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Abstract

An efficient palladium-free Stille cross-coupling reaction of allylic bromides and functionalized organostannylfUran using catalytic copper halide has been developed. The coupling reaction was optimized using CuI and low catalyst loading (down to 5 mol %). The reaction was conveniently carried out at ambient temperature in the presence of inorganic base to afford the coupling product in good-to-excellent yields. The utility of this reaction was demonstrated in the synthesis of a furan with sensitive functionalities. A sulfolene moiety was utilized as a masking group for the sensitive diene. Noyori asymmetric reduction, Achmatowicz reaction, and Kishi reduction steps converted sulfolene to a highly substituted tetrahydropyran intermediate used in the synthesis of the highly potent antitumor agents, spliceostatins, and their derivatives.
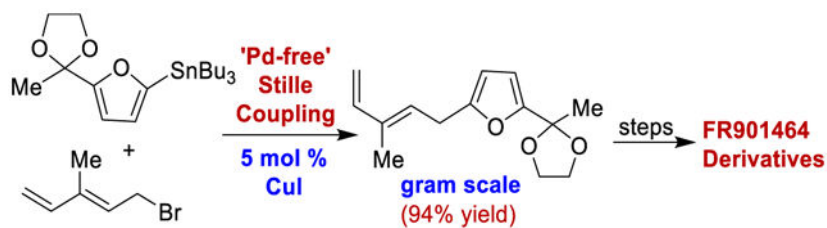
Graphical Abstract

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The authors declare no competing financial interest.

INTRODUCTION

The Stille cross-coupling reaction is one of the most powerful and widely used carbon–carbon bond forming reactions in organic synthesis.[1,2] Because of stability and functional group tolerance of stannanes, broad scope of reaction partners, and high degree of chemoselectivity, the Stille reaction has been extensively employed in natural product as well as pharmaceutical research.[3-5] The Stille cross-coupling reactions of organic electrophiles and organostannanes are traditionally carried out in the presence of various palladium catalysts.[6-8] Effective catalytic methods to carry out these reactions at ambient temperature using palladium catalysts under mild and green reaction conditions are limited,[9] and because of the costly nature of palladium, other catalysts are desired. Interestingly, the Pd-catalyzed Stille reaction in the presence of the cocatalytic amount of the copper catalyst has been shown to improve otherwise sluggish reactions.[10,11] To this end, copper was sought to catalyze the process on its own, and early work in this area includes the report of Liebeskind and Allred who reported an efficient Stille coupling of stannanes and vinyl iodide using stoichiometric amounts of copper (Scheme 1, first entry).[12] Kang and co-workers in 1997 reported Stille coupling of vinyl stannanes and vinyl iodides in the presence of 10 mol % CuI at >100 °C (second entry).[13]

Takeda and co-workers reported the coupling of vinyltin with allyl chloride using stoichiometric CuI at room temperature in 1995, which led to a mixture of isomers due to poor regiocontrol (third entry).[14] These reactions represent early development of the palladium-free, copper-catalyzed Stille reaction. However, the use of stoichiometric copper, higher reaction temperature, directing groups, harsh reaction conditions, and lack of regioselectivity limit the scope and utility of these reactions.[15-18] In our continuing interest in the chemistry and biology of spliceostatin derivatives,[19-23] we sought to develop a convergent synthesis of the core structure of spliceostatin A and further FR901464 derivatives using Stille cross-coupling as the key reaction. In particular, we planned to explore the potential of the Pd-free, copper-catalyzed reaction under mild reactions. Herein, we report a highly efficient Cu-catalyzed Stille cross-coupling reaction of organostannane derivative and (*E*)-5-bromo-3-methylpenta-1,3-diene. The resulting coupling product was converted to spliceostatin key subunit for the synthesis of important bioactive structural variants. Extensive structure–activity relationship studies have shown the importance of the tetrahydropyran and diene moieties of spliceostatins and their structural derivatives.[22-27]

RESULTS AND DISCUSSION

For initial investigation, we prepared multigram quantities of organostannane derivative, as shown in Scheme 2. Commercially available 2-acetalylfuran (**1**) was converted to organostannane derivative **2** in a two-step sequence. The reaction of 2-acetylfuran with ethylene glycol and catalytic amount of *p*-TsOH in refluxing toluene using a Dean–Stark apparatus to eliminate generated water afforded the corresponding dioxolane derivative.[28] Deprotonation of the resulting furan derivative with *n*BuLi in tetrahydrofuran (THF) at −78 °C followed by the reaction with *n*Bu$_3$SnCl provided organostannane **2** in 64% yield over two steps. For our investigation, we first attempted Cu-catalyzed cross-coupling of **2** with allyl bromide under a variety of reaction conditions. The results are shown in Table 1. The cross-coupling reaction was carried out by dissolving stannane **2** in a mixture (3:1) of dimethyl sulfoxide (DMSO) and THF at 23 °C. To this solution, CuI (0.5 equiv) and carbonate additive Na$_2$CO$_3$ (0.1 equiv) were added, followed by allyl bromide (2 equiv). The resulting mixture was stirred at 23 °C for 4.5 h. The reaction resulted in 73% yield of desired dioxolane derivative **3** along with a small amount of protodestannylated byproduct **4**. The ratio of desired product **3** and protodestannylated byproduct **4** was 5:1, as determined by ^{1}H NMR (400 MHz). These products were difficult to separate by silica gel chromatography. We chose to add carbonate additives to inhibit the protodestannylation reaction to form byproduct **4** by sequestering any adventitious acid formed in the system.[14] Interestingly, the combined yield of products **3** and **4** as well as the ratio was improved when the order of addition was modified by the addition of mixture of stannane, Na$_2$CO$_3$, and allyl bromide to a flame-dried flask containing CuI under an argon atmosphere at 23 °C (entry 2). The use of CuCN as the catalyst resulted in lower yield (entry 3). The choice of CuI (0.5 equiv) in dimethylformamide (DMF) afforded improvement of both the yield and ratio of **3:4** (entry 4). CuBr·DMS (0.5 equiv) furnished comparable results as CuI (entries 4 and 5). We then supported that the copper salts were needed for the reaction by a control experiment without CuI, which resulted in no cross-coupling products. We subsequently observed that the cross-coupling reaction could be carried out effectively using lower catalyst loading (entry 6). Using 5 mol % CuI and Na$_2$CO$_3$ (0.1 equiv), the cross-coupling reaction was carried out at 23 °C for 3.5 h. This condition resulted in 89% yield of desired coupling product **3** along with a very small amount of protodestannylated byproduct **4** (^{1}H NMR ratio > 20:1, entry 7). The use of 5 mol % CuCl in DMF with or without various carbonate additives was then tested and resulted in good results, albeit the ratio of products **3:4** decreased when no additive was present (entries 8–11). The use of Cs$_2$CO$_3$ resulted in a very good yield of product **3** and only a small amount of protodestannylated product **4** (ratio > 20:1), presumably because of increased solubility of Cs$_2$CO$_3$ in DMF (entry 11). The ketone product **5** formed likely due to the counter acids (entries 12 and 13). Catalytic Cu$_2$O (5 mol %) also showed a good yield of product **3**; however, CuTC (5 mol %) provided a poor yield of desired product **3** and protodestannylated derivative **4** was obtained in larger amount (entries 14 and 15). Based on our survey of various Cu(I) catalysts, additives, and reaction of 5 mol % CuOAc or Cu(OTf)·PhH in the presence of a Cs$_2$CO$_3$ additive that resulted in mainly the conditions, it was concluded that CuI (5 mol %) in the presence of Cs$_2$CO$_3$ additive (0.1 equiv) would provide the best result, as this condition effectively suppressed the formation of the protodestannylated product. This reaction was carried out and resulted

in 90% yield of our desired product **3** on a gram scale (entry 16). It should be noted that purification of these compounds was achieved using a modified procedure of Curran and co-workers.[29] The reaction products were passed through 10% K_2CO_3 in silica plug several times in a row to afford compounds **3** and **5** without coeluting tributyltin salts.

