Synthesis of Stereodefined Polysubstituted Olefins. 1. Sequential Intermolecular Reactions Involving Selective, Stepwise Insertion of Pd(0) into Allylic and Vinylic Halide Bonds. The Stereoselective Synthesis of Disubstituted Olefins[1]

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Palladium-catalyzed allylic substitution and cross-coupling reactions have been combined into a sequential procedure to provide a range of disubstituted olefin products starting from two-, three-, and four-carbon common olefin templates. Diverse application of this template strategy is demonstrated in a variety of model studies and in a parallel synthesis (combinatorial) approach to prepare an allylic amine molecular library. An approach toward the preparation of astaxanthin β-D-diglucoside, an interesting antioxidant whose total synthesis has yet to be reported, using the olefin-template approach is also discussed.

Introduction

A major challenge in synthetic chemistry is the efficient stereodefined synthesis of di-, tri-, and tetrasubstituted olefins.[2] Olefins with varying substitution patterns are found ubiquitously in the structure of numerous natural products and pharmaceutical agents.[3] Olefin-containing compounds also serve a very important role as substrates to produce other functionalities such as diols, epoxides, aziridines, and halohydrins, to name just a few. Therefore, the efficient stereoselective synthesis of polysubstituted olefins is an area of intense ongoing synthetic interest.[4−7]

If olefin formation is a central event in the production of the final target, that is, the bonds between the olefinic carbons are established during this event, the approach is convergent because both "halves" of the target can be prepared separately and then brought together in one operation. However, if such procedures lack stereospecificity, the whole synthesis can become jeopardized because of decreased yield and difficulties in product purification because of similarities of the physical properties of olefin stereoisomers. Such approaches to an olefin-containing target include variations of the Wittig reaction.[4,5] Related two-step transformations include the Peterson and Julia olefination reactions.[6,7] The best stereoselectivity in these transformations has been displayed in the formation of cis and trans disubstituted olefin products.[8] A further synthetic consideration with these procedures is that they all involve the addition of a reactive intermediate, that is, an anion, onto a carbonyl group, which is followed by elimination to yield the olefin. This means that substrates are limited to quite simple functionality or the use of protecting groups is necessary.

An alternate strategy to stereoselective olefin synthesis is to start with the olefin carbons of the target bound together in an alkyne precursor. Transition-metal-catalyzed hydrogenation and dissolving metal reduction of alkynes provides cis and trans disubstituted olefins, respectively, with a very high degree of stereoselectivity.[9] Hydroboration[10] and hydroalumination[11] provide cis di-

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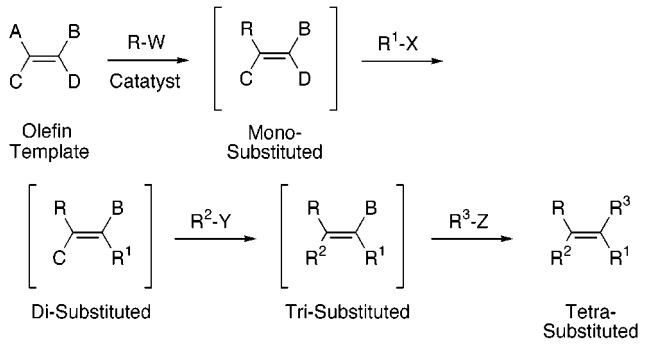
substituted olefins via syn hydrometalation, and electrophilic capture of the aluminate intermediate[12] can provide trisubstituted olefin targets. The use of coordinatively saturated aluminate hydride donors, such as $LiAlH_4$[13] or RedAl[14], provide the corresponding anti hydroaluminated intermediate that can be either quenched to provide the trans product or captured with an electrophile to provide the corresponding trisubstituted olefin.[13c] These reactions require an allylic or homoallylic coordinating functionality, such as an alcohol, to promote the hydroalumination in a regio- and stereoselective fashion and are thus limited to such substrates.

Transition-metal-catalyzed hydro-[15] and carbometalation[16] reactions can produce tri- and tetrasubstituted olefins, respectively. Terminal alkynes can provide trisubstituted olefins quite regio- and stereoselectively via carbometalation, although the carbon fragments are restricted to simple alkyl groups such as methyl. In the absence of some directing influence, internal alkynes tend not to carbometalate with strong regioselectivity unless ready equilibration is possible.[17] Thus, tetrasubstituted olefins are not obtainable with reliable stereoselectivity using such methodology.

Another approach to the stereoselective synthesis of polysubstituted olefins is to start with the double bond intact and suitably functionalized to serve as the building block from which to approach the substituted olefin product. In this regard, metal-catalyzed reactions and, in particular, cross-coupling reactions have been among the most successful approaches. These substitutions are known to proceed with a high degree of stereocontrol, that is, retention of configuration.[18] *The implicit advantage of this approach is that the stereochemistry of the olefin can be strictly controlled, and the overall approach still represents a convergent strategy, depending on the nature of the partners involved.*

Scheme 1



This report discusses approaches to olefin structures using suitably functionalized "olefin templates". These templates are elaborated to a variety of olefin-containing products by selective and sequential reaction of their functional groups by one catalyst in one reaction vessel.[19] The template therefore serves as a building block to allow the product to be constructed in a convergent fashion and in one operation. Such an approach could be considered to be an efficient alternative to the one-step methods discussed above.[4,5] The general strategy for our approach to olefin construction is outlined in Scheme 1.[20] The chemical reactivity of groups A through D can be differentiated on the basis of steric or electronic properties or both. Using a single catalyst, then, these groups can be transformed in a selective and predictable fashion. For example, if only A and D (or A and B) are suitable functional groups (i.e., the remaining substituents are hydrogens), then disubstituted olefin products can be approached. If A, C, and D are functional groups (i.e., B = H), trisubstituted products are possible, and so on. This report details the preparation of disubstituted olefin targets.

We focused on functional groups that could be substituted for in a chemo- and stereoselective fashion using Ni or Pd catalysis. Such catalysis is very flexible, promoting both allylic substitution of stabilized leaving groups[21] with either soft or hard nucleophiles and cross coupling of vinyl halides[18] with compounds possessing activated

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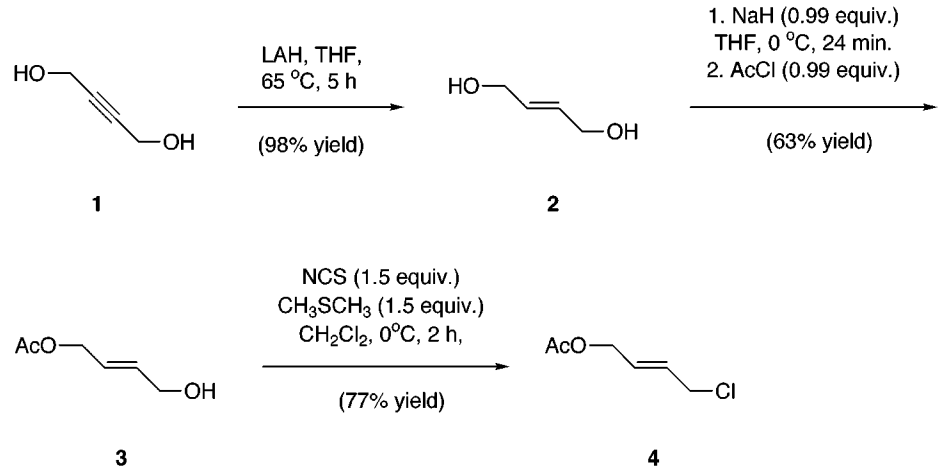
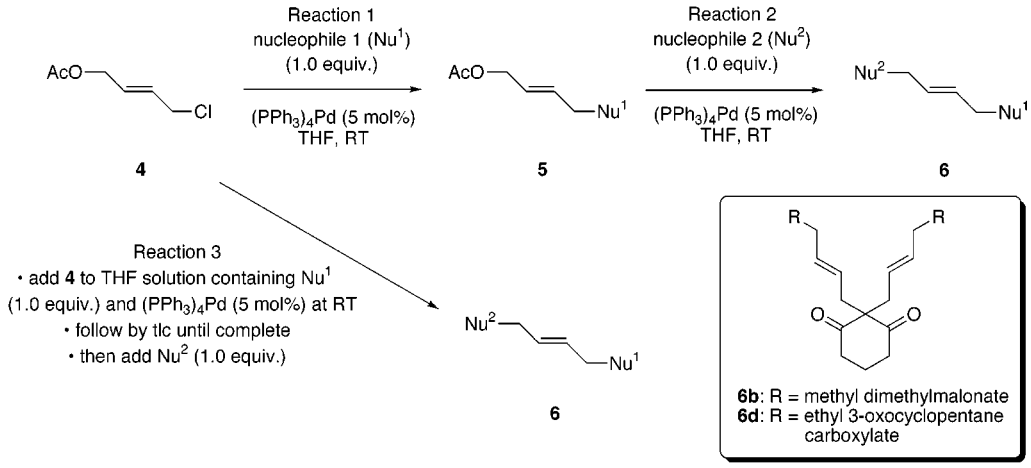
Scheme 2



Scheme 3



C−metal or C−H bonds. We envisioned that these reactions, although mechanistically different, could be combined into one sequence to potentially broaden the general utility of this tandem or sequential reaction methodology. A significant advantage of this olefin-template approach is the inherent chemoselectivity of late transition metals that ligate preferentially to soft ligands, that is, olefins in this case, thereby eliminating the need for protecting-group chemistry.

For this general strategy to be widely applied and easily adapted by other researchers, a key feature will be the availability of templates that are substituted with a number of functional groups possessing widely different chemical reactivities. This implies that such templates must be prepared readily and efficiently and that they must be stable enough for a long shelf life, despite the dense placement of reactive functional groups on these small carbon frameworks. Fortunately, despite the difficulty in preparing all carbon olefin products stereoselectively, which is the main driving force behind this work, there is considerable precedent for the preparation of a variety of geometrically pure functionalized alkenes which we can adopt and modify to prepare our templates. Considerable effort has been invested into the stereoselective production of olefin compounds substituted with halogens, pseudo-halogens, and/or metal moieties.[22] We have prepared templates containing two, three, or four carbons and have embarked on a series of model studies to test template stability to reaction conditions, selectivity of catalyst insertion, and the efficiency of the sequential reaction strategy.

Results and Discussion

The first template we examined was a four-carbon unit that we envisioned would allow for successive selective allylic substitution reactions. Compound **4** was prepared from 1,4-butyne diol which is commercially available and inexpensive (Scheme 2).

