418 mmol) in DCE (0.75 mL) was then added and the reaction stirred at room temperature until full consumption of aldehyde **4** was observed by TLC (~1 h). Cs_2CO_3 (67.0 mg, 0.206 mmol) was then added in one portion followed by the slow addition of Ac_2O (46 mg, 0.453 mmol, 43 μL) in DCE (0.5 mL) over 11 h via a syringe pump. The reaction was then diluted with CH_2Cl_2 (2 mL) and filtered through a short plug of silica gel eluting with CH_2Cl_2 (50 mL), and the filtrate was concentrated under reduced pressure. The crude mixture was purified directly by flash chromatography eluting with the indicated solvent mixture to give diarylethynyl methane **21**.

*2,4-Dimethoxy-5-(phenylethynyl)-10,11-dihydro-5H-dibenzo[a,d][7]annulene (**21a**).* Purification by flash chromatography eluting with hexanes/CH_2Cl_2 (1:1) provided 56 mg (77%) of **21a** as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 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{^{1}H} NMR (125 MHz) δ 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) Calcd for $C_{25}H_{22}O_2$, 354.1620; Found, 354.160. mp = 109−111 °C.

*2,4-Dimethoxy-1-(3-phenyl-1-(o-tolyl)prop-2-yn-1-yl)benzene (**21b**).* Purification by flash chromatography eluting with hexanes/EtOAc (10:1) provided 50 mg (77%) of **21b** as a clear, yellow oil. ^{1}H NMR (500 MHz) δ 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{^{1}H} (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. HRMS (ESI) Calcd for $C_{24}H_{23}O_2$, 343.1693; Found, 343.1692.

*N,N-Dimethyl-4-(3-phenyl-1-(1-tosyl-1H-indol-3-yl)prop-2-yn-1-yl)aniline (**21c**).* Purification by flash chromatography eluting with hexanes/CH_2Cl_2 (1:1) provided 71 mg (68%) of **21c** as a clear, orange oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 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{^{1}H} NMR (125 MHz) δ 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.

*3-(1-(4-Methoxyphenyl)-3-phenylprop-2-yn-1-yl)-1-methyl-1H-indole (**21d**).* Purification by flash chromatography eluting with hexanes/CH_2Cl_2 (1:1) provided 65 mg (90%) of **21d** as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) 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). ^{13}C{^{1}H} 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) Calcd for $C_{25}H_{22}NO$, 352.1696; Found, 352.1670. mp = 120−121 °C.

*3-(1-(4-Methoxyphenyl)hept-2-yn-1-yl)-1-methyl-1H-indole (**21e**).* Purification by flash chromatography eluting with hexanes/CH_2Cl_2 (2:1) provided 54 mg (80%) of **21e** 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{^{1}H} 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) Calcd for $C_{23}H_{26}NO$, 332.2009; Found, 332.2012.

*3-(4-(Benzyloxy)-1-(4-methoxyphenyl)but-2-yn-1-yl)-1-methyl-1H-indole (**21f**).* Purification by flash chromatography eluting with hexanes/CH_2Cl_2 (1:1) provided 43 mg (53%) of **21f** as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55−7.53 (m, 1 H), 7.40−7.38 (m, 2 H), 7.34−7.26 (m, 6 H), 7.23−7.19 (m, 1 H), 7.07−7.03 (m, 1 H), 6.92 (s, 1 H), 6.87−6.84 (m, 2 H), 5.27 (br s, 1 H), 4.61 (s, 2 H), 4.28 (d, J = 2.0 Hz, 2 H), 3.79 (s, 3 H), 3.74 (s, 3 H). ^{13}C{^{1}H} 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) Calcd for $C_{27}H_{25}NO_2Na$, 418.1778; Found, 418.1789.

*3-(1-(Furan-2-yl)-3-phenylprop-2-yn-1-yl)-1-methyl-1H-indole (**21g**).* Purification by flash chromatography eluting with hexanes/CH_2Cl_2 (3:1) provided 44 mg (68%) of **21g** as a dark yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 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{^{1}H} NMR (125 MHz) δ 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) Calcd for $C_{22}H_{17}NO$, 312.1383; Found, 312.1355.

*1-Methyl-3-(3-phenyl-1-(thiophen-2-yl)prop-2-yn-1-yl)-1H-indole (**21h**).* Purification by flash chromatography eluting with hexanes/CH_2Cl_2 (2:1) provided 48 mg (71%) of **21h** as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 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{^{1}H} NMR (125 MHz) δ 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. mp = 118−121 °C (decomposed).