Following the optimization of the CuI-catalyzed cross-coupling reaction with allyl bromide, we then focused on the Cu-catalyzed cross-coupling reaction of stannane derivative **2** with (*E*)-5-bromo-3-methyl-penta-1,3-diene **6**,[30] as shown in Scheme 3. The product **7** is the precursor for amine derivative **8**. The amine derivative **8** can be readily converted to spliceostatins, thailanstatin, and their derivatives.[19-23] Spliceostatin derivatives have been shown to inhibit premessenger RNA splicing in eukaryotic cells.[31-33] As shown in Scheme 4, for the cross-coupling reaction, stannane **2** and Cs_2CO_3 were mixed together in DMF at 23 °C. To this mixture was then added CuI (5 mol %) under an argon atmosphere at 23 °C, followed by bromide **6**. The reaction mixture was stirred at 23 °C for 48 h. This reaction condition resulted in a mixture of products, which include desired coupling product **7** as a *E/Z* mixture, the γ-alkylated product **11**, and protodestannylated product **4** (Table 2, entry 1).

The ^{1}H NMR (400 MHz) analysis determined that ratios of (*E*)-**7**:(*Z*)-**7**:**11**:**4** to be **5:1.5:1:2**. This product mixture could not be separated by silica gel chromatography. The identity of *E* and *Z* isomers (*E*)-**7** and (*Z*)-**7** was determined by ^{1}H NMR NOESY experiments of their respective ketone derivatives (*E*)-**12** and (*Z*)-**12**.

In order to improve on the ratio of (*E*)-**7** to the rest of the undesired byproducts, another optimization was carried out. The use of a mixture (3:1) of DMSO and THF as the solvent resulted in a reduction of combined yield as well as reduction of *E/Z* ratio (2.5:1) (entry 2). In this reaction condition, the ketone products were formed exclusively because of deprotection of the dioxolane-protecting group. Otherwise, we deprotected the dioxalane group by exposure of the mixture to the catalytic amount of *p*-TSA in acetone at 23 °C for 2 h. Changing the order of addition as before and adding a mixture of stannane **2**, Cs_2CO_3, and bromide **6** to flame-dried CuI (5 mol %) however did not improve the ratio as it did in the prior model substrate reaction (entry 3). Interestingly, the use of THF as the solvent significantly improved the *E/Z* ratio of the coupling products (>20:1), but the reaction did not go to completion. The combined yield of products was 87% based on the recovery of starting stannane **2** (entry 4). The improvement of *E/Z* ratio is presumably due to solvent ligation on the metal center, resulting in a square planar transition state shown in Figure 1. The proposed Cu(III) η^3 allyl complexation resulting in the *Z*-isomer or the γ-alkylated intermediate would be less stable or may not form, leading to the majority (*E*)-isomer.[34-37] We then attempted the coupling reaction in a mixture (3:1) of THF and DMF using 0.2 equiv of Cs_2CO_3 as the additive. This condition provided an excellent yield of coupling products with a significant improvement of *E/Z* ratio (>20:1); however, the ratio of (*E*)-**7** to **4** was still 5:1 (entry 5). The coupling reaction in acetonitrile also provided excellent *E/Z* ratios, up to 94% yield on a gram scale over a single step to yield (*E*)-**7** or 85% over two steps to yield the respective ketone (*E*)-**12** as the sole detectable product by ^{1}H NMR. These reaction conditions were reproducible on a decagram scale and required no aqueous workup, simply following purification using the procedure described by Curran and co-workers.[29]

With the successful Stille coupling of stannane **2** and bromide **6**, we then planned to convert product (*E*)-**7** to functionalized tetrahydropyran derivative **8**. As shown in Scheme 5, methyl ketone (*E*)-**7** was subjected to Noyori asymmetric reduction[38,39] using the RuCl(mesitylene) [(*R*,*R*)-Ts-DPEN] (1 mol %) catalyst in the presence of Et$_3$N and formic acid at 50 °C for 12 h to afford optically active alcohol **15** in 99% yield. Achmatowicz reaction[40,41] of **15** with *tert*-butylhydroperoxide and vanadyl acetylacetonate provided the corresponding dihydropyran hemiacetal. Subjection of the resulting hemiacetal with Kishi reduction[42] with excess of Et$_3$SiH in the presence of trifluoroacetic acid (TFA) in CH$_2$Cl$_2$ at 0 °C to 23 °C resulted in triene derivative **16** as a major product and a trace amount of desired reduction product **17**. Other attempts to carry out this reduction by using other Lewis and Brønstead acids did not improve the desired product yield for compound **17**. We therefore devised an alternate route involving the protection of diene in (*E*)-**12** as a sulfolene derivative first and then carried out Achmatowicz reaction and Kishi reduction. Presumably, the protection of the diene functionality will help to slow down the competing *β*-elimination from the oxocarbenium ion intermediate. We attempted masking diene with Na$_2$S$_2$O$_5$ in a mixture (4:1) of HFIP and water, as described by Larionov and co-workers.[43] However, these reaction conditions resulted in only 6% yield of desired sulfolene derivative **18**. Further improvement of this reaction was then made by carrying out the reaction with sodium bisulfite in the presence of KHSO$_4$ in a mixture (4:1) of dioxane and water. Sulfolene derivative **18** was obtained in 62% isolated yield (99% BRSM). Asymmetric reduction[38,39] of **18** using Noyori's Ru-catalyst **14** in the presence of Et$_3$N and formic acid afforded optically active alcohol **19**. However, alcohol **19** turned out to be very unstable; thus, we were unable to determine its optical purity at this step. We therefore decided to carry forward the subsequent Achmatowicz reaction steps. Accordingly, treatment of crude alcohol **19** with oxone and KBr in the presence of NaHCO$_3$ as greener Achmatowicz conditions provided the corresponding dihydropyran hemiacetal.[44] This hemiacetal too turned out to be unstable, and we decided to carry out Kishi reduction and then remove the sulfolene group. The results of this four-step sequence are shown in Table 3. Initial reduction attempt of hemiacetal with 2 equiv of BF$_3$·OEt$_2$ in the presence of 2.5 equiv of Et$_3$SiH at −78 °C resulted in the reduction product **20**, which was heated in toluene using an oil bath at 150 °C to afford desired enones **17** and **16** in 28% yield over four steps (entry 1). The ratio of desired enone **17** and triene **16** was 10:1 as determined by ^{1}H NMR (400 MHz) analysis. We then carried out further optimization of the Kishi reduction step. We lowered the equivalences of the Lewis acid and reductant, obtaining enone **17** as the sole reaction product at −78 °C, however with a slight reduction of yield to 24% for four steps (entry 2). When the reaction was warmed to 0 °C, there was complete degradation of the product (entry 3). Kishi reduction[42] using a Brønsted acid at −45 °C in lieu of a Lewis acid resulted in 33% yield and a 2:1 mixture of **17:16** (entry 4). Letting the reaction warm only slightly as well as increasing the number of equivalences of the reducing agent decreased the yield but maintained excellent selectivity (entry 5). The corresponding reaction in the presence of Brønsted acid at −78 °C for 7 h only resulted in triene product **17** (entry 6). The Kishi reduction with 2 equiv of BF$_3$·Et$_2$O and 6 equiv of Et$_3$SiH at −78 °C for 7 h resulted in desired enone **16** in 60% over four steps and good ratio (>10:1, entry 7). We were able to support the cis-relationship via 2D NMR correlation of H$_a$ and H$_b$ in enone **17** and determine its *ee* to be >98% via chiral HPLC coming from the desymmetrization at the

Noyori reduction step (see Supporting Information). Enone **17** was then converted to tetrahydropyran derivative **8** in a two-step sequence involving (1) reaction of **17** with the LiCuMe$_2$ complex at −78 °C for 2 h and (2) reductive amination of the resulting ketone with NaBH(OAc)$_3$ and ammonium acetate in the presence of TFA at 23 °C for 44 h to furnish **8** in 82% over two steps. Tetrahydropyran derivative **8** was obtained as a single diastereomer (>20:1 by ^{1}H NMR analysis) and has been previously transformed into spliceostatins and their bioactive derivatives.[19-23]