A number of Pd-catalyzed substitutions of the Cl on **4** were conducted with carbon nucleophiles, and the transformations were found to be regioselective in the presence of the acetate moiety and stereoselective; that is, none of the cis isomer was observed within the limits of detection of ^{1}H or ^{13}C NMR spectroscopy (see reaction 1 in Scheme 3 and Table 1). A key aspect with this template concept in a solution-phase-synthesis format is that this transformation, that is, the first in this or any sequence, is essentially quantitative and clean. There is only 1 equiv of nucleophile used, and the crude ^{1}H NMR spectrum revealed that only the desired product is present. This prevents undesirable over-reaction with the

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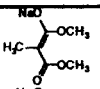
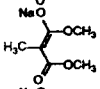
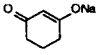
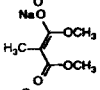
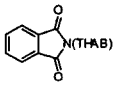
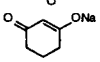
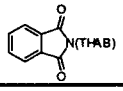
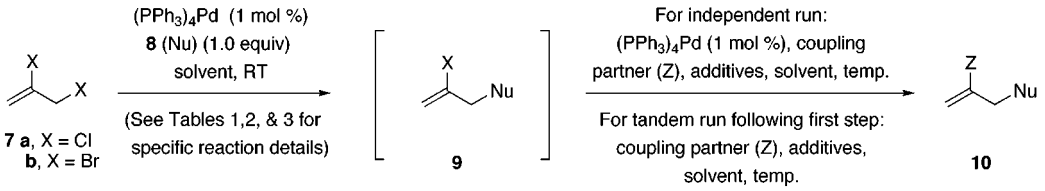
Table 1. Pd-Catalyzed Allylic Substitutions of 1-Acetoxy-4-chloro-2-butene (4) with Soft Nucleophiles

Entry	aNu1	aNu2	Reaction 1 (R1) Product No. (yield)[b]	Reaction 2 (R2) Product No. (yield)[b]	Overall Yield R1 X R2	Reaction 3 Product No. (yield)[b]
1			**5a** (90)	**6a** (83)	75	**6a** (80)
2			**5b** (90)	**6b** (58)	52	**6b** (72)[c]
3			**5c** (90)	**6c** (63)	57	**6c** (66)
4			**5d** (83)	**6d** (58)	48	**6d** (72)[c]
5			**5e** (83)	**6e** (63)	53	**6e** (65)

[a] All anions were generated by dissolving the pro-nucleophile in THF at RT, adding NaH, and stirring for 15 min. [b] Yields were determined on isolated material following silica gel chromatography. [c] Additions with sodium 1,3-cyclohexadionate produced only the diallylated products, and yields are based on incorporating $^1/_2$ equiv of this nucleophile with 1 equiv of **4**.

Scheme 4



first nucleophile at the acetate site in either the first or second step in this two-step sequence and simplifies its purification. Next, substitution of the acetate was carried out (reaction 2 in Scheme 3 and Table 1), and it too proceeded well and with complete stereocontrol. Finally, the reactions were run together in sequence (reaction 3 in Scheme 3 and Table 1), and in every case the yield surpassed the overall recovery obtained by running the reactions separately. Similar results have been obtained with hard, nitrogen-based nucleophiles.[23] Although it does not affect the efficiency of the tandem process per se, additions with sodium 1,3-cyclohexadionate nucleophile resulted in diallylation only (Table 1, entries 2 and 4). Monoallylated product was not detected in the crude ^{1}H NMR spectra.

Next, we wanted to truncate the template by one carbon, which meant combining allylic substitution and cross-coupling procedures. 2,3-Dihalo-1-propenes (**7**) were used to test the viability and effectiveness of the reaction sequence (see Scheme 4 and Table 2). Of course, in this case there is no concern over olefin stereochemistry. Cleavage of the allylic halide, the first step in this dimechanistic sequence, was very rapid and selective in the presence of the vinyl halide.[24] Allylic substitutions with a number of stabilized anions (**8**) on **7** (X = Cl or Br) were high yielding and complete almost instantaneously.

The isolated allylic substitution products (**9**) were then subjected to a variety of coupling reactions at the remaining vinylic halide site (Scheme 4 and Table 3). Coupling with terminal alkynes was the first reaction studied (entries 1−5).[18a] Coupling with 1-hexyne proceeded with some dimerization of the alkyne, which is likely a function of the CuI cocatalyst.[18b] Vinyl chlorides and bromides are less reactive than the corresponding iodide or triflate compounds.[25] Such vinyl functional groups would likely speed up the rate of oxidative insertion and reduce this side reaction; thus less alkyne would be required. Further, in agreement with the literature, piperidine appears to be the base of choice for

Table 2. Pd-Catalyzed Allylic Substitution of 2,3-Dihalo-1-propenes (7) with Soft Nucleophiles

Entry	Starting Dihalide	X	Nucleophile **8** (Nu)[a]	Solvent	Product Number	Percent Yield[b]
1	**7a**	Cl		THF	**9a**	88[c]
2	**7b**	Br		THF	**9b**	90
3	**7b**	Br		THF	**9c**	98
4	**7b**	Br		benzene	**9c**	82
5	**7b**	Br		1,4-dioxane	**9c**	97
6	**7b**	Br		THF	**9d**	98
7	**7b**	Br		benzene	**9d**	98
8	**7b**	Br		1,4-dioxane	**9d**	92

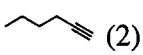
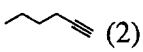
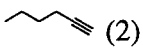
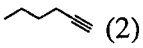
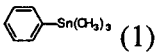
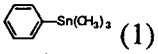
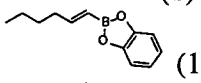
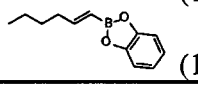
[a] 1 equiv of the nucleophile was used. [b] All yields are reported on isolated material following silica gel chromatography. [c] Diallylated malonate (5%) was also recovered.

(23) (a) Tanigawa, Y.; Nishimura, K.; Kawasaki, A. *Tetrahedron Lett.* **1982**, *23*, 5549−5552. (b) Murahashi, S.-I.; Taniguchi, Y.; Imada, Y.; Tanigawa, Y. *J. Org. Chem.* **1989**, *54*, 3292−3303.

(24) (a) Semmelhack, M. F.; Brickner, S. J. *J. Am. Chem. Soc.* **1981**, *103*, 3945−3947. (b) Castano, A. M.; Aranyos, A.; Szabó, K. J.; Bäckvall, J.-E. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2551−2553.

(25) (a) Ratovelomanana, V.; Linstrumelle, G. *Synth. Commun.* **1981**, *11*, 917−923. (b) Ratovelomanana, V.; Linstrumelle, G. *Tetrahedron Lett.* **1981**, *22*, 3811−3812. (c) Rossi, R.; Carpita, A.; Quirioci, M. G.; Gaudenzi, M. L. *Tetrahedron* **1982**, *38*, 631−637.

Table 3. Pd-Catalyzed Cross Coupling of the Vinyl Halide on Substitution Products 9 with Activated C−H and C−M (M = Metal) Coupling Partners

Entry	Starting Vinyl Halide	Coupling Partner (Z) (No. of Equiv.)	Additives (No. of Equiv.)	Solvent	Temp. (°C)	Product Number	Percent Yield[a]
1	**9a**	 (2)	*n*-butylamine (1), CuI (1 %)	THF	60	**10a**	58
2	**9b**	 (2)	*n*-butylamine (1), CuI (1 %)	THF	60	**10a**	65
3	**9b**	 (2)	piperidine (1), CuI (1 %)	THF	60	**10a**	88
4	**9c**	 (2)	piperidine (1), CuI (1 %)	THF	60	**10c**	65
5	**9d**	 (2)	piperidine (1), CuI (1 %)	THF	60	**10d**	90
6	**9c**	 (1)	LiCl (3)	dioxane	100	**10e**	58
7	**9d**	 (1)	LiCl (3)	dioxane	100	**10f**	76
8	**9c**	 (1.1)	NaOEt (2)	benzene	80	**10g**	75
9	**9d**	 (1.1)	NaOEt (2)	benzene	80	**10h**	60

[a] All yields are reported on isolated material following silica gel chromatography.

these reactions.[18b] Next, we explored coupling between vinyl bromides **9c** and **9d** with trimethyl(phenyl)tin[26] (Table 3, entries 6 and 7). Coupling proceeded well, providing the corresponding products **10e** and **10f**. Coupling between **9c** and **9d** with ((*trans*)-1-hexenyl)-catecholborane[18c] proceeded well, providing diene products **10g** and **10h**, respectively (Table 3, entries 8 and 9). Therefore, the remaining vinyl bromide can be coupled effectively with a wide range of partners to give products possessing diene, enyne, and aryl-substituted alkene moieties.

In a separate operation, nucleophilic substitution and coupling reactions were performed in sequence (tandem). For alkyne coupling, a solution containing CuI, base, and hexyne was added *with no additional Pd catalyst* to the allylic substitution mixture when that reaction was judged complete by TLC, and then the solution was warmed (see Table 4, entries 1−4).

Tandem sequences with trimethyl(phenyl)tin and *E*-1-hexenyl boronic acid as the cross-coupling partners were also conducted (see Table 4, entries 5−8). For both of these sequences, when the allylic substitution was judged complete, the mixture was easily transferred via cannula to a second flask containing the coupling reagent and the appropriate additives in a small volume of solvent that *contained no Pd catalyst*. The reactions were heated as indicated and monitored. Yields obtained in the tandem sequences generally compared favorably with the overall yields of the two reactions performed independently.

We have completed a number of tandem sequences on 1,3-dibromo-1-propene (**11**) to provide 1,2-disubstituted olefins (see Scheme 5). Compound **11**, obtained from Aldrich, was a 60:40 mixture of *E* and *Z* isomers. However, the mixture was sufficient to test the viability of the sequence. Allylic substitution with a number of soft nucleophiles was rapid and highly efficient (>95% yield), and one example is shown in Scheme 5.[27] Cross coupling of **12** with a number of boronic acids proceeded smoothly to give the corresponding disubstituted olefin products **13** and **15**. Sonogashira coupling has been attempted only with hexyne (**14**), and the results are promising. Reaction sequences were carried out on **11** in a manner similar to that described for the sequences involving template **7**. In all tandem sequences attempted, comparable yields to that obtained in independent transformations have been achieved and the crude mixtures were readily purified.