General Procedure for the Synthesis of Iodoenynes. A vial, equipped with a magnetic stir bar, was charged with Cp_2TiCl_2 (6.2 mg, 25 μmol) and zinc dust (69 mg, 1.05 mmol) and then purged with nitrogen for 5 min. Dry, degassed CH_2Cl_2 (1.0 mL) was added, and the resulting gray slurry was stirred vigorously at room temperature until it took on a blue/green color. A solution of aldehyde **22a**, **22b**, or **29** (0.50 mmol) and alkynyl iodide **5** (0.75 mmol) and Ac_2O (70 μL, 0.75 mmol) in CH_2Cl_2 (1.0 mL) was then added dropwise. The resulting mixture was stirred at room temperature until TLC indicated full consumption of the starting aldehyde (∼2−4 h). The crude mixture was then diluted with CH_2Cl_2 (2 mL) and filtered through a plug of silica eluting with 100% Et_2O (55 mL). The filtrate was concentrated under reduced pressure and purified by flash column chromatography eluting with the indicated solvent system to yield the desired iodoenyne **25**, **28**, or **30**.

*(E)-(6-Iodohex-3-en-1-yn-1-yl)benzene, (Z)-(6-Iodohex-3-en-1-yn-1-yl)benzene (**25a**).* The reaction was performed on a 0.5 mmol scale. Purification by flash chromatography eluting with 100% hexanes provided 99 mg (71%) of **25a** as a clear, yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ: (E)-isomer: 7.44−7.52 (comp, 2 H), 7.30−7.37 (comp, 3 H), 6.16 (dt, J = 7, 15.5 Hz, 2 H), 5.80−5.83 (m, 1 H), 3.20 (t, J = 7 Hz, 2 H), 2.76 (app qd, J = 1.5, 7 Hz, 2 H). (Z)-isomer: 7.44−7.52 (comp, 2 H), 7.30−7.37 (comp, 3 H), 5.97 (dt, J = 7, 10.5 Hz, 1 H), 5.85−5.87 (m, 1 H), 3.26 (t, J = 7 Hz, 2 H), 2.98−3.03 (m, 2 H). ^{13}C{^{1}H} NMR (125 MHz) δ 142.1, 141.4, 132.3, 131.7, 128.5, 128.5, 128.5, 128.4, 123.4, 123.4, 112.4, 111.7, 94.9, 89.6, 87.7, 85.8, 37.2, 34.3, 3.9, 3.7. IR (neat) 3079, 3059, 3027, 2958, 2926, 2202, 2123, 1669, 1597, 1572, 1489, 1441, 1423, 1368, 1299, 1279, 1217, 1171, 1103, 1069. HRMS (ESI) Calcd for $C_{12}H_{11}I$, 281.9906; Found, 281.9921.

*(E)-1-(6-Iodohex-3-en-1-yn-1-yl)-2-methylbenzene, (Z)-1-(6-Iodohex-3-en-1-yn-1-yl)-2-methylbenzene (**25b**).* The reaction was performed on a 0.5 mmol scale. Purification by flash chromatography eluting with hexanes provided 121 mg (81%) of **25b** as a clear, yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ: (E)-isomer: 7.39−7.40 (m, 1 H), 7.11−7.25 (comp, 3 H), 6.14 (dt, J = 7, 15.5 Hz, 1 H), 5.84 (dt, J = 1.5, 16 Hz, 1 H), 3.19 (t, J = 7 Hz, 2 H), 2.75 (app qd, J = 1.5, 7 Hz, 2 H), 2.43 (s, 3 H). (Z)-isomer: 7.41−7.42 (m, 1 H), 7.11−7.25 (comp, 3 H), 5.95 (dt, J = 7, 11 Hz, 1 H), 5.87−5.90 (m, 1 H), 3.24 (t, J = 7 Hz, 2 H), 3.00 (app q, J = 7 Hz, 2 H), 2.46 (s, 3 H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ: (E)-isomer: 141.7, 140.2, 132.0, 129.6, 128.4, 125.7, 123.1, 112.6, 91.6, 88.5, 37.3, 20.9, 3.7. (Z)-isomer: 141.0, 140.1, 132.0, 129.7, 128.6, 125.8, 123.2, 112.0, 93.9, 89.7, 34.4, 21.1, 3.7. IR (neat) cm^{-1} 3062, 3021, 2961, 2923, 2225, 2188, 1722, 1693, 1601, 1573, 1485, 1456, 1380, 1290, 1239, 1173, 1116, 1071, 1046. HRMS (ESI) Calcd for $C_{13}H_{13}I$, 296.0062; Found, 296.0057.