CONCLUSIONS

In conclusion, we have investigated the Cu-catalyzed Stille cross-coupling reaction of a functionalized furanyl stannane derivative and allylic bromides using a variety of reaction conditions. We have examined a variety of Cu(I) salts and inorganic bases as additives in a range of solvent systems. The use of catalytic CuI (5 mol %) in the presence of Cs$_2$CO$_3$ in DMF or CH$_3$CN at room temperature provided very good-to-excellent yields of coupling products. Of particular note, the reaction of the functionalized furanyl stannane derivative **2** with (*E*)-5-bromo-3-methyl-1,3-pentadiene **6** proceeded smoothly to provide an excellent yield of the corresponding coupling product with diene (*E*)-**7**. The diene product was converted to a highly functionalized tetrahydropyran derivative **8** in an optically active form. A sulfolene derivative was formed using sodium bisulfite to mask the diene functionality during the Achmatowicz reaction and subsequent oxo-carbenium ion-mediated reduction step. Noyori's RuCl(mesitylene)[(*R,R*)-Ts-DPEN] catalyst (1 mol %) was utilized to provide an optically active alcohol for the described Achmatowicz reaction. Further scope and utility of sulfolene formation using sodium bisulfite is being investigated. The resulting pyranone derivative was converted to highly functionalized tetrahydropyran intermediate **8**. This was previously converted to FR901464 derivatives, which exhibited very potent inhibition of spliceosome with possible clinical application as an anticancer therapeutic.

EXPERIMENTAL SECTION

All chemicals and reagents were purchased from commercial suppliers and used without further purification unless otherwise noted. THF was distilled from Na/benzophenone prior to use. All reactions were performed in oven-dried round-bottom flasks, followed by flamedrying under vacuum in the case of moisture-sensitive reactions. The flasks were fitted with a rubber septa and kept under a positive pressure of argon. A cannula was used for transferring moisture-sensitive liquids. Heated reactions were carried out using an oil bath on a hot plate equipped with a temperature probe. TLC analysis was conducted using glass-backed thin-layer silica gel chromatography plates (60 Å, 250 μm thickness, F-254 indicator). Flash chromatography was done using a 230–400 mesh, a 60 Å pore diameter silica gel. Organic solutions were concentrated at 30–35 °C on rotary evaporators capable of achieving a minimum pressure of ~25 Torr and further concentrated on a Hi-vacuum pump capable of achieving a minimum pressure of ~4 Torr. ^{1}H NMR spectra were recorded on 400, 500, and 800 MHz spectrometers. ^{13}C NMR spectra were recorded at 100, 125, and 200 MHz on the respective NMRs. Chemical shifts are reported in parts per million and referenced to the deuterated residual solvent peak (CDCl$_3$, 7.26 ppm for ^{1}H and 77.16 ppm for ^{13}C). NMR data are reported as δ value (chemical shift), *J*-value (Hz), and integration,

where s = singlet, br s = broad singlet, d = doublet, t = triplet, q = quartet, p = quintet, m = multiplet, dd = doublet doublets, and so on. Optical rotations were recorded on a digital polarimeter. Low-resolution mass spectra (LRMS) spectra were recorded using a quadrupole LCMS under positive electrospray ionization (ESI$^+$). High-resolution mass spectrometry (HRMS) spectra were recorded at the Purdue University Department of Chemistry Mass Spectrometry Center. These experiments were performed under ESI$^+$ and positive atmospheric pressure chemical ionization (APCI$^+$) conditions using an Orbitrap XL Instrument.

2
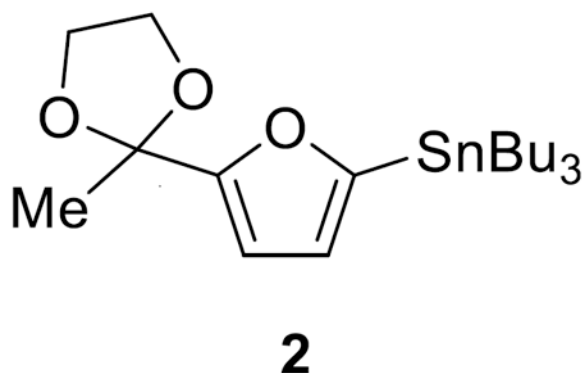
Tributyl(5-(2-methyl-1,3-dioxolan-2-yl)furan-2-yl)stannane (2).

To a two-neck oven-dried 1 L round-bottom flask, furyl dioxolane (12.9 g, 117 mmol, 1.0 equiv) was dissolved in freshly distilled THF (195 mL), followed by tetramethylethylenediamine (40 mL, 269 mmol, 2.3 equiv) and cooled to −78 °C. *n*-Butyl lithium (1.6 M in hexane, 95 mL, 152 mmol, 1.3 equiv) was added slowly, changing the color of the reaction from gold to orange and then dark green. The flask was warmed to a range of −40 °C to −20 °C for a duration of 2.5 h. At this time, the flask was cooled back to −78 °C. In a separate flask, tributyltin chloride (ClSnBu$_3$, 41.3 mL, 152 mmol, 1.3 equiv) in freshly distilled THF (195 mL) was cooled to −78 °C as well and cannulated into the reaction flask at the same temperature. The flask turned brown with a golden fringe to orange. The reaction was allowed to warm slowly to ambient temperature over the course of 20 h. The dark orange solution was quenched with saturated NaHCO$_3$ (300 mL), extracted with diethyl ether three times, washed with brine, dried over Na$_2$SO$_4$, and concentrated under reduced pressure. The crude material was purified via column chromatography using Harrowven and co-workers' procedure[29] (10% K$_2$CO$_3$/silica stationary phase) and a 2–10% ethyl acetate/hexane gradient. Furyl organostannyl dioxolane **2** was isolated as a brown oil (31.9 g, 61%). TLC: silica gel (20% ethyl acetate/hexane) R_f = 0.47. ^{1}H NMR (500 MHz, CDCl$_3$): δ 6.44 (d, J = 3.1 Hz, 1H), 6.30 (d, J = 3.1 Hz, 1H), 4.06–4.00 (m, 4H), 1.75 (s, 3H), 1.59–1.53 (m, 6H), 1.35–1.30 (m, 6H), 1.14–1.00 (m, 6H), 0.89 (t, J = 7.3 Hz, 9H). ^{13}C{^{1}H} NMR (200 MHz, CDCl$_3$): δ 161.2, 159.2, 121.7, 106.3, 105.1, 65.2, 29.1, 27.3, 24.4, 13.8, 10.3. HRMS-APCI (+) *m/z*: calcd for C$_{20}$H$_{37}$O$_3$Sn^{116} [M + H]$^+$, 441.1755; found, 441.1762.

Stille Cross-Coupling of Stannane 2 and Allyl Bromide.

To a two-neck oven-dried round-bottom flask containing furyl organostannyl dioxolane **2** (1.0 equiv) and solvent (0.1 M), additive (0.1 equiv) and Cu(I) catalyst (5–50 mol %) were added. Allyl bromide (2.0 equiv) was then added neat. After the reaction via TLC analysis (3–120 h depending on the desired product and scale of reaction), saturated KF (0.1 M) was added and stirred for a few minutes. The quenched reaction was then diluted with ethyl acetate, extracted three times with the said solvent, washed with brine/saturated LiCl, dried with Na_2SO_4, and concentrated under reduced pressure. The crude material was then passed through a 10% K_2CO_3/silica plug[29] using 10% ethyl acetate/hexane as the eluent. Allyl furyl dioxolane **3** and protodestannylated byproduct **4** coeluted, and thus, the ratios were calculated via ^{1}H NMR. Allyl furyl ketone **5** was isolable, if formed. The same stationary phase for the plug could be used several times before being replaced due to decreased flow and blockage. *If a change of addition was indicated, **2** was dissolved in the solvent, followed by an additive and bromide. In a separate flask, CuI was then flame-dried under vacuum to form a canary yellow color and then cooled under argon, and the reaction flask was cannulated to the copper flask and stirred. Equivalences, workup, and purification all remained the same.