What remained unclear from the allylic substitution reactions with **11** was the stereoselectivity of that transformation. That is, the ratio of *E* to *Z* isomers in the starting material was, at least on the surface, maintained in **12**. Initially, we had anticipated that the *E* and *Z* mixture of 1,3-dibromo-1-propene (**11**) would be funneled into an all-*E* product. This would occur via isomerization of the π-allyl Pd complex to the corresponding σ-bound species that would allow equilibration of the two forms via bond rotation. There is a precedent for such funneling of cis and trans precursor mixtures to all-*E* products in Pd-catalyzed allylic substitution reactions.[23] To that end, *E*-1,3-dibromo-1-propene (*E*-**11**) was prepared using the procedure outlined in Scheme 6.[28−30] Treatment of *E*-**11** with the identical Pd-catalyzed allylic substitution conditions outlined in Scheme 5 with

(26) Stille, J. K. *Pure Appl. Chem.* **1985**, *57*, 1171−1180.

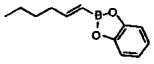
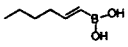
(27) Ratios of cis and trans isomers were determined by ^{1}H NMR spectroscopy on the crude reaction mixture.

(28) Hydrostannylation was performed using the conditions outlined in Jung and Light: Jung, M. E.; Light, L. A. *Tetrahedron Lett.* **1982**, *23*, 3851−3854.

(29) Bromine/tin exchange was effected using the protocol outlined in Eaborn et al.: Eaborn, C.; Najam, A. A.; Walton, D. R. M. *J. Chem. Soc., Perkin Trans. 1* **1972**, 2481−2484.

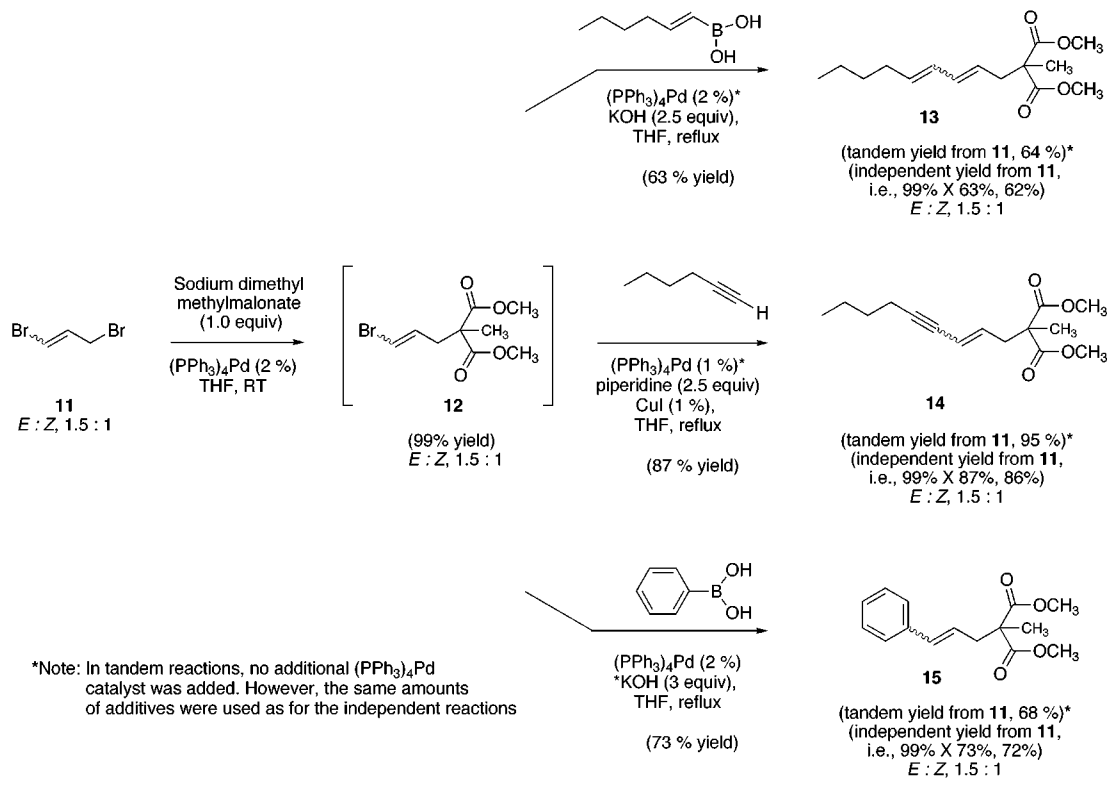
(30) Conversion of the allylic alcohol to the corresponding bromide was done using the following protocol: Corey, E. J.; Kim, C. U.; Takeda, M. *Tetrahedron Lett.* **1972**, *42*, 4339−4342.

Table 4. Pd-Catalyzed Tandem Allylic Substitution/Cross Coupling of 2,3-Halo-1-propenes (7) with Soft Nucleophiles and Activated C−H and C−M (M = Metal) Coupling Partners

entry	starting dihalide	nucleophile Nu (1.0 equiv.)	coupling partner (Z) (No. of equiv.)[a]	additives (No. of equiv.)	solvent	temp. (°C)	product number	percent yield[b,c]
1	**7a**		 (2)	*n*-butylamine (1), CuI (1 %)	THF	60	**10a**	60 (51)
2	**7b**		 (2)	*n*-butylamine (1), CuI (1 %)	THF	60	**10a**	60 (59)
3	**7b**		 (2)	piperidine (1), CuI (1 %)	THF	60	**10c**	78 (64)
4	**7b**		 (2)	piperidine (1), CuI (1 %)	THF	60	**10d**	68 (88)
5	**7b**		 (1)	LiCl (3)	dioxane	100	**10e**	82 (56)
6	**7b**		 (1)	LiCl (3)	dioxane	100	**10f**	59 (70)
7	**7b**		 (1.1)	NaOEt (2)	dioxane	80	**10g**	76 (62)
8	**7b**		 (1.1)	KOH (2)	benzene	80	**10h**	51 (59)

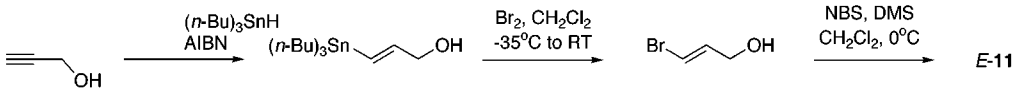
[a] When the allylic substitution was judged complete by TLC analysis, the coupling partner and appropriate additives were then added and the second transformation was pushed to completion. [b] All yields are reported on isolated material following silica gel chromatography. [c] Yields of the corresponding independent two-step sequence with the same reagents and substrates are given in brackets.

Scheme 5



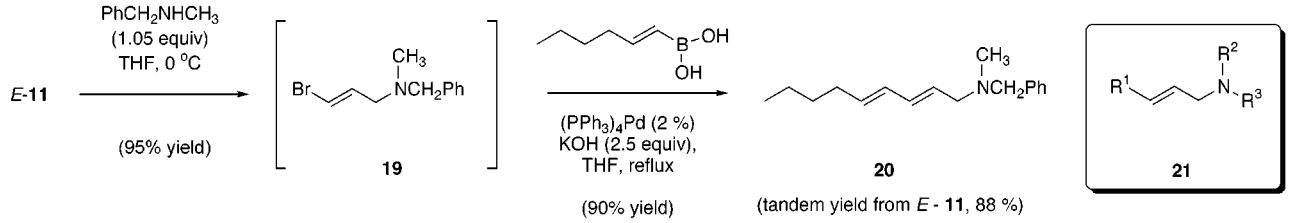
sodium dimethyl methylmalonate nucleophile resulted in a 1.5:1 ratio of *E*-**12**/*Z*-**12**. This indicates that the Pd intermediate has ample time to equilibrate before nucleophilic attack takes place and that 1.5:1 is the thermodynamic product ratio, irrespective of the ratio of **11** entering the transformation. This experiment indicates that the 1,3-dibromo-1-propene template is not apt to be suitable for the stereoselective production of *E* olefin products using Pd-catalyzed allylic substitutions in the first step. Sterically, Br is not large enough to drive the equilibrium to the all-*E* product as has been observed with other larger groups.[23]

Scheme 6

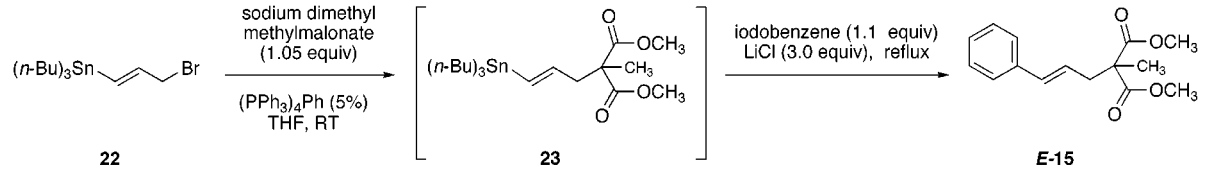


16 **17** (45% yield) **18** (70% yield)

Scheme 7



Scheme 8



22 **23**

Despite the stereoselectivity issues with *E*-**11**, this template and the corresponding *Z* compound are suitable for substitutions that use nucleophiles which are active enough not to require Pd catalysis. For example, suitable nucleophiles would include enolates and nitrogen-based compounds. Although the olefin is activating, such reactions do not involve the double bond per se, and therefore olefin stereochemistry of the starting template should be preserved in the product. A subsequent cross-coupling reaction using Ni or Pd can then take place stereospecifically using a suitable partner. Such sequences have been done using *E*-1,3-dichloro-propene with amine nucleophiles and terminal alkynes (i.e., Sonogashira coupling) as a one-[31] and two-pot sequence.[32] Although this template is conveniently available commercially, vinyl chlorides react sluggishly in most organometallic cross-coupling reactions.[25a,b] Therefore, the development of a reliable protocol for the stereoselective production of *E*-**11** represents a useful advancement for this chemistry. For demonstration purposes, one uncatalyzed allylic substitution/catalyzed cross-coupling sequence is shown in Scheme 7. These tandem procedures are high yielding, as this single example demonstrates, and the stereochemistry was rigorously maintained in all cases attempted providing the all-*E* products.

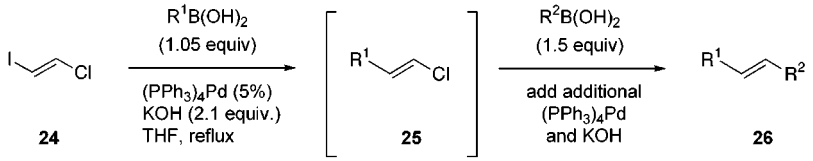
To illustrate the utility of this template strategy, we have used this protocol in a parallel synthesis format to prepare a molecular library containing approximately 600 allylic amine compounds resembling **20** (i.e., **21**) that are presently being screened for biological activity in a variety of therapeutic areas in collaboration with Eli Lilly and Co.[33] Allylic amines are known to possess biological activity in a range of areas. Representative allylic amine drugs include Pyrrobutamine, an antihistamine, and Zimeldine, an antidepressant. The controlled, stepwise nature of the procedure allowed the maximum incorporation of diversity while making product handling as easy as possible for the simultaneous preparation of so many compounds.