*(E)-1-Chloro-4-(6-iodohex-3-en-1-yn-1-yl)benzene, (Z)-1-Chloro-4-(6-iodohex-3-en-1-yn-1-yl)benzene (**25c**).* The reaction was performed on a 0.4 mmol scale. Purification by flash chromatography eluting with 100% hexanes provided 54 mg (43%) of **25c** as a clear, yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ: (E)-isomer: 7.26−7.39 (comp, 4 H), 5.40 (dt, J = 7.5, 12 Hz, 1 H), 6.15 (dt, J = 7, 16, Hz, 1 H), 5.78 (app d, J = 16, 1 H), 3.19 (t, J = 7 Hz, 2 H), 2.74 (app qd, J = 1.5, 7 Hz, 2H). (Z)-isomer: 7.26−7.39 (comp, 4 H), 5.97 (dt, J = 7, 10.5, Hz, 1 H), 5.82 (app d, J = 10.5, 1 H), 3.24 (t, J = 7 Hz, 2 H), 2.97 (app qd, J = 1, 7 Hz, 2H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ: (E)-isomer: 141.9, 134.4, 132.9, 128.8, 111.5, 88.7, 88.4, 37.2, 3.6. (Z)-isomer: 142.6, 134.5, 132.9, 128.9, 112.2, 93.7, 86.8, 34.3, 3.7. IR (neat) 3024, 2952, 2925, 1649, 1589, 1488, 1417, 1395, 1246, 1171, 1092, 1014. HRMS (ESI) Calcd for $C_{12}H_{10}ClI$, 315.9516; Found, 315.9478.

*(E)-1-(6-Iodohex-3-en-1-yn-1-yl)-4-(trifluoromethyl)benzene, (Z)-1-(6-iodohex-3-en-1-yn-1-yl)-4-(trifluoromethyl)benzene (**25d**).* The reaction was performed on a 0.4 mmol scale. Purification by flash chromatography eluting with 100% hexanes provided 97 mg (69%) of **25d** as a clear, yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ: (E)-isomer: 7.51−7.59 (comp, 4 H), 6.21 (dt, J = 7, 16 Hz, 1 H), 5.80 (app d, J = 16 Hz, 1 H), 3.20 (t, J = 7.5 Hz, 2 H), 2.76 (app qd, J = 1.5, 7.3 Hz, 2 H). (Z)-isomer: 7.51−7.59 (comp, 4 H), 6.02 (dt, J = 7, 11 Hz, 1 H), 5.85 (app d, J = 11 Hz, 1 H), 3.25 (t, J = 7 Hz, 2 H), 2.99 (app qd, J = 1.5, 7 Hz, 2 H). IR (neat) 2958, 2204, 1616, 1513, 1405, 1323, 1249, 1167, 1126, 1105, 1067, 1017. HRMS (ESI) Calcd for $C_{13}H_{10}IF_3$, 349.9779; Found, 349.9793.

*(E)-1-Iododec-3-en-5-yne, (Z)-1-Iododec-3-en-5-yne (**25e**).* The reaction was performed on a 0.4 mmol scale. Purification by flash chromatography eluting with 100% hexanes to 3:1 hexanes/CH_2Cl_2 to 100% CH_2Cl_2 provided 22 mg (21%) of **25e** as a clear, yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ: (Z)-isomer: 5.95 (dt, J = 7, 16 Hz, 1 H), 5.53−5.58 (m, 1 H), 3.14 (t, J = 7 Hz, 2 H), 2.66 (app qd, J = 1.5, 7 Hz, 2H), 2.29 (td, J = 2, 7 Hz, 2 H), 1.38−1.56 (comp, 4 H), 0.92 (t, J = 7.5 Hz, 3 H). (E)-isomer: 5.79 (dt, J = 7, 10.5 Hz, 1 H), 5.58−5.62 (m, 1 H), 3.19 (t, J = 7.5 Hz, 2 H), 2.87 (app qd, J = 1.5, 7.25 Hz, 2H), 2.29 (td, J = 2, 7 Hz, 2 H), 1.38−1.56 (comp, 4 H), 0.93 (t, J = 7 Hz, 3 H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ: (Z)-isomer: 140.4, 112.8, 90.8, 77.0, 37.1, 31.0, 22.2, 19.3, 13.8, 4.0. (E)-isomer: 139.9, 112.2, 96.3, 78.7, 34.1, 31.0, 22.2, 19.4, 13.8, 4.1. IR (neat) 3023, 2957, 2929, 2859, 2213, 1628, 1463, 1427, 1395, 1378, 1363, 1298, 1229, 1170. HRMS (ESI) Calcd for $C_{10}H_{15}I$, 262.0219; Found, 262.0202.