3
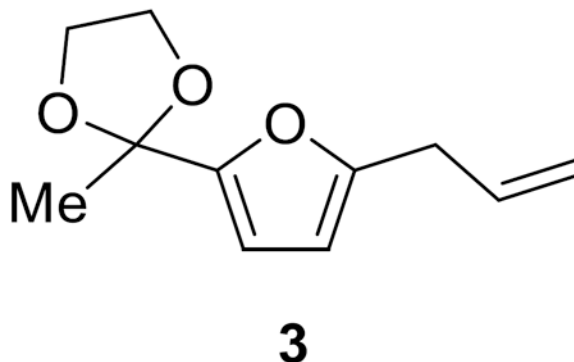
2-(5-Allylfuran-2-yl)-2-methyl-1,3-dioxolane (3).

Clear oil, 396 mg. TLC: silica gel (10% ethyl acetate/hexane) R_f = 0.40. ^{1}H NMR (400 MHz, CDCl₃): δ 6.21 (d, J = 3.1 Hz, 1H), 5.97–5.87 (m, 2H), 5.16–5.08 (m, 2H), 4.05–3.98 (m, 4H), 3.38 (dq, J = 6.6, 1.4 Hz, 2H), 1.72 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, CDCl₃): δ 154.1, 153.1, 133.8, 117.1, 107.3, 105.9, 104.9, 65.2, 32.8, 24.5. HRMS-APCI (+) *m/z*: calcd for $C_{11}H_{15}O_3$ [M + H]⁺, 195.1016; found, 195.1018.

4
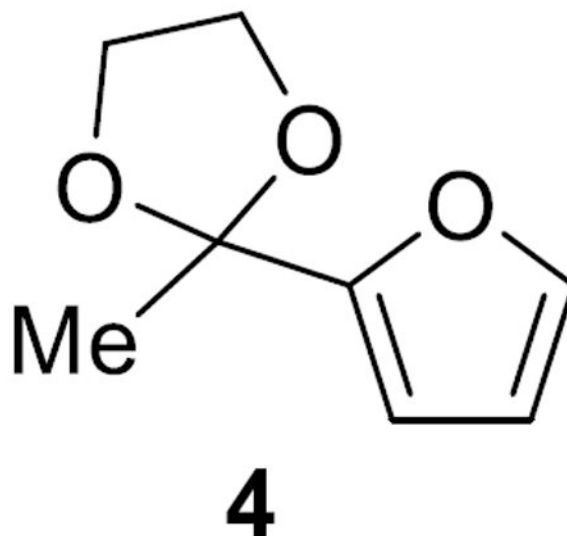
## 2-(Furan-2-yl)-2-methyl-1,3-dioxolane (4).[45]

To a one-neck oven-dried 500 mL round-bottom flask equipped with a Dean–Stark apparatus and a reflux condenser, 2-acetyl furan **1** (10 g, 91 mmol, 1.0 equiv) was added, followed by benzene (PhH, 181 mL, 0.5 M). To this, ethylene glycol (7.6 mL, 136 mmol, 1.5 equiv) and p-toluenesulfonic acid monohydrate (PTSA·H$_2$O, 863 mg, 4.5 mmol, 5 mol %) were added sequentially, and the reaction was refluxed at 150 °C in order to remove water. The reaction mixture changed to golden color after several hours, and a dark maroon color was developed overnight. After the reaction via TLC analysis (75 h), the flask was cooled to ambient temperature, and the reaction was quenched with 1 M NaOH (200 mL), extracted with ethyl acetate three times, dried with Na$_2$SO$_4$, and concentrated under reduced pressure. The crude mixture was purified via silica column chromatography using 10% ethyl acetate/ hexane as the eluent. Furyl dioxolane intermediate **4** was isolated as a brown liquid (12.8 g, 92%). TLC: silica gel (10% ethyl acetate/hexane) R_f = 0.39. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.37 (t, J = 1.3 Hz, 1H), 6.32–6.30 (m, 2H), 4.07–3.99 (m, 4H), 1.74 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ 154.6, 142.5, 110.0, 106.6, 104.9, 65.3, 24.5.

5
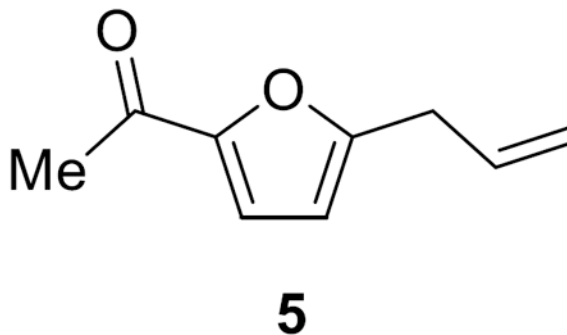
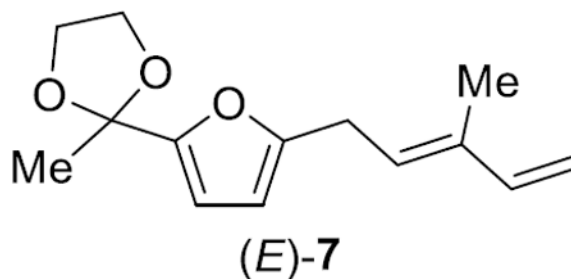## 1-(5-Allylfuran-2-yl)ethan-1-one (5).[19,22]

Clear oil, 26 mg. TLC: silica gel (10% ethyl acetate/hexane) R_f = 0.24. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.11 (d, J = 3.5 Hz, 1H), 6.19 (d, J = 3.5 Hz, 1H), 5.93 (ddt, J = 16.8, 10.1, 6.7

Hz, 1H), 5.22–5.16 (m, 2H), 3.47 (d, $J = 6.7$ Hz, 2H), 2.43 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, CDCl$_3$): δ 186.4, 159.6, 151.9, 132.4, 119.2, 118.3, 108.8, 33.0, 25.9. LRMS-ESI (+) m/z: 151.1 [M + H]$^+$.

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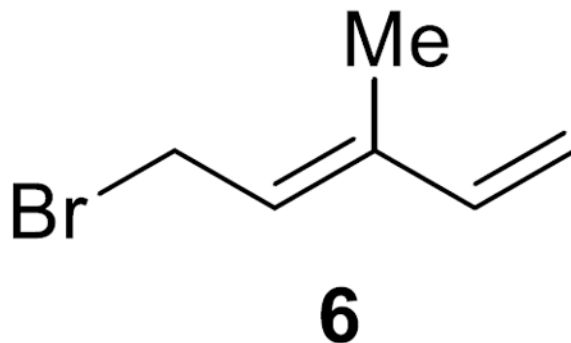
(*E*)-5-Bromo-3-methylpenta-1,3-diene (6).[30]

To a one-neck oven-dried 250 mL round-bottom flask, diene alcohol **23** was dissolved in diethyl ether (Et$_2$O, 94 mL, 0.27 M) and cooled to 0 °C. Tribromophosphine (1.3 mL, 13.9 mmol, 0.55 equiv) was added (fuming occurred), and the reaction was stirred for 1.5 h at 0 °C. The reaction was then quenched with brine (100 mL), brought to ambient temperature, and extracted with ether three times. The organic layer was dried over Na$_2$SO$_4$ and concentrated under reduced pressure on ice. The crude material was then diluted with cold hexane, filtered through a cotton plug to remove majority of the phosphine oxide, and concentrated again under reduced pressure on ice to yield diene bromide **6** as a yellow liquid (4 g, >99%) and was used without further purification. TLC: silica gel (10% ethyl acetate/ hexane) $R_f = 0.66$, clearly degrading on silica. ^{1}H NMR (400 MHz, CDCl$_3$): δ 6.38 (ddd, $J = 17.4, 10.7, 0.7$ Hz, 1H), 5.78 (t, $J = 8.9$ Hz, 1H), 5.30 (d, $J = 17.4$ Hz, 1H), 5.12 (d, $J = 10.7$ Hz, 1H), 4.13 (d, $J = 8.6$ Hz, 2H), 1.85 (d, $J = 1.3$ Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, CDCl$_3$): δ 140.2, 139.9, 126.8, 114.9, 29.0, 11.6.