To extend the generality of this process for this template substitution pattern, we wanted to ensure that the possibility existed to perform both reactions in the sequence utilizing Pd catalysis without compromising stereoselectivity. To realize this, we had to redesign the template with suitable functionality. Changing the vinyl bromide on *E*-**11** to a vinyl stannane changes the nature of that site from being an oxidative insertion partner to being the metal−metal exchange partner for a cross-coupling reaction. Most importantly, it places a much larger group at this site, which should exert a greater steric effect in the allylic substitution reaction. Providing that the stannane is stable enough to survive a Pd-catalyzed allylic substitution, it should provide exclusively the *E* disubstituted product starting with either *E*- or *Z*-**22**, which was prepared by Corey−Kim allylic bromination of **17**.[30] Treatment of **22** with standard allylic substitution conditions (Scheme 8) cleanly provided **23** as one stereoisomer which was then subsequently coupled in sequence with iodobenzene to provide *E*-**15** selectively. Therefore, by a simple reversal of the role of the terminal vinyl coupling site, a two-component "one-pot" convergent sequence is indeed possible. We are continuing to investigate other pseudo-halide insertion partners, such as phosphonates, at the terminal vinyl site that may provide the *E* product where the bromide failed. This will increase the flexibility and hence utility of this methodology.

We have further shortened the template to just two carbons, providing compound **24**[34] (Scheme 9) which now can be elaborated to the target olefin by successive cross-

(31) Gotteland, J. P.; Halazy, S. *Synlett* **1995**, 931−932.
(32) Alami, M.; Ferri, F.; Gaslain, Y. *Tetrahedron Lett.* **1996**, *37*, 57−58.
(33) Siegel, M. G.; Organ, M. G.; Mayhew, D.; Dixon, C. E.; Cooper, J. T.; Kaldor, S. W. *J. Comb. Chem.*, in press.
(34) Negishi, E.; Okukado, N.; Lovich, S. F.; Luo, F.-T. *J. Org. Chem.* **1984**, *49*, 2629−2632.

Scheme 9



coupling reactions.[35] Work has been done with commercially available dichloroethylene to undergo selective coupling at one Cl site, but over-reaction at both sites has proven difficult to control. In the case of Sonogashira couplings, for example, it has been reported that a minimum 2-fold excess of *cis*-dichloroethylene relative to the alkyne was required to suppress enediyne formation[36] and a 5-fold excess is required for 1,1-dichloroethylene.[37] Both *E*-[38] and *Z*-bis(tri-*n*-butylstannyl)ethylene[39] have been used quite effectively in sequential inter/intramolecular reactions with tethered vinyl iodides to form medium and large ringed structures. However, their satisfactory use in selective monocoupling reactions, to our knowledge, is unknown. Thus, by creation of a template with different insertion or metal coupling partners on it, the reactions with those functional groups should be controllable and perhaps even combinable into a one-pot convergent synthetic strategy. Iodides are reported to be the most reactive of the halide or pseudohalide oxidative insertion functional groups;[25] thus we reasoned that we could react the iodide of **24** in the presence of the chloride without having to resort to using large excesses of the template to prevent overcoupling. This not only makes the coupling process more efficient but makes sequential reactions possible because there would not be any unreacted starting materials left over from the first transformation to interfere with the subsequent step. The reactions carried out to date with a limited number of boronic acids are shown in Scheme **9**, and the data are summarized in Table 5. In all cases, the reaction sequence cleanly provided the desired product without having to resort to high excesses of either the boronic acid or the template.

To demonstrate the utility of this template, we are using it as a central building block in the total synthesis of astaxanthin β-D-diglucoside (**27**)[40] (see retrosynthetic analysis presented in Figure 1), which has yet to be synthesized nonbiologically. Compounds resembling **27** are being synthesized to accelerate the discovery of strongly active oxygen scavengers (antioxidants). These compounds also show promise for use in slowing cancer development and the enhancement of the immune response. The symmetry of **27** will allow us to use template **24** five times in our approach which includes a one-pot sequence for the preparation of the penultimate structure **28** from **24**, **29**, and **30**. We have been able to selectively couple TMS−acetylene to template **24** at the iodo site, which when desilylated provided compound **31**. We have subsequently shown that **31** can be successfully coupled to a model structure of **30** that lacks the hydroxy and ketone moieties. Progress on this synthesis is continuing and will be communicated when the full chain has been assembled.

Table 5. Pd-Catalyzed Tandem Cross-Coupling Sequence with 1-Chloro-2-iodoethylene (24) with a Variety of Boronic Acids

Entry	R^1	[a]R^2	Product (yield)[b]
1			**26a** (50)
2			**26a** (52)
3			**26b** (52)
4			**26b** (65)
5			**26c** (74)[c]

[a] When the first cross coupling was judged complete by TLC analysis, the second coupling partner was then added and the second transformation was pushed to completion. [b] All yields are reported on isolated material following silica gel chromatography. [c] This compound has been reported previously; see: Jeffery, T. *Tetrahedron Lett.* **1992**, *33*, 1989−1992.

In summary, a number of two-, three-, and four-carbon olefin templates have been designed and constructed that are shelf stable and allow for the selective sequential substitution of their functional groups to produce products with the same substitution pattern, in this case, disubstituted olefins. The utility of the method has been demonstrated in a combinatorial synthesis format resulting in the production of a molecular library containing 600 allylic amines which are being screened for biological efficacy in a number of therapeutic areas. Further, other templates are being utilized in the total synthesis of a number of natural products in our laboratories, including astaxanthin β-D-diglucoside.

High conversion in the first step of these sequences is key to the success of the strategy. *This not only precludes any undesired side reactions in subsequent steps with residual starting materials but it also reduces the complexity of purification.* Preliminary data in this report indicate that Pd(0)-catalyzed allylic substitution and cross-coupling reactions can be combined in a convergent one-pot approach to the synthesis of a variety of disubstituted olefin products. Investigations involving other olefin templates, nucleophiles, coupling partners, and catalysts are underway, as is the expansion of this methodology in different synthetic projects. Approaches to tri- and tetrasubstituted olefins have also been achieved using this template methodology, and this will be communicated shortly.

Experimental Section

General Methods. All reaction flasks were prepared by adding a stir bar and sealing the flask with a rubber septum. The flask was then flame-dried and purged with dried argon.

(35) During the revision of this paper, 1-bromo-2-iodoethene was demonstrated to be used in a similar fashion for the preparation of Xerulin; see: Negishi, E.-i.; Alimardanov, A.; Xu, C. *Org. Lett.* **2000**, *2*, 65−67.

(36) Ratovelomanana, V.; Linstrumelle, G. *Tetrahedron Lett.* **1984**, *25*, 6001−6004.

(37) Ratovelomanana, V.; Hammoud, A.; Linstrumelle, G *Tetrahedron Lett.* **1987**, *28*, 1649−1652.

(38) Nicolaou, K. C.; Chakraborty, T. K.; Piscopio, A. D.; Minowa, N.; Bertinato, P. *J. Am. Chem. Soc.* **1993**, *115*, 4419−4420.

(39) (a) Shair, M. D.; Yoon, T.; Chou, T.-C.; Danishefsky, S. J. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2477−2479. (b) Yoon, T.; Shair, M. D.; Danishefsky, S. J.; Schulte, G. K. *J. Org. Chem.* **1994**, *59*, 3752−3754.

(40) Yokoyama, A.; Shizuri, Y.; Misawa, N. *Tetrahedron Lett.* **1998**, *39*, 3709−3712.

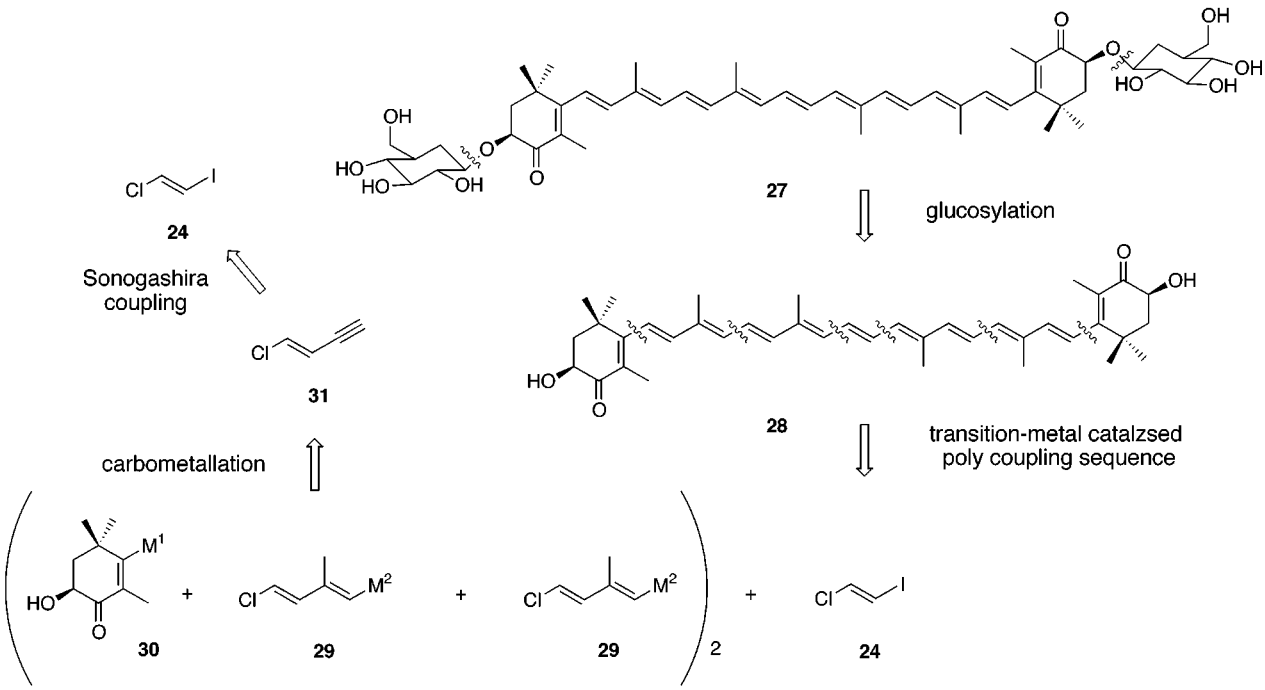


Figure 1. Retrosynthetic analysis for the total synthesis of astaxanthin β-D-diglucoside.