*(E)-4-Iodobut-1-en-1-yl Acetate, (Z)-4-Iodobut-1-en-1-yl Acetate (**27**).* The reaction was performed on a 0.4 mmol scale. Purification by flash chromatography eluting with 100% hexanes to 3:1 hexanes/CH_2Cl_2 to 100% CH_2Cl_2 provided 39 mg (41%) of **27** as a clear, yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ: (E)-isomer: 7.18 (dt, J = 7, 17 Hz, 1 H), 5.40 (dt, J = 7.5, 12 Hz, 1 H), 3.16 (t, J = 7 Hz, 2 H), 2.57 (app qd, J = 1.5, 7 Hz, 2H), 2.16 (s, 3 H). (Z)-isomer: 7.16 (dt, J = 1.5, 11 Hz, 1 H), 4.88 (app q J = 7 Hz, 1 H), 3.17 (t, J = 7 Hz, 2 H), 2.74 (app qd, J = 1.5, 7 Hz, 2H), 2.13 (s, 3 H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ: (E)-isomer: 167.9, 137.3, 113.4, 31.7, 20.8, 5.4. (Z)-isomer: 169.1, 135.6, 112.2, 28.9, 20.9, 4.4. IR (neat) 2959, 2931, 1759, 1672, 1427, 1369, 1303, 1217, 1174, 1151, 1103, 1081, 1062. HRMS (ESI) Calcd for $C_6H_9O_2I$, 239.9647; Found, 239.9623.

*(E)-(6-Cyclohexyl-6-iodohex-3-en-1-yn-1-yl)benzene, (Z)-(6-Cyclohexyl-6-iodohex-3-en-1-yn-1-yl)benzene (**28a**); (E)-(5-Cyclohexyl-6-iodohex-3-en-1-yn-1-yl)benzene, (Z)-(5-Cyclohexyl-6-iodohex-3-en-1-yn-1-yl)benzene (**28b**).* The reaction was performed on a 0.26 mmol scale. Purification by flash chromatography eluting with 100% hexanes provided a combined 63 mg (66%) of **28a** and **28b** as a clear, yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ: (E)-**28a**: 7.42−7.45 (comp, 2 H), 7.29−7.34 (comp, 3 H), 6.22 (dt, J = 7, 16 Hz, 1 H), 5.78 (dt, J = 1.5, 16 Hz, 1 H), 4.08−4.12 (m, 1 H), 2.72−2.86 (comp, 2 H), 1.53−1.94 (comp, H), 1.02−1.36 (comp, H). (Z)-**28a**: 7.42−7.45 (comp, 2 H), 7.29−7.34 (comp, 3 H), 6.04 (dt, J = 7, 10.5 Hz, 1 H), (dt, J = 1.5, 11 Hz, 1 H), 4.19 (ddd, J = 4, 6, 8.4 Hz, 1 H), 2.97−3.08 (m, 2 H), 1.53−1.94 (comp, H), 1.02−1.36 (comp, H). (E)-**28b**: 7.42−7.45 (comp, 2 H), 7.29−7.34 (comp, 3 H), 6.01 (dd, J = 9.5, 16 Hz, 1 H), 5.72 (app d, J = 16 Hz, 1 H), 3.31 (dd, J = 5.5, 9.8 Hz, 1 H), 3.22 (dd, J = 7, 9.5 Hz, 1 H), 2.72−2.86 (comp, 1 H), 1.53−1.94 (comp, H), 1.02−1.36 (comp, H). (Z)-**28b**: 7.42−7.45 (comp, 2 H), 7.29−7.34 (comp, 3 H), 5.76−5.86 (comp, 2 H), 3.34 (dd, J = 5, 10 Hz, 1 H), 3.29 (dd, J = 6.5, 9.5 Hz, 1 H), 2.65−2.82 (comp, 1 H), 1.53−1.94 (comp), 1.02−1.36 (comp). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 144.9, 142.5, 142.0, 131.71, 131.70, 131.68, 131.64, 128.57, 128.55, 128.52, 128.48, 128.43, 123.60, 123.52, 112.41, 112.40, 111.5, 111.4, 94.7, 94.2, 89.4, 88.0, 86.5, 86.2, 46.4, 46.3, 44.5, 44.2, 41.8, 41.75, 41.73, 38.7, 33.1, 32.9, 31.7, 31.3, 30.9, 29.9, 29.5, 26.6, 26.52,

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26.50, 26.48, 26.45, 26.22, 26.18, 26.17, 26.09, 11.6, 11.2. IR (neat) 3056, 2924, 2851, 1664, 1596, 1489, 1366, 1298, 1271, 1155, 1029. HRMS (ESI) Calcd for $C_{18}H_{21}I$, 364.0688; Found, 364.0697.