(*E*)-7

(*E*)-1-(5-(3-Methylpenta-2,4-dien-1-yl)furan-2-yl)ethan-1-one (*E*)-7.

To a two-neck oven-dried 100 mL round-bottom flask, furyl organostannyl dioxolane **2** (970 mg, 2.2 mmol, 1.0 equiv) was dissolved in acetonitrile (MeCN, 15 mL). To this, Cs$_2$CO$_3$ (143 mg, 0.4 mmol, 0.2 equiv) was added. Diene bromide **6** (705 mg, 4.4 mmol, 2.0 equiv) in 7 mL of MeCN was then cannulated to the reaction mixture, then copper(I)iodide (CuI, 21 mg, 0.1 mmol, 5 mol %) was added, and the reaction was stirred. After the reaction via TLC analysis (24–96 h depending on the scale of reaction), it was concentrated under reduced

pressure. The crude material was purified via column chromatography using Harrowven and co-workers' procedure[29] (10% K_2CO_3/silica stationary phase) and 10% ethyl acetate/hexane as the eluent. Dioxolane furyl diene (E)-**7** was isolated as a yellow liquid (479 mg, 94%). TLC: silica gel (10% ethyl acetate/hexane) R_f = 0.39. ^{1}H NMR (400 MHz, CDCl$_3$): δ 6.41 (ddd, J = 17.4, 10.7, 0.7 Hz, 1H), 6.20 (d, J = 3.1 Hz, 1H), 5.89 (dt, J = 3.1, 1.0 Hz, 1H), 5.64 (t, J = 7.3 Hz, 1H), 5.16 (d, J = 17.4 Hz, 1H), 5.00 (d, J = 10.7 Hz, 1H), 4.05–4.00 (m, 4H), 3.48 (d, J = 7.4 Hz, 2H), 1.80 (d, J = 1.1 Hz, 3H), 1.72 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ 154.3, 153.0, 141.1, 136.1, 127.0, 111.9, 107.3, 105.5, 104.8, 65.2, 27.4, 24.4, 11.9. HRMS-APCI (+) m/z: calcd for $C_{14}H_{19}O_3$ [M + H]$^+$, 235.1329; found, 235.1332.

(2R,3R,5S,6S)-2,5-Dimethyl-6-((E)-3-methylpenta-2,4-dien-1-yl)tetrahydro-2H-pyran-3-amine (8).[19-23]

To an oven-dried 10 mL round-bottom flask β-methyl, ketone **21** (30 mg, 0.14, 1.0 equiv)


8
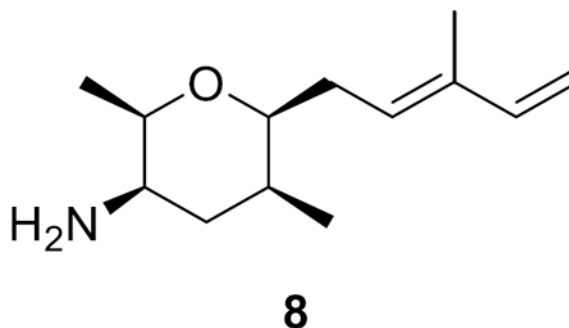
was dissolved in THF (2.88 mL, 0.05 M) and cooled to 0 °C. Ammonium acetate (NH$_4$OAC, 222 mg, 2.88 mmol, 20 equiv), sodium triacetoxy borohydride [NaBH(OAc)$_3$, 152.6 mg, 0.72 mmol, 5.0 equiv], and TFA (11 μL, 0.14 mmol, 1.0 equiv) were added sequentially, and the reaction was warmed slowly to ambient temperature. Fuming and bubbling were observed upon addition of reagents. After TLC analysis indicated that the reaction was complete (44 h), it was quenched with saturated NaHCO$_3$ (3.0 mL), extracted with ethyl acetate three times, washed with brine, dried with Na$_2$SO$_4$, and concentrated under reduced pressure. The crude material was purified via silica column chromatography using 10% MeOH/DCM as the eluent to yield amine **8** as a clear oil (24.8 mg, 82% yield) as the sole detectable isomer via ^{1}H NMR. TLC: silica gel [5% methanol/dichloromethane (DCM)] R_f = 0.07. $[\alpha]_D^{20}$ − 4.0 (c 0.708, CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$): δ 6.36 (dd, J = 17.4, 10.7 Hz, 1H), 6.05 (br s, 2H), 5.44 (t, J = 7.2 Hz, 1H), 5.10 (d, J = 17.3 Hz, 1H), 4.94 (d, J = 10.7 Hz, 1H), 3.62 (br s, 1H), 3.52–3.44 (m, 1H), 3.09 (br s, 1H), 2.40 (dt, J = 14.2, 6.7 Hz, 1H), 2.24 (dt, J = 15.1, 7.5 Hz, 1H), 2.15 (d, J = 14.7 Hz, 1H), 2.02–2.00 (m, 1H), 1.80–1.72 (m, 4H), 1.26 (d, J = 6.6 Hz, 3H), 1.12 (d, J = 7.4 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ 141.5, 135.8, 128.3, 111.2, 80.9, 75.1, 49.3, 35.6, 31.9, 28.6, 17.8, 14.5, 12.1. LRMS-ESI (+) m/z: 210.1 [M + H]$^+$.

(E)-12
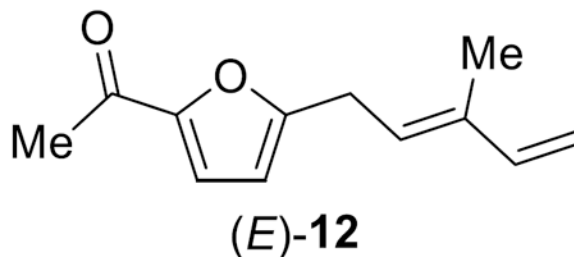
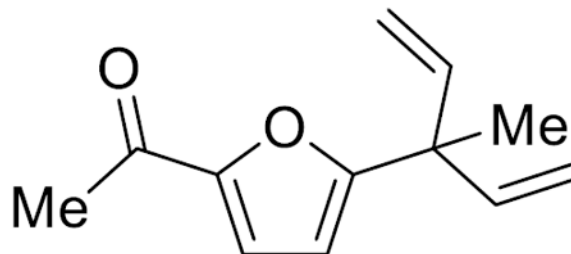## (E)-1-(5-(3-Methylpenta-2,4-dien-1-yl)furan-2-yl)ethan-1-one (E)-12.

To a two-neck oven-dried 500 mL round-bottom flask, CuI (215 mg, 1.1 mmol, 0.05 equiv) was flame-dried under vacuum until it formed canary yellow and then cooled under argon and diluted with 75 mL of acetonitrile (MeCN). Cs_2CO_3 (2.2 g, 6.8 mmol, 0.3 equiv) was then added, and the solution turned yellow/gold. To this, stannane **2** (10 g, 23 mmol, 1.0 equiv) was dissolved in MeCN (75 mL) and added. Finally, bromide **6** (6.2 g, 39 mmol, 1.7 equiv) in 75 mL MeCN was then added, and the reaction was stirred. The reaction slowly turned milky white and then teal. After the reaction via TLC analysis (24–96 h depending on the scale of reaction), it was concentrated under reduced pressure. The crude material was purified via column chromatography using Harrowven and co-workers' procedure[29] (10% K_2CO_3/silica stationary phase) and 2–10% ethyl acetate/hexane as the eluent. The fractions containing dioxolane furyl diene (E)-**7** were concentrated under reduced pressure and carried on to the next step.