For cases in which a reaction was done under refluxing conditions, the complete glass apparatus was assembled and sealed with a septum on the top of the condenser, after which it was flame-dried and purged. THF was distilled from sodium benzophenone ketyl. Dioxane was distilled over sodium metal. Benzene was distilled from CaH_2. All reagents were commercially available and were used without further purification unless otherwise specified.

***E*-1-Acetyl-2-buten-4-ol (3).** To a 250 mL flask affixed with a reflux condenser was added 50 mL of THF, and the solution was cooled to 0 °C. When at temperature, 1.06 g of lithium aluminum hydride (LAH) (28 mmol) was added. In a separate 100 mL flask were added 50 mL of THF and 2.0 g of 2-butyne-1,4-diol (**1**) (23 mmol). After complete dissolution of **1**, the solution was cooled to 0 °C and it was added via cannula to the LAH suspension over 30 min. Following complete addition of **1**, the reaction mixture was refluxed for 3 h and cooled to 0 °C, and 3 M NaOH was added slowly until no gas evolution was observed. The reaction mixture was then adjusted to a pH of 8; silica gel was added, and the solvent was removed in vacuo. The free-flowing product/silica gel mixture was then loaded on top of a prepacked silica gel column and flashed (50% ethyl acetate in hexanes), providing 2.0 g of **2** (99% yield) as a pale yellow oil.

To a 250 mL flask (cooled to 0 °C) was added 50 mL of dry THF and 272 mg of sodium hydride (60% oil dispersion, 0.11 mmol). To this, 1.0 g of **2** (11 mmol) was added dropwise, and the solution was stirred for 45 min at room temperature, at which time 891 mg of acetyl chloride (0.81 mL, 11 mmol) was added dropwise over 30 min. The reaction was stirred for 1 h at room temperature and then quenched with saturated ammonium chloride solution. The phases were separated; the aqueous layer was extracted with ether (three times), and the pooled organic layer was washed with water and dried over anhydrous $MgSO_4$. Following solvent removal in vacuo, the mixture was purified by flash chromatography (30% ether in hexanes), providing 943 mg of **3** (63% yield) as a clear, colorless oil. IR (thin film): 3418 (br), 1737 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 5.95−5.75 (m, 2H), 4.59−4.57 (d, J = 5.2 Hz, 2H), 4.19−4.17 (d, J = 4.2 Hz, 2H), 2.07 (s, 3H), 1.68 (s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz, APT pulse sequence: evens up (+), odds down (−)): δ 170.83(+), 133.60(−), 125.05(−), 64.28(+), 62.69(+), 20.94(−). HRMS calcd for $C_6H_{10}O_3 + H^+$ ($M + H^+$): 131.0701. Found: 131.0706.

***E*-1-Acetyl-4-chloro-2-butene (4).** To a 50 mL flask was added 20 mL of CH_2Cl_2. The flask was cooled to 0 °C, and 298 mg of dimethyl sulfide (0.34 mL, 4.6 mmol) and 612 mg of *N*-chlorosuccinimide (4.6 mmol) were added. The white suspension was stirred for 15 min, at which point 500 mg of *E*-1-acetyl-2-buten-4-ol (**3**) (3.82 mmol) was added dropwise. The reaction mixture was allowed to come to room temperature over 4 h, after which it was quenched with water. The phases were then separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were then dried over anhydrous $MgSO_4$, after which the solvent was removed in vacuo. The crude mixture was then purified by flash chromatography (5% ether in hexanes), providing 435 mg of **4** (77% yield) as a clear oil. IR (thin film): 1740 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 5.88−5.84 (m, 2H), 4.55−4.54 (d, J = 3.7 Hz, 2H), 4.03−4.02 (d, J = 5.1 Hz, 2H), 2.04 (s, 3H). ^{13}C NMR ($CDCl_3$): 172.13, 131.28, 130.07, 65.15, 45.45, 22.41. Anal. Calcd for $C_6H_9ClO_2$: C, 48.50; H, 6.11. Found: C, 48.31; H, 5.93.

Because of the large number of model compounds prepared in this study, only the synthetic procedures for the preparation of final targets of tandem sequences will be reported, along with their spectral characterizations. Conditions and yields for the independently performed substitution and cross-coupling reactions are outlined in the reaction schemes and tables throughout this paper in sufficient detail to carry out these transformations in any laboratory.

The general procedure for the tandem reaction of *E*-1-acetyl-4-chloro-2-butene (template **4**) is outlined below. All reactions in this series were done following the procedure for the preparation of **6a**.

Compound 6a. To a 10 mL flask was added 2.0 mL of THF and 14.8 mg of sodium hydride (60% oil dispersion, 0.37 mmol). To this suspension was added 49.2 mg of dimethyl methylmalonate (45 μL, 0.34 mmol). The mixture was stirred for 15 min, and then 19.4 mg of tetrakis(triphenylphosphine)-palladium (5%, 0.018 mmol) was added. Compound **4** (50 mg, 0.34 mmol) was added, and the reaction was followed by TLC until complete. To a second 10 mL flask was added 2 mL of THF, 14.8 mg of sodium hydride (60% oil dispersion, 0.37 mmol), and 52.6 mg of ethyl 2-oxocyclopentane carboxylate (50 μL, 0.34 mmol). After being stirred for 15 min, the second solution was then transferred via cannula to the first reaction mixture. When the reaction was complete, the mixture was

quenched with saturated NH_4Cl. The layers were separated, and the aqueous layer was extracted with ether (three times). The combined organic layers were washed with water and dried over anhydrous $MgSO_4$. Following solvent removal in vacuo, the mixture was purified by flash chromatography (5% diethyl ether in hexanes), providing 92 mg of compound **6a** (80% yield) as a clear oil. IR (thin film): 1747, 1732 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 5.34−5.38 (m, 2H), 4.12 (q, J = 7.4 Hz, 2H), 3.67 (s, 6H), 1.86−2.57 (m, 10H), 1.33 (s, 3H), 1.21 (t, J = 7.4 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 214.51, 172.24, 170.77, 129.38, 128.66, 61.42, 60.03, 53.60, 52.46, 38.83, 37.84, 36.55, 32.03, 19.43, 19.77, 14.04. Anal. Calcd for $C_{18}H_{26}O_7$: C, 61.00; H, 7.39. Found: C, 60.92; H, 7.42.

Compound 6b. Following the tandem protocol for the preparation of **6a**, 50 mg of **4** (0.34 mmol), 14.8 mg of sodium hydride (60% oil dispersion, 0.37 mmol), 44.8 mg of dimethyl methylmalonate (41 μL, 0.31 mmol), 14.8 mg of sodium hydride (60% oil dispersion, 0.37 mmol), 37.3 mg of 1,3-cyclohexadione (0.34 mmol), and 19.4 mg of tetrakis(triphenylphosphine)-palladium (5%, 0.017 mmol) gave after flash chromatography (40% ether in hexanes) 62 mg of compound **6b** (72% yield) as a clear oil. IR (thin film): 1732, 1695 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 5.31−5.17 (m, 4H), 3.66 (s, 12H), 2.52−2.36 (m, 12H), 1.86 (m, 2H), 1.28 (s, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 209.74, 172.11, 128.85, 128.67, 68.36, 53.52, 52.38, 39.44, 38.99, 38.67, 19.71, 16.48. HRMS calcd for $C_{26}H_{36}O_{10}$ (M^+): 509.2369. Found: 509.2368.

Compound 6c. Following the tandem protocol for the preparation of **6a**, 50 mg of **4** (0.34 mmol), 14.8 mg of sodium hydride (60% oil dispersion, 0.37 mmol), 49.2 mg of dimethyl methylmalonate (44.8 μL, 0.34 mmol), 62.3 mg of potassium phthalimide (0.34 mmol), 146 mg of tetrahexylammonium bromide (0.34 mmol), and 19.4 mg of tetrakis(triphenylphosphine)palladium (5%, 0.017 mmol) gave after flash chromatography (25% ether in hexanes) 77 mg of compound **6c** (66% yield) as a clear, colorless oil. IR (thin film): 1771, 1715 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.66−7.82 (m, 4H), 5.55−5.61 (m, 2H), 4.19 (d, J = 5.2 Hz, 2H), 3.65 (s, 6H), 2.53 (d, J = 5.9 Hz, 2H), 1.33 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 172.06, 167,73, 133.87, 132.10, 128.81, 127.94, 123.18, 53.55, 52.39, 39.24, 38.47, 19.86. HRMS calcd for $C_{18}H_{19}O_6N + H^+$ ($M + H^+$): 346.1290. Found: 346.1306.

Compound 6d. Following the tandem protocol for the preparation of **6a**, 25 mg of **4** (0.17 mmol), 7.4 mg of sodium hydride (60% oil dispersion, 0.19 mmol), 26.3 mg of ethyl 2-oxocyclopentane carboxylate (25 μL, 0.17 mmol), 7.4 mg of sodium hydride (60% oil dispersion, 0.19 mmol), 18.9 mg of 1,3-cyclohexadione (0.17 mmol), and 9.7 mg of tetrakis-(triphenylphosphine)palladium (5%, 0.009 mmol) gave after flash chromatography (40% ether in hexanes) 64.5 mg of compound **6d** (72% yield) as a clear, colorless oil. IR (thin film): 1748, 1722, 1694 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 5.20−5.29 (m, 4H), 4.10 (q, J = 7.4 Hz, 4H), 1.83−2.52 (m, 26H), 1.20 (t, J = 7.4 Hz, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 214.40, 210.00, 170.86, 129.28, 128.61, 68.31, 61.39, 59.84, 39.65, 39.31, 38.09, 36.41, 32.14, 19.48, 16.51, 14.04. HRMS calcd for $C_{30}H_{40}O_8 + H^+$ ($M + H^+$): 529.2802. Found: 529.2799.

Compound 6e. Following the tandem protocol for the preparation of **6a**, 25 mg of **4** (0.17 mmol), 7.4 mg of sodium hydride (60% oil dispersion, 0.19 mmol), 24.9 mg of ethyl 2-oxocyclopentane carboxylate (25 μL, 0.34 mmol), 31.3 mg of potassium phthalimide (0.17 mmol), 87.7 mg of tetrahexylammonium bromide (0.17 mmol), and 9.7 mg of tetrakis(triphenylphosphine)palladium (5%, 0.009 mmol) gave after flash chromatography (25% ether in hexanes) 39 mg of **6e** (65% yield) as a clear, colorless oil. IR (thin film): 1738 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): 7.83−7.67 (m, 4H), 5.59−5.56 (m, 2H), 4.21 (m, 2H), 4.11 (q, J = 7.4 Hz, 2H), 2.61−1.16 (m, 8H), 1.19 (t, J = 7.4 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 214.45, 170.85, 167.81, 133.94, 132.16, 129.03, 127.91, 123.26, 61.43, 59.84, 39.35, 38.07, 36.05, 32.11, 19.52, 14.03. HRMS calcd for $C_{20}H_{21}O_5N$: 355.1420. Found: 355.1428.