*((3E,5E)-8-Iodoocta-3,5-dien-1-yn-1-yl)benzene, ((3Z,5E)-8-Iodoocta-3,5-dien-1-yn-1-yl)benzene, ((3E,5Z)-8-Iodoocta-3,5-dien-1-yn-1-yl)benzene (**30**).* The reaction was performed on a 0.4 mmol scale. Purification by flash chromatography eluting with 8:1 hexanes/CH_2Cl_2 to 4:1 hexanes/CH_2Cl_2 provided 57 mg (44%) of **30** as a clear, yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ: (*E*,*E*)-isomer: 7.41−7.50 (m, 2 H), 7.29−7.34 (m, 3 H), 6.65 (dd, *J* = 10.5, 15.5 Hz, 1 H), 5.79 (d, *J* = 15.5 Hz, 1 H), 6.20 (dd, *J* = 11, 15 Hz, 1 H) 5.74 (dt, *J* = 7, 15.5 Hz, 1 H), 3.17 (t, *J* = 7 Hz, 2 H), 2.69 (app q, *J* = 7 Hz, 2 H). (*E*,*Z*)- and (*Z*,*E*)-isomers: 7.41−7.50 (m, 4 H), 7.29−7.34 (m, 6 H), 6.90−6.95 (m, 1 H), 6.74−6.80 (m, 1 H), 6.41 (app t, *J* = 11 Hz, 1 H), 6.20−6.24 (comp, 1 H), 5.81−5.89 (comp, 2 H), 5.65 (d, *J* = 10.5 Hz, 1 H),), 5.49 (dt, *J* = 7.5, 11 Hz, 1 H), 3.14−3.21 (comp, 4 H), 2.80−2.85 (m, 2 H), 2.76 (app q, *J* = 7.25 Hz, 2 H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 142.6, 141.4, 139.6, 136.5, 136.1, 135.2, 132.5, 132.2, 131.9, 131.68, 131.66, 131.64, 131.63, 130.2, 130.0, 128.55, 128.52, 128.49, 128.47, 128.45, 128.43, 128.39, 128.37, 128.33, 128.3, 128.2, 95.8, 93.0, 92.2, 89.1,87.9, 87.5, 86.8, 84.6, 39.1, 37.0, 36.9, 32.2, 29.9, 15.3, 4.5, 4.4, 4.3, 3.7, 3.1. IR (neat) 3098, 3077, 3057, 3024, 2957, 2924, 1636, 1599, 1488, 1441, 1422, 1243, 1170, 1067. HRMS (ESI) Calcd for $C_{14}H_{13}I$, 308.0062; Found, 308.0052.

*((2-Phenylcyclopent-1-en-1-yl)ethynyl)benzene (**32**).* A vial, equipped with a magnetic stir bar, was charged with Cp_2TiCl_2 (3.9 mg, 16 μmol) and zinc dust (43 mg, 66 mmol) and then purged with nitrogen for 5 min. Dry, degassed CH_2Cl_2 (0.5 mL) was added, and the resulting gray slurry was stirred vigorously at room temperature until it took on a blue/green color. A solution of aldehyde **31** (50 mg, 0.31 mmol) and alkynyl iodide **5a** (100 mg, 0.47 mmol) in CH_2Cl_2 (0.5 mL) was then added dropwise. The resulting mixture was stirred at room temperature until TLC indicated full consumption of the starting aldehyde (~2 h). A solution of Ac_2O (40 μL, 0.47 mmol) in CH_2Cl_2 (0.5 mL) was then added over 11 h via a syringe pump. Upon completion of the syringe pump addition, the reaction was heated to 50 °C for ~20 h. The crude mixture was cooled to room temperature, diluted with CH_2Cl_2 (2 mL), and filtered through a plug of silica eluting with 100% Et_2O (55 mL). The filtrate was concentrated under reduced pressure and purified by flash column chromatography eluting with 100% hexanes to provide 15 mg (20%) of **32** as a clear, yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91−7.92 (m, 2 H), 7.45−7.48 (m, 2H), 7.25−7.39 (m, 6 H), 2.89−2.93 (m, 2 H), 2.78−2.82 (m, 2 H), 2.03 (pent, *J* = 7.5 Hz, 2 H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 146.3, 136.6, 131.6, 128.5, 128.3, 128.2, 127.8, 127.2, 124.0, 118.7, 95.3, 88.4, 39.3, 36.1, 22.7. HRMS (ESI) Calcd for $C_{19}H_{16}$, 244.1252; Found, 244.1248.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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