To a one-neck oven-dried 1 L round-bottom flask, dioxolane furyl diene (E)-**7** (5.29 g, 22.6 mmol, 1.0 equiv) was dissolved in acetone (280 mL, 0.08 M), and p-toluenesulfonic acid monohydrate (4.7 g, 24.8 mmol, 1.1 equiv) was added. The reaction changed from yellow to a greenish-gold color. After the reaction via TLC analysis (2 h), it was concentrated under reduced pressure and purified via silica column chromatography using 5% ethyl acetate/hexane as the eluent. Ketone furyl diene (E)-**12** was isolated as a yellow oil (3.58 g, 83–85% over two steps depending on the scale). TLC: silica gel (20% ethyl acetate/hexane) $R_f =$ 0.24. ^1H NMR (400 MHz, $CDCl_3$): δ 7.09 (d, $J = 3.5$ Hz, 1H), 6.39 (ddd, $J = 17.4, 10.7, 0.7$ Hz, 1H), 6.15 (dt, $J = 3.5, 1.0$ Hz, 1H), 5.63 (dddd, $J = 7.4, 6.8, 1.4, 0.7$ Hz, 1H), 5.18 (d, $J = 17.2$ Hz, 1H), 5.02 (d, $J = 10.7$ Hz, 1H), 3.55 (d, $J = 7.4$ Hz, 2H), 2.42 (s, 3H), 1.80 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 159.8, 151.8, 140.7, 137.0, 125.2, 119.2, 112.6, 108.5, 27.7, 25.8, 12.0. HRMS-ESI (+) m/z: calcd for $C_{12}H_{14}O_2Na$ [M + Na]+, 213.0886; found, 213.0885.

(Z)-12
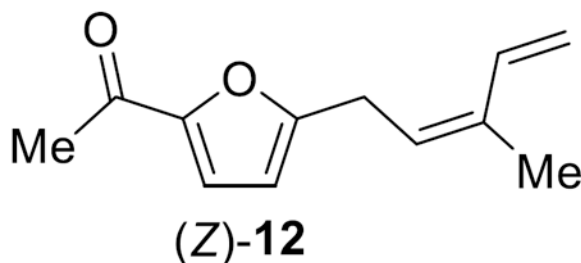
**(*Z*)-1-(5-(3-Methylpenta-2,4-dien-1-yl)furan-2-yl)ethan-1-one (12).**

Yellow oil, 37 mg. Part of mixture of isomers, only ^{1}H NMR shifts could be determined. TLC: silica gel (20% ethyl acetate/hexane) $R_f = 0.24$. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.12–7.09 (m, 1H), 6.76 (ddd, $J = 17.2$, 10.8, 0.9 Hz, 1H), 6.17–6.15 (m, 1H), 5.54 (t, $J = 7.6$ Hz, 1H), 5.35–5.28 (m, 1H), 5.22–5.15 (m, 1H), 3.62–3.58 (m, 2H), 2.49 (s, 3H), 1.88 (d, $J = 1.3$ Hz, 3H). HRMS-APCI (+) *m/z*: calcd for C$_{12}$H$_{15}$O$_2$ [M + H]$^+$, 191.1067; found, 191.1068.

13

1-(5-(3-Methylpenta-1,4-dien-3-yl)furan-2-yl)ethan-1-one (13).

Yellow oil, 20 mg. TLC: silica gel (20% ethyl acetate/hexane) $R_f = 0.24$. ^{1}H NMR (800 MHz, CDCl$_3$): δ 7.11 (d, $J = 3.5$ Hz, 1H), 6.22 (d, $J = 3.5$ Hz, 1H), 6.04 (dd, $J = 17.4$, 10.5 Hz, 2H), 5.18 (d, $J = 10.5$ Hz, 2H), 5.04 (d, $J = 17.4$ Hz, 2H), 2.44 (s, 3H), 1.54 (s, 3H). ^{13}C{^{1}H} NMR (200 MHz, CDCl$_3$): δ 186.7, 163.8, 152.3, 141.6, 118.3, 114.7, 108.6, 46.1, 26.0, 23.5. HRMS-APCI (+) *m/z*: calcd for C$_{12}$H$_{15}$O$_2$ [M + H]$^+$, 191.1067; found, 191.1069.
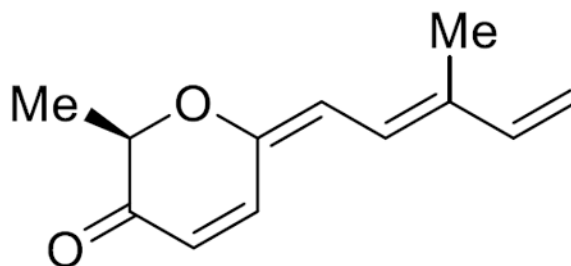
16

(*R,E*)-2-Methyl-6-((*E*)-3-methylpenta-2,4-dien-1-ylidene)-2*H*-pyran-3(6*H*)-one (16).

Orange amorphous solid, 10 mg. TLC: $R_f = 0.21$ (silica gel, 10% ethyl acetate/hexane). ^{1}H NMR (800 MHz, CDCl$_3$): δ 6.98 (d, $J = 9.8$ Hz, 1H), 6.57–6.51 (m, 2H), 6.02 (d, $J = 12.0$ Hz, 1H), 5.98 (d, $J = 9.8$ Hz, 1H), 5.33 (d, $J = 17.3$ Hz, 1H), 5.16 (d, $J = 10.6$ Hz, 1H), 4.64 (q, $J = 7.0$ Hz, 1H), 1.92 (d, $J = 1.3$ Hz, 3H), 1.49 (d, $J = 6.9$ Hz, 3H). ^{13}C{^{1}H} NMR (200 MHz, CDCl$_3$): δ 195.3, 147.3, 141.3, 141.1, 139.3, 124.9, 121.5, 116.0, 114.7, 78.0, 18.2, 12.4. HRMS-APCI (+) *m/z*: calcd for C$_{12}$H$_{15}$O$_2$ [M + H]$^+$, 191.1067; found, 191.1068.
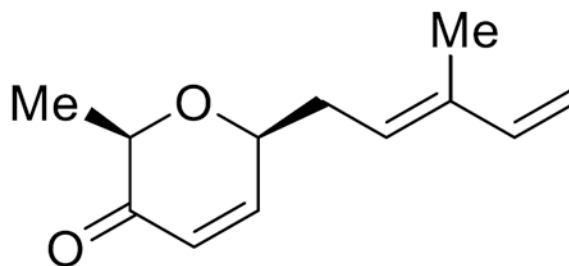
17

(2*R*,6*S*)-2-Methyl-6-((*E*)-3-methylpenta-2,4-dien-1-yl)-2*H*-pyran-3(6*H*)-one (17).

To a one-neck oven-dried 10 mL round-bottom flask, crude alcohol sulfolene **19** (80.6 mg assumed, 0.31 mmol, 1.0 equiv) was dissolved in a THF/H_2O mixture (2.5/0.6 mL, 0.1 M) and cooled to 0 °C. Potassium bromide (KBr, 3.7 mg, 0.03 mmol, 0.1 equiv), sodium bicarbonate ($NaHCO_3$, 13 mg, 0.16 mmol, 0.5 equiv), and oxone (213 mg, 0.35 mmol, 1.1 equiv) were added sequentially, and the reaction was stirred at 0 °C for 1.5 h. After the reaction via TLC analysis, it was quenched with saturated $NaHCO_3$ (3 mL), extracted three times with ethyl acetate, washed with brine, dried with Na_2SO_4, and concentrated under reduced pressure. The crude material (clear oil) was then taken immediately for the next reaction. TLC: silica gel (60% ethyl acetate/hexane) R_f = 0.30.

To a one-neck oven-dried 10 mL round-bottom flask, crude hemiacetal (42.8 mg, 0.16 mmol, 1.0 equiv) was dissolved in DCM (1.6 mL, 0.1 M) and cooled to −78 °C. To this, triethylsilane (Et_3SiH, 151 μL, 0.94 mmol, 6.0 equiv) and boron trifluoride etherate ($BF_3 \cdot Et_2O$, 39 μL, 0.31 mmol, 2.0 equiv) were added sequentially and stirred at this temperature for at least 7 h. The reaction turned a dark orange gold or orange pink color. The reaction was then removed from the −78 °C bath and quenched slowly with the addition of saturated $NaHCO_3$ (2 mL, bubbled violently). The organic layer was then extracted with DCM five times, dried with Na_2SO_4, and concentrated under reduced pressure. The crude material **20** (yellow oil) was then taken immediately for the next reaction. TLC analysis (R_f = 0.54, silica gel, 60% ethyl acetate/hexane) during the reaction seems not to be reliable as it shows full conversion almost immediately, but if analysis is carried out, TLC of the crude material then shows the starting material (almost no conversion). It was found that letting the reaction run for 7 h instead and then working it up showed full conversion via crude TLC.