The general procedure for the sequential reaction of 2,3-dibromo-1-propene (**7b**) with stabilized nucleophiles (allylic substitution) and hexyne (Sonogashira coupling) is outlined below for the preparation of compound **10a**.

Compound 10a. To a 10 mL flask was added 34.9 mg of NaH (60% mineral oil dispersion, 0.79 mmol, 1.0 equiv) and 5.0 mL of THF. To this suspension was added 158.6 mg of dimethyl malonate (0.79 mmol, 1.0 equiv) dropwise, and the solution was stirred for 15 min at room temperature. The addition of 46.0 mg of tetrakis(triphenylphosphine)palladium-(0) (0.039 mmol, 5 mol %) was followed by 158.6 mg of 2,3-dibromo-1-propene (**7b**) (0.79 mmol, 1.0 equiv). When the reaction's progress was deemed complete by TLC analysis (which was typically <1 min for all nucleophiles), a THF solution (3.0 mL) containing hexyne (195.5 mg, 2.38 mmol, 3 equiv), CuI (7.56 mg, 0.040 mmol, 5 mol %), and piperidine (135.1 mg, 1.59 mmol, 2 equiv) was added via cannula. The reaction was then warmed to 60 °C, and the progress was again monitored by TLC analysis. When the reaction was complete, the solution was cooled to room temperature and quenched with saturated NH_4Cl (5.0 mL). The layers were separated; the aqueous layer was twice extracted with ether, and the organic layers were pooled and dried over anhydrous $MgSO_4$. Solvent removal in vacuo and flash chromatography (5% ethyl acetate in hexanes) provided 120 mg of **10a** (60% yield) as a yellow oil. IR (thin film): 1741 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 5.27 (s, 1H), 5.22 (s, 1H), 3.73 (s, 6H), 2.27 (d, J = 7.5 Hz, 2H), 2.29 (t, J = 7.5 Hz, 1H), 1.46 (m, 6H), 0.91 (t, J = 7.5 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 169.2, 127.9, 122.0, 91.6, 79.3, 52.5, 50.6, 36.6, 30.7, 21.9, 18.9, 13.5. HRMS m/z (M^+) calcd for $C_{14}H_{20}O_4$: 252.1361. Found: 252.1361.

Compound 10c. Following the general procedure for the preparation of **10a**, 60.0 mg of **7b** (0.30 mmol, 1.0 equiv), 46.0 mg of dimethyl methylmalonate (0.32 mmol, 1.05 equiv), 14.4 mg of NaH (60% mineral oil dispersion, 0.36 mmol, 1.2 equiv), 6.9 mg of tetrakis(triphenylphosphine)palladium(0) (0.006 mmol, 2 mol %), 49.3 mg of 1-hexyne (0.60 mmol, 2.0 equiv), 63.9 mg of piperidine (0.75 mmol, 2.5 equiv), and 1.14 mg of CuI (0.006 mmol, 2 mol %) afforded 62.4 mg of **10c** (78% yield) as a yellow oil. IR (thin film): 1737 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 5.36 (d, J = 2.2 Hz, 1H), 5.19 (s, 1H), 3.71 (s, 6H), 2.78 (s, 2H), 2.26 (t, J = 7.0 Hz, 2H), 1.47 (s, 3H), 1.45 (m, 4H), 0.90 (t, J = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz, APT pulse sequence: evens up (+), odds down (−)): δ 173.7-(+), 128.3(+), 126.2(+), 92.7(+), 82.3(+), 55.1(+), 54.0(−), 44.0-(+), 32.2(+), 23.6(+), 21.1(−), 20.6(+), 15.1(−).

Compound 10d. Following the general procedure for the preparation of **10a**, 75.0 mg of **7b** (0.38 mmol, 1.0 equiv), 58.5 mg of ethyl 2-oxocyclopentane carboxylate (0.38 mmol, 1.0 equiv), 15.0 mg of NaH (60% mineral oil dispersion, 0.38 mmol, 1.0 equiv), 8.7 mg of tetrakis(triphenylphosphine)palladium-(0) (0.008 mmol, 2 mol %), 92.5 mg of 1-hexyne (1.13 mmol, 3.0 equiv), 47.9 mg of piperidine (0.56 mmol, 1.5 equiv), and 1.4 mg of CuI (0.008 mmol, 2 mol %) afforded 62.4 mg of **10c** (68% yield) as a yellow oil. IR (thin film): 1754, 1725 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 5.23 (d, J = 1.5 Hz, 1H), 5.20 (s, 1H), 4.14 (q, J = 7.4 Hz, 2H), 2.69 (dd, J = 14.0, 8.5 Hz, 2H), 2.26 (m, 5H), 1.99 (m, 2H), 1.44 (m, 5H), 1.24 (t, J = 7.4 Hz, 3H), 0.90 (t, J = 7.4 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz, APT pulse sequence: evens up (+), odds down (−)): δ 214.3-(+), 170.5(+), 127.2(+), 124.2(+), 91.8(+), 80.7(+), 65.2(+), 61.5(+), 60.0(+), 40.7(+), 38.0(+), 31.6(+), 22.0(+), 19.6(+), 18.9(+), 13.6(−), 13.5(−). HRMS m/z (M^+) calcd for $C_{17}H_{24}O_3$: 276.1726. Found: 276.1717.

The general procedure for the sequential reaction of 2,3-dibromo-1-propene (**7b**) with stabilized nucleophiles (allylic substitution) and trimethylphenyltin (Stille coupling) is outlined below for the preparation of compound **10e**.

Compound 10e. To a 10 mL flask was added 3.5 mg of NaH (60% mineral oil dispersion, 0.15 mmol, 1.05 equiv) and 2.0 mL of 1,4-dioxane. To this suspension was added 22.2 mg of dimethyl methylmalonate (0.15 mmol, 1.1 equiv) dropwise, and the solution was stirred for 15 min at room temperature. The addition of 3.2 mg of tetrakis(triphenylphosphine)palladium-(0) (0.003 mmol, 2 mol %) was followed by 27.6 mg of 2,3-dibromo-1-propene (**7b**) (0.14 mmol, 1.0 equiv). When the

reaction's progress was deemed complete by TLC analysis, trimethyltin (50 mg, 0.207 mmol, 1.5 equiv) and LiCl (17.5 mg, 0.41 mmol, 3 equiv) were added directly to the mixture. The reaction was then warmed to 95 °C, and the progress was again monitored by TLC analysis. When the reaction was complete, the solution was cooled to room temperature and quenched with saturated NH_4Cl (1.0 mL). The layers were separated; the aqueous layer was twice extracted with ether, and the organic layers were pooled and dried over anhydrous $MgSO_4$. Solvent removal in vacuo and flash chromatography (10% ether in pentane) provided 120 mg of **10e** (82% yield) as a yellow oil. IR (thin film): 3081, 1736 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.28 (m, 5H), 5.26 (s, 1H), 5.10 (s, 1H), 3.74 (s, 6H), 3.16 (s, 2H), 1.31 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 172.1, 144.5, 141.5, 128.0, 127.4, 126.8, 118.2, 53.4, 52.1, 40.6, 19.9. HRMS *m/z* (M^+) calcd for $C_{15}H_{18}O_4$: 262.1205. Found: 262.1208.

Compound 10f. Following the general procedure for the preparation of **10e**, 3.5 mg of NaH (60% mineral oil dispersion, 0.15 mmol, 1.1 equiv), 21.7 mg of ethyl 2-oxocyclopentane carboxylate (0.14 mmol, 1.05 equiv), 26.4 mg of **7b** (0.13 mmol, 1.0 equiv), 4.6 mg of tetrakis(triphenylphosphine)palladium-(0) (0.004 mmol, 3%), 40 mg of trimethyltin (0.17 mmol, 1.25 equiv), and 17 mg of LiCl (0.40 mmol, 3 equiv) afforded 21 mg of **10f** (59% yield) as a clear oil. IR (thin film): 3081, 1752, 1723 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.29 (m, 5H), 5.26 (s, 1H), 5.10 (s, 1H), 3.96 (m, 2H), 3.31 (d, J = 14.0 Hz, 1H), 2.82 (d, J = 14.0 Hz, 1H), 2.33 (m, 2H), 2.01 (m, 2H), 1.83 (m, 2H), 1.17 (t, J = 7.4 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 214.1, 170.1, 145.0, 141.4, 128.1, 127.6, 126.8, 117.1, 61.4, 60.7, 39.1, 37.7, 32.0, 19.4, 13.9. HRMS *m/z* (M^+) calcd for $C_{17}H_{20}O_3$: 272.1412. Found: 272.1415

The general procedure for the sequential reaction of 2,3-dibromo-1-propene (**7b**) with stabilized nucleophiles (allylic substitution) and (*E*)-1-hexenyl-catecholborane (Suzuki coupling) is outlined below for the preparation of compound **10g**.

Compound 10g. To a 10 mL flask was added 7.0 mg of NaH (60% mineral oil dispersion, 0.29 mmol, 1.2 equiv) and 2.0 mL of 1,4-dioxane. To this suspension was added 38.9 mg of dimethyl methylmalonate (0.27 mmol, 1.1 equiv) dropwise, and the solution was stirred for 15 min at room temperature. The addition of 5.6 mg of tetrakis(triphenylphosphine)-palladium(0) (0.005 mmol, 2 mol %) was followed by 48.4 mg of **7b** (0.24 mmol, 1.0 equiv). When the reaction's progress was deemed complete by TLC analysis, (*E*)-1-hexenyl-catecholborane (54 mg, 0.27 mmol, 1.1 equiv) and 483 μL of a 2 M NaOEt solution (0.48 mmol, 2 equiv) were quickly added directly to the mixture. The reaction was then warmed to 55 °C, and the progress was again monitored by TLC analysis. When the reaction was complete, the solution was cooled to room temperature and quenched with saturated NH_4Cl (1.0 mL). The layers were separated, the aqueous layer was twice extracted with ether, and the organic layers were pooled and dried over anhydrous $MgSO_4$. Solvent removal in vacuo and flash chromatography (5% ether in pentane) provided 49 mg of **10g** (76% yield) as a clear oil. IR (neat): 1737 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 5.99 (d, J = 15.5 Hz, 1H), 5.70 (dt, J = 15.5, 7.4 Hz, 1H), 5.03 (s, 1H), 4.79 (s, 1H), 3.70 (s, 6H), 2.85 (s, 2H), 2.06 (m, 2H), 1.38 (s, 3H), 1.34 (m, 4H), 0.89 (t, J = 7.4 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 172.6, 141.3, 132.3, 131.2, 116.6, 54.0, 52.4, 36.7, 32.5, 31.5, 22.3, 20.2, 13.9. HRMS *m/z* (M^+) calcd for $C_{15}H_{24}O_4$: 268.1675. Found: 268.1684.