To a one-neck oven-dried 50 mL round-bottom flask equipped with a reflux condenser, the crude sulfolene enone **20** (40 mg assumed, 0.16 mmol, 1.0 equiv) was dissolved in toluene (15.7 mL, 0.01 M) and heated in an oil bath to reflux (150 °C). After the reaction via TLC analysis (3 h), the flask was cooled to ambient temperature and concentrated under reduced pressure. The crude material was then purified via 10% K_2CO_3/silica chromatography[4] using 1–10% ethyl acetate/hexane as the gradient. Enone diene **17** was isolated as a yellow oil (18 mg, 60% over four steps, >10:1 ratio of **17:16**, >98% *ee*). TLC: silica gel (10% ethyl acetate/hexane) R_f = 0.20. $[\alpha]_D^{20}$ + 76.2 (*c* 0.362, CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$): δ 6.90 (d, *J* = 10.3 Hz, 1H), 6.39 (dd, *J* = 17.3, 10.6 Hz, 1H), 6.10 (d, *J* = 10.2 Hz, 1H), 5.55 (t,

J = 7.1 Hz, 1H), 5.16 (d, J = 17.4 Hz, 1H), 5.01 (d, J = 10.7 Hz, 1H), 4.41 (t, J = 6.4 Hz, 1H), 4.09 (q, J = 6.5 Hz, 1H), 2.60–2.50 (m, 2H), 1.78 (s, 3H), 1.39 (d, J = 6.6 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, CDCl$_3$): δ 197.1, 150.8, 141.0, 137.2, 127.0, 126.2, 112.1, 77.3, 74.0, 33.8, 15.6, 12.2. HRMS-ESI (+) m/z: calcd for C$_{12}$H$_{17}$O$_2$ [M + H]$^+$, 193.1223; found, 193.1227.
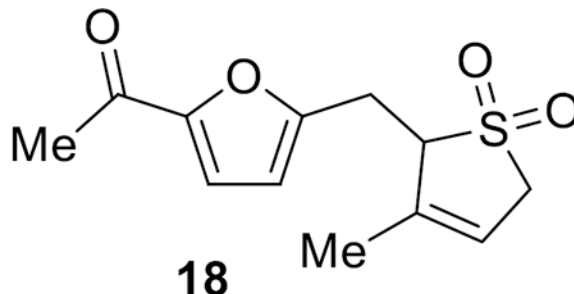
1-(5-((3-Methyl-1,1-dioxido-2,5-dihydrothiophen-2-yl)-methyl)furan-2-yl)ethan-1-one (18).

A thick-walled sealed tube reaction vessel was fitted with a stir bar and septa. The apparatus was flame-dried under vacuum and then cooled under argon. Solvents were prebubbled with argon for at least 10 min beforehand, and then in a one-neck oven-dried round-bottom flask, ketone furyl diene (E)-**12** (110 mg, 0.6 mmol 1.0 equiv) was dissolved in the freshly bubbled 1:1 mixture of 1,4-dioxane and H$_2$O (2.9 mL, 0.2 M) and cannulated to the sealed tube. KHSO$_4$ (472 mg, 3.5 mmol, 6.0 equiv) and NaHSO$_4$ (903 mg, 8.7 mmol, 15.0 equiv) were added to the reaction vessel, and the tube was sealed and heated in an oil bath to the desired temperature. After 24 h, the vessel was cooled down to 0 °C and opened. If TLC analysis showed that the reaction was still in progress, it was resealed and heated back up until the reaction was either complete or if TLC analysis showed no further progression. The reaction was then diluted with ethyl acetate (0.1 M) and H$_2$O (0.1 M) and extracted with ethyl acetate four times. Organic layers were then washed with brine, dried with Na$_2$SO$_4$, and concentrated under reduced pressure. The crude material was purified via silica gel column chromatography using 10–70% ethyl acetate/hexane as the gradient to recover any unreacted ketone furyl diene **12** and sulfolene ketone **18** as clear yellow oils. Sulfolene ketone **18** was solidified to a yellow white solid (92 mg, 6–62%, 6->99% BRSM) once concentrated under reduced pressure with diethyl ether three times iteratively. TLC: silica gel (60% ethyl acetate/hexane) R_f = 0.24. ^1H NMR (400 MHz, CDCl$_3$): δ 7.11 (d, J = 3.5 Hz, 1H), 6.45 (dt, J = 3.5, 0.8 Hz, 1H), 5.70 (tt, J = 3.1, 1.6 Hz, 1H), 3.94–3.85 (m, 1H), 3.77–3.61 (m, 2H), 3.35–3.19 (m, 2H), 2.43 (s, 3H), 1.85–1.83 (m, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, CDCl$_3$): δ 186.2, 155.5, 152.2, 137.6, 119.1, 118.4, 111.2, 65.5, 55.9, 26.9, 26.0, 18.2. HRMS-ESI (+) m/z: calcd for C$_{12}$H$_{14}$O$_4$SNa [M + Na]$^+$, 277.0505; found, 277.0502.
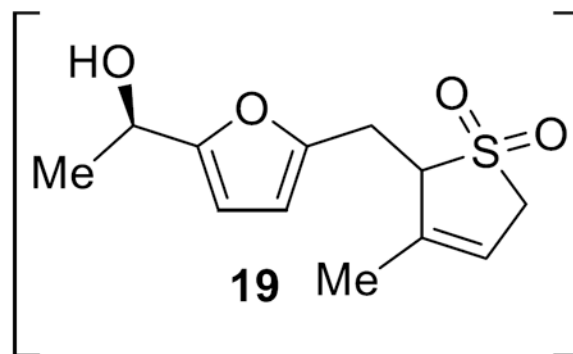
2-((5-(((R)-1-Hydroxyethyl)furan-2-yl)methyl)-3-methyl-2,5-dihydrothiophene-1,1-dioxide (19).
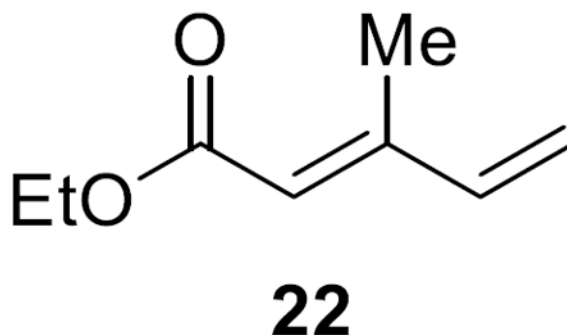
To a one-neck oven-dried 10 mL round-bottom flask equipped with a reflux condenser, ketone sulfolene **18** (80 mg, 0.31 mmol, 1.0 equiv) was dissolved in DCM (3.1 mL, 0.1 M). Triethylamine (329 μL, 2.4 mmol, 7.5 equiv) and formic acid (HCO$_2$H, 89 μL, 2.4 mmol, 7.5 equiv) were added sequentially, and the evolution of H$_2$ gas was observed. [*N*-[(1*R*,2*R*)-2-(Amino-κN)-1,2-diphenylethyl]-4-methylbenzenesulfonamidato-κN]chloro[(1,2,3,4,5,6-η)-1,3,5-trimethylbenzene]-ruthenium (RuCl-[(*R,R*)-TsDPEN] (mesitylene), 2 mg, 0.003 mmol, 1 mol %) was added last, and the reaction was heated in an oil bath to reflux (30 °C). After the reaction via TLC analysis (24–48 h), the solution was cooled and concentrated down under reduced pressure and passed through 10% K$_2$CO$_3$/silica plug, using 65% ethyl acetate/hexane as the eluent. The solution was concentrated down under reduced pressure again, and the crude material **19** (clear oil) was then taken immediately for the next reaction. Of particular note, for any transfer of the crude mixture, ethyl acetate was found to be the most suitable solvent. If the crude came into contact with DCM or deuterated chloroform for the NMR analysis, it appeared to degrade very quickly afterward before the next reaction could be carried out. NMR data were recorded quickly in a single time; however, the sample degraded before the material could be recovered and used in the next step. The use of a 10% K$_2$CO$_3$/silica plug appeared to less degrade **19** as opposed to traditional silica and celite plugs. HRMS data were recorded as well. TLC: silica gel (60% ethyl acetate/hexane) R_f = 0.22. ^{1}H NMR (400 MHz, CDCl$_3$): δ 6.16–6.12 (m, 2H), 5.66 (br s, 1H), 4.81 (q, J = 6.6 Hz, 1H), 3.82 (t, J = 6.4 Hz, 1H), 3.72–3.58 (m, 2H), 3.29–3.07 (m, 2H), 2.14 (br s, 1H), 1.79 (br s, 3H), 1.50 (d, J = 6.6, Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ (157.1, 157.0), (149.7, 149.6), 138.4, 118.0, (108.7, 108.7), (106.3, 106.2), (65.9, 65.8), (63.7, 63.6), 55.7, 26.9, (21.4, 21.3), 18.3. HRMS-ESI (+) *m/z*: calcd for C$_{12}$H$_{16}$O$_4$SNa [M + Na]$^+$, 279.0662; found, 279.0665.
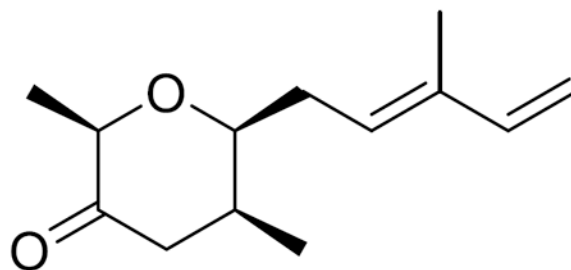
21