Compound 10h. Following the general procedure for the preparation of **10g**, 6.3 mg of NaH (60% mineral oil dispersion, 0.26 mmol, 1.05 equiv), 39.3 mg of ethyl 2-oxocyclopentane carboxylate (0.25 mmol, 1.0 equiv), 50.3 mg of **7b** (0.25 mmol, 1.0 equiv), 5.8 mg of tetrakis(triphenylphosphine)palladium-(0) (0.005 mmol, 2%), 48 mg of (*E*)-1-hexenylboronic acid (0.38 mmol, 1.5 equiv), and 314 μL of a 2 M KOH solution (0.63 mmol, 2.5 equiv) afforded 36 mg of **10f** (51% yield) as a clear oil. IR (neat): 1753, 1726 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 6.00 (d, J = 16.2 Hz, 1H), 5.70 (dt, J = 16.2, 6.6 Hz, 1H), 4.99 (s, 1H), 4.80 (s, 1H), 4.14 (q, J = 7.0 Hz, 2H), 2.89 (d, J = 14.7 Hz, 1H), 2.61 (d, J = 14.7 Hz, 1H), 2.44 (m, 2H), 2.02 (m, 4H), 1.34 (m, 6H), 1.24 (t, J = 7.0 Hz, 3H), 0.89 (t, J = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 214.9, 171.0, 141.9, 132.4, 131.6, 116.3, 61.5, 60.4, 38.1, 35.1, 32.5, 32.2, 31.4, 22.2, 19.5, 14.0, 13.9. HRMS *m/z* (M^+) calcd for $C_{17}H_{26}O_3$: 278.1882. Found: 278.1891.

Compound 12. Into a 100 mL flask was added 240 mg of sodium hydride (60% mineral oil dispersion, 6.0 mmol, 1.2 equiv) and 35 mL of dry THF. Slow addition of 804 mg of dimethyl methylmalonate (5.5 mmol, 1.1 equiv) was followed by the addition of 9.0 mg of tetrakis(triphenylphosphine)-palladium(0) (0.008 mmol, 0.16%) and 1.0 g of 1,3-dibromo-1-propene (**12**) (5.0 mmol, 1.0 equiv, 1.5:1 mixture of geometric isomers). When complete, the reaction was quenched with 10 mL of water, the layers were separated, and the aqueous layer was twice extracted with ether. The combined organic layers were dried over anhydrous $MgSO_4$. Following solvent removal in vacuo, flash chromatography (5% ethyl acetate in hexanes) provided 1.31 g of **12** (99% yield) as a clear oil. The spectral analysis was performed on the mixture of geometric isomers. IR (thin film): 1734 cm^{-1}. Anal. Calcd for $C_9H_{13}O_4Br$: C, 40.77; H, 4.94. Found: C, 40.55; H, 5.00. ^1H NMR ($CDCl_3$, 300 MHz) δ *E* isomer: 6.31 (m, 1H), 6.10 (m, 1H), 3.74, (s, 6H), 2.79 (dd, J = 6.6, 1.5 Hz, 2H), 1.44 (s, 3H); *Z* isomer: 6.10 (m, 2H), 3.73 (s, 6H), 2.59 (d, J = 7.4 Hz, 2H), 1.41 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz, APT pulse sequence: evens up (+), odds down (−)) δ *E* isomer: 171.9(+), 132.1(−), 129.3(−), 53.3(+), 52.5(−), 35.9(+), 20.0(−); *Z* isomer: 171.8(+), 132.1(−), 129.3(−), 53.1(+), 52.5(−), 39.1(+), 19.9(−).

Preparation of 13. Following the general procedure outlined for the preparation of **10g**, 17.6 mg of sodium hydride (60% mineral oil dispersion, 0.44 mmol, 1.1 equiv), 58.5 mg of dimethyl methylmalonate (0.40 mmol, 1.0 equiv), 9.2 mg of tetrakis(triphenylphosphine)palladium(0) (0.008 mmol, 2%), 80 mg of 1,3-dibromo-1-propene (**11**) (0.40 mmol, 1.0 equiv), 81.8 mg of hexenylboronic acid (0.64 mmol, 1.6 equiv), and 500 μL of a 2 M KOH solution (1.0 mmol, 2.5 equiv) afforded 69 mg of **13** (64% yield). The spectral analysis was performed on the mixture of geometric isomers. IR (thin film): 1737 cm^{-1}. HRMS *m/z* (M^+) calcd for $C_{15}H_{24}O_4$: 268.1675. Found: 268.1674. ^1H NMR ($CDCl_3$, 300 MHz) δ *E* isomer: 6.01 (m, 2H), 5.60 (dt, J = 14.0, 7.0 Hz, 1H), 5.38 (dt, J = 14.0, 7.4 Hz, 1H), 3.70 (s, 6H), 2.57 (d, J = 7.4 Hz, 2H), 2.07 (m, 2H), 1.38 (s, 3H), 1.30 (m, 4H), 0.89 (t, J = 7.4 Hz, 3H); *Z* isomer: 6.27 (dd, J = 14.7, 11.0 Hz, 1H), 6.01 (m, 1H), 5.70 (dt, J = 14.7, 7.0 Hz, 1H), 5.15 (dt, J = 10.3, 8.1 Hz, 1H), 3.70 (s, 6H), 2.74 (d, J = 8.1 Hz, 2H), 2.07 (m, 2H), 1.40 (s, 3H), 1.30 (m, 4H), 0.90 (t, J = 7.4 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ *E* isomer: 172.4, 134.8, 134.3, 129.7, 124.7, 53.9, 52.4, 39.0, 32.2, 31.37, 22.2, 19.88, 13.87; *Z* isomer: 172.4, 136.6, 135.2, 125.1, 122.1, 53.8, 52.4, 33.7, 32.5, 31.43, 22.2, 19.79, 14.06.

Compound 14. Following the general procedure outlined in the preparation of **10a**, 60 mg of **11** (0.30 mmol), 46.0 mg of dimethyl methylmalonate (0.32 mmol, 1.05 equiv), 13.2 mg of NaH (60% mineral oil dispersion, 0.33 mmol, 1.1 equiv), 7.0 mg of tetrakis(triphenylphosphine)palladium(0) (0.006 mmol, 2 mol %), 49.3 mg of 1-hexyne (0.60 mmol), 63.9 mg of piperidine (0.75 mmol, 2.5 equiv), and 1.1 mg of CuI (0.006 mmol, 2 mol %) yielded 76 mg of **10** (95% yield). The spectral analysis was performed on the mixture of geometric isomers. IR (thin film): 1783, 1737 cm^{-1}. HRMS *m/z* (M^+) calcd for $C_{15}H_{22}O_4$: 266.1518. Found: 266.1508. ^1H NMR ($CDCl_3$, 300 MHz) δ *E* isomer: 5.86 (dt, J = 15.8, 7.5 Hz, 1H), 5.51 (d, J = 15.8 Hz, 1H), 3.71 (s, 6H), 2.61 (d, J = 7.5 Hz, 2H), 2.25 (dt, J = 7.5, 1.5 Hz, 2H), 1.48 (m, 4H), 1.36 (s, 3H), 0.89 (t, J = 7.5 Hz, 3H); *Z* isomer: 5.68 (dt, J = 11.8, 7.5 Hz, 1H), 5.55 (d, J = 11.8 Hz, 1H), 3.71 (s, 6H), 2.85 (d, J = 7.5 Hz, 2H), 2.31 (dt, J = 7.5, 2.2 Hz, 2H), 1.48 (m, 4H), 1.40 (s, 3H), 0.90 (t, J = 7.4 Hz, 3H). ^{13}C NMR ($CDCl_3$, 300 MHz, APT pulse sequence: evens up (+), odds down (−)) δ *E* isomer: 172.0(+), 136.0(−), 114.4(−), 90.1(+), 76.7(+), 53.5(+), 52.4(−), 39.2(+), 30.7(+), 21.9(+), 19.9(−), 18.9(+), 13.5(−); *Z* isomer: 172.2(+), 135.2(−), 113.4(−), 95.6(+), 78.5(+), 53.6(+), 52.5(−), 36.0(+), 30.8(+), 21.9(+), 19.8(−), 19.1(+), 13.5(−).

Compound 15. Following the general procedure outlined for the preparation of **10g**, 8.6 mg of sodium hydride (60% mineral oil dispersion, 0.36 mmol, 1.2 equiv), 43.8 mg of

dimethyl methylmalonate (0.30 mmol, 1.0 equiv), 3.5 mg of tetrakis(triphenylphosphine)palladium(0) (0.003 mmol, 1%), 60 mg of 1,3-dibromo-1-propene (**11**) (0.30 mmol, 1.0 equiv), 43.9 mg of phenyl boronic acid (0.36 mmol, 1.2 equiv), and 375 μL of a 2 M KOH solution (0.75 mmol, 2.5 equiv) afforded 79 mg of **15** (68% yield). The spectral analysis was performed on the mixture of geometric isomers. IR (neat): 3082, 3055, 1737 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ *E* isomer: 7.20 (m, 5H), 6.51 (d, $J = 15.4$ Hz, 1H), 6.05 (dt, $J = 15.4$, 7.0 Hz, 1H), 3.68 (s, 6H), 2.72 (d, $J = 7.4$ Hz, 2H), 1.41 (s, 3H); *Z* isomer: 7.20 (m, 5H), 6.39 (d, $J = 12.0$ Hz, 1H), 5.50 (dt, $J = 12.0$, 7.0 Hz, 1H), 3.63 (s, 6H), 2.88 (d, $J = 7.0$ Hz, 2H), 1.35 (s, 3H). ^{13}C ($CDCl_3$, 75 MHz): δ 174.0(+), 173.9(+), 138.2(+), 138.1(+), 135.7(−), 133.9(−), 130.3(−), 130.0(−), 129.8(−), 129.3(−), 128.4(−), 127.8(−), 127.4(−), 125.7(−), 55.9(+), 55.6(+), 54.1(−), 52.8(−), 41.0(+), 35.7(+), 20.35(−), 15.4(−). HRMS *m/z* (M^+) calcd for $C_{15}H_{18}O_4$: 262.1205. Found: 262.1209.

Compound 19. To a prepared flask was added 2 mL of dry THF, 51.2 mg of *E*-1,3-dibromo-1-propene (*E*-**11**) (0.26 mmol), and 77.6 mg of *N*-benzyl-*N*-methyl amine (0.64 mmol, 82.6 μL). The solution was stirred at room temperature for 2 h, at which time fine white crystals were observed. After the reaction was quenched with H_2O, the layers were separated. The aqueous layer was extracted twice with diethyl ether, and the organic layers were combined. The organic phase was dried over anhydrous $MgSO_4$. Solvent removal in vacuo followed by purification via flash chromatography (0−5% ethyl acetate in hexanes) provided 58.4 mg of **6** (95% yield). IR (neat): 3061, 3027 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.32 (m, 5H), 6.30 (m, 2H), 3.54 (s, 2H), 3.22 (d, $J = 5.0$ Hz, 2H), 2.24 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.7, 132.3, 129.0, 128.3, 127.1, 109.5, 61.9, 56.2, 42.2. Anal. Calcd for $C_{11}H_{14}NBr$: C, 55.02; H, 5.88; N, 5.83. Found: C, 55.36; H, 5.96; N, 5.73.

Compound 20. To a 10 mL flask was added 2 mL of dry THF, 26 mg of *E*-1,3-dibromo-1-propene (*E*-**11**) (0.13 mmol, 1.0 equiv), and 47 mg of *N*-benzyl-*N*-methyl amine (0.39 mmol, 3.0 equiv). The solution was stirred at room temperature for 2 h, at which time fine white crystals were observed and the reaction was judged complete by TLC. To this solution was added 49.1 mg of hexenylboronic acid (0.39 mmol, 3.0 equiv), 7 mg of tetrakis(triphenylphosphine)palladium(0) (0.006 mmol, 5%), and 50 μL of 1 M KOH (0.39 mmol, 3.0 equiv). The solution was heated to reflux for 16 h, at which time the reaction was judged complete. The reaction was quenched with 3 mL of water; the layers were separated, and the aqueous layer was twice extracted with ether. The combined organic layers were dried over anhydrous $MgSO_4$. Following solvent removal in vacuo, flash chromatography (20% ethyl acetate in hexanes) provided 27.4 mg of **20** (88% yield) as a clear oil. IR (neat): 3020 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.30 (m, 5H), 6.13 (m, 2H), 5.67 (m, 2H), 3.49 (s, 2H), 3.05 (d, $J = 6.6$ Hz, 2H), 2.18 (s, 3H), 2.08 (m, 2H), 1.32 (m, 4H), 0.90 (t, $J = 7.4$ Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 139.1, 134.3, 133.3, 129.8, 129.1, 128.4, 128.2, 126.9, 61.7, 59.6, 42.1, 32.3, 31.4, 22.2, 13.9. HRMS *m/z* (M^+) calcd for $C_{17}H_{25}N$: 243.1988. Found: 243.1976.

Compounds **26** were all prepared following the general procedure outlined below for the preparation of **26a** in Table 5, entry 1.

Compound 26a (Table 5, Entry 1). Into a 25 mL flask was added 68 mg of phenyl boronic acid (0.55 mmol, 1.05 equiv), 2 mL of THF, and 30 mg of tetrakis(triphenylphosphine)palladium(0) (0.025 mmol, 4.5 mol %). To the resulting solution was added 100 mg of *E*-1-chloro-2-iodoethylene (**24**) (0.53 mmol, 1.0 equiv) and 1.1 mL of 1 M KOH (3.1 mmol, 5.8 equiv). The mixture was then heated to reflux for 12 h and monitored by TLC. When this reaction was judged complete, 120 mg of 4-methoxy-phenyl boronic acid (0.79 mmol), 30 mg of tetrakis(triphenylphosphine)palladium(0) (0.00259 mmol, 2.3 mol %), and 1.59 mL of 1 M KOH (5 mmol, 9 equiv) were added and the mixture was again heated to reflux for 2 days. At this time, the dark mixture was cooled to room temperature and diluted with 20 mL of ether. The layers were separated, and the aqueous layer was extracted twice with ether. The organic layers were then combined and dried over anhydrous $MgSO_4$. Following solvent removal in vacuo, the residue was loaded on top of a prepacked silica gel column and flashed (2% ether in pentane), providing 56 mg of **26a** (50% yield) as a white solid. Mp = 82 °C. IR (neat): 3084 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.49 (d, $J = 8.0$ Hz, 2H), 7.45 (d, $J = 8.0$ Hz, 2H), 7.37 (t, $J = 7.6$ Hz, 2H), 7.26−7.21 (m, 1H), 7.05 (d, $J = 16$ Hz, 1H), 6.93 (d, $J = 16$ Hz, 1H), 6.7 (d, $J = 8$ Hz, 2H), 3.86 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz, APT pulse sequence: evens up (+), odds down (−)): δ 160.0(+), 138.0(+), 130.8(+), 128.8(−), 128.3(−), 127.89(−), 127.39(−), 126.8(−), 126.43(−), 114.3(−), 55.52(−). HRMS *m/z* (M^+) calcd for $C_{15}H_{14}O$: 210.1044. Found: 210.1038.

Compound 26a (Table 5, Entry 2). Following the general procedure for the preparation of **26a**, 84.6 mg of 4-methoxyphenyl boronic acid (0.55 mmol, 1.05 equiv), 30 mg tetrakis-(triphenylphosphine)palladium(0) (0.025 mmol, 5 mol %), 100 mg of **24** (0.53 mmol, 1.0 equiv), 1.1 mL of 1 M KOH (1.1 mmol, 2.1 equiv), 96 mg of phenyl boronic acid (0.79 mmol, 1.4 equiv), 10.4 mg of tetrakis(triphenylphosphine)palladium(0) (0.0089 mmol, 1.6 mol %), and 1.59 mL of 1 M KOH (0.5 mmol, 0.9 equiv) provided 58 mg of **26a** (52% yield).

Compound 26b (Table 5, Entry 3). Following the general procedure for the preparation of **26a**, 142 mg of phenyl boronic acid (1.16 mmol, 1.1 equiv), 61 mg of tetrakis(triphenylphosphine)palladium(0) (0.053 mmol, 5 mol %), 200 mg of **24** (1.06 mmol, 1.0 equiv), 1.16 mL of 2 N NaOH (2.3 mmol, 2.0 equiv), 248 mg of octenyl boronic acid (1.59 mmol, 1.5 equiv), 61 mg of tetrakis(triphenylphosphine)palladium(0) (0.0053 mmol, 5 mol %), and 1.59 mL of 2 N NaOH (3.18 mmol, 3 equiv) provided 118 mg of **26b** (52% yield). IR (neat): 3054 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.38 (d, $J = 7.5$ Hz, 4H), 7.19 (t, $J = 7.4$ Hz, 1H), 6.76 (dd, $J = 15.6$, 10.3 Hz, 1H), 6.45 (d, $J = 15.7$ Hz, 1H), 6.21 (dd, $J = 15.7$, 10.5 Hz, 1H), 5.84 (dt, $J = 15.1$, 7.3 Hz, 1H), 2.16 (m, 2H), 1.45−1.27 (m, 8H), 0.99 (t, $J = 6.7$ Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz, APT pulse sequence: evens up (+), odds down (−)): δ 137.7(+), 136(−), 130.4(−), 129.9(−), 129.5(−), 128.5(−), 127.03(−), 126.1(−), 32.8(+), 31.7(+), 29.3(+), 28.9(+), 22.6(+), 14.07(−). HRMS *m/z* (M^+) calcd for $C_{16}H_{22}$: 214.1721. Found: 214.1713.

Compound 26b (Table 5, Entry 4). Following the general procedure for the preparation of **26a**, 107 mg of octenyl boronic acid (0.68 mmol, 1.3 equiv), 42 mg of tetrakis(triphenylphosphine)palladium(0) (0.036 mmol, 6.8 mol %), 100 mg of **24** (0.53 mmol, 1.0 equiv), 1.4 mL of 1 M KOH (1.3 mmol, 2.5 equiv), 97 mg of phenyl boronic acid (0.79 mmol), 30 mg of tetrakis-(triphenylphosphine)palladium(0) (0.0025 mmol, 4.7 mol %), and 1.58 mL of 1 M KOH (1.58 mmol, 3.0 equiv) provided 73 mg (65% yield) of **26b**.

Compound 26c (Table 5, Entry 5). Following the general procedure for the preparation of **26a**, 107 mg of octenyl boronic acid (0.68 mmol), 30 mg of tetrakis(triphenylphosphine)-palladium(0) (0.0259 mmol, 4.9 mol %), 100 mg of **24** (0.53 mmol), 1.38 mL of 1 M KOH (1.31 mmol, 2.5 equiv), 120 mg of 4-methoxy-phenyl boronic acid (0.79 mmol), 30 mg of tetrakis(triphenylphosphine)palladium(0) (0.0259 mmol, 4.9 mol %), and 1.58 mL of 1.0 KOH (1.5 mmol, 2.8 equiv) provided 96 mg of **26c** (74% yield) as a yellowish oil. IR (neat): 3052 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): 7.33 (d, $J = 8.0$ Hz, 2H), 6.86 (d, $J = 8.0$ Hz, 2H), 6.65 (dt, $J = 15.5$, 10 Hz, 1H), 6.41 (d, $J = 16.0$ Hz, 1H), 6.20 (dt, $J = 15.0$, 9.9 Hz, 1H), 5.78 (dt, $J = 15.5$, 7.5 Hz, 1H), 3.83 (s, 3H), 2.13 (q, $J = 6.1$ Hz, 2H), 1.61−1.22 (m, 10H), 0.87 (t, $J = 6.1$ Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz, APT pulse sequence: evens up (+), odds down (−)): 159.1(+), 135.1(−), 131.0(+), 130.8(−), 129.6(−), 127.7(−), 127.4(−), 114.2(−), 55.4(−), 33.1(+), 31.9(+), 29.5(+), 29.1(+), 22.8(+), 14.3(−) ppm (known compound[39]).

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Supporting Information Available: ^1H or ^{13}C NMR spectra for all compounds prepared in this study. This material is available free of charge via the Internet at http://pubs.acs.org.

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