(2*R*,5*S*,6*S*)-2,5-Dimethyl-6-((*E*)-3-methylpenta-2,4-dien-1-yl)dihydro-2*H*-pyran-3(4*H*)-one (21).[19,21,22]

To a one-neck oven-dried 10 mL round-bottom flask, copper (I) iodide (CuI, 108 mg, 0.56 mmol, 3.0 equiv) was flame-dried under vacuum until it formed a canary yellow color and then cooled under argon. Diethyl ether (Et$_2$O, 1.0 mL) was then added, the solution was cooled to 0 °C, and methyl lithium (MeLi, 3.1 M in diethyl ether, 371 μL, 1.15 mmol, 6.1 equiv) was added and stirred at 0 °C for 30 min. The reaction turned from a yellow color to orange and then became clear. In a separate flask, enone diene **17** (12 mg, 0.06 mmol, 1.0 equiv) was dissolved in Et$_2$O (1.35 mL) and cooled to −78 °C. The solution of the starting material was then cannulated to the *in situ* formed Gilman reagent at −78 °C and stirred. The reaction turned from a yellow to orange yellow color and eventually grew darker over time. Hours later, it developed a dark brown-green color. After the reaction via TLC analysis (5 h), it was removed from the bath and quenched slowly with H$_2$O (2.5 mL) and brought to ambient temperature. The crude mixture was extracted with ethyl acetate three times, washed with brine, dried with Na$_2$SO$_4$, and concentrated under reduced pressure. The crude material was purified via silica column chromatography using 5% ethyl acetate/hexane as the eluent. β-Methyl ketone **21** was isolated as a clear yellow oil (34.5 mg, 91%). TLC: silica gel (10% ethyl acetate/hexane) R_f = 0.36. $[\alpha]_D^{20}$ − 19.6 (*c* 0.467, CHCl$_3$); ^{1}H NMR ^{1}H NMR (400 MHz, CDCl$_3$): δ 6.39 (dd, *J* = 17.4, 10.7 Hz, 1H), 5.50 (t, *J* = 7.4 Hz, 1H), 5.14 (d, *J* = 17.3 Hz, 1H), 4.98 (d, *J* = 10.7 Hz, 1H), 3.96 (q, *J* = 6.5 Hz, 1H), 3.90 (td, *J* = 7.0, 1.7 Hz, 1H), 2.64 (dd, *J* = 15.2, 6.1 Hz, 1H), 2.48 (dt, *J* = 14.0, 6.7 Hz, 1H), 2.38–2.25 (m, 3H), 1.78 (s, 3H), 1.28 (d, *J* = 6.5 Hz, 3H), 0.98 (d, *J* = 7.0 Hz, 3H). ^{13}C{^{1}H} NMR (200 MHz, CDCl$_3$): δ 208.9, 141.3, 136.1, 128.1, 111.6, 79.7, 78.9, 46.9, 35.1, 31.6, 15.2, 13.3, 12.1. LRMS-ESI (+) *m/z*: 209.1 [M + H]$^+$.

22

Ethyl (*E*)-3-Methylpenta-2,4-dienoate (22).[30]

To a two-neck oven-dried 500 mL round-bottom flask, MePPh$_3$Br (8.4 g, 23.5 mmol, 1.07 equiv) was added with a stir bar and stirred under vacuum while heating the flask to 110 °C in an oil bath overnight. The flask was cooled under argon and then freshly distilled THF (157 mL, 0.14 M) was added, followed by *n*-butyllithium (*n*-BuLi, 1.6 M in hexane, 15 mL, 24 mmol, 1.1 equiv) at −78 °C. The solution changed from white slurry to golden. The flask was then allowed to warm to 0 °C over the course of an hour and then recooled to −45 °C, and ethyl-3-methyl-4-oxocronate (3 mL, 22 mmol, 1.0 equiv) was added slowly. The reaction changed from golden orange to pink. After 2 hours, the reaction was removed from a −45 °C bath and quenched with H$_2$O (150 mL), turning purple. The crude mixture was extracted three times with diethyl ether and then concentrated under reduced pressure on ice because of product volatility. The crude mixture was purified via a short silica plug using 5% diethyl ether/hexane as the eluent. Diene ester **22** was isolated as a clear liquid. The product was then used without any further purification. TLC: silica gel (10% ethyl acetate/hexane) R_f = 0.24 ^{1}H NMR (400 MHz, CDCl$_3$): δ 6.40 (ddd, *J* = 17.4, 10.6, 0.8 Hz, 1H), 5.79 (s, 1H), 5.61 (d, *J* = 17.4 Hz, 1H), 5.38 (d, *J* = 10.6 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 2.27 (d, *J* = 1.2 Hz, 3H), 1.28 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (126 MHz, CDCl$_3$): δ 167.1, 152.1, 140.3, 120.2, 119.5, 60.0, 14.5, 13.2.

23
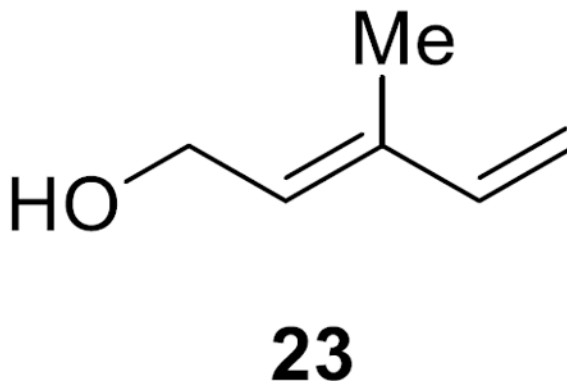
(*E*)-3-Methylpenta-2,4-dien-1-ol (23).[30]

To a two-neck oven-dried 500 mL round-bottom flask, lithium aluminum hydride (LAH, 1 g, 27 mmol, 1.5 equiv) was added to diethyl ether (135 mL). In a separate flask, diene ester **22** (2.5 g, 18 mmol, 1.0 equiv) was dissolved in diethyl ether (Et$_2$O, 43 mL) and cannulated

to the flask containing LAH at 0 °C. The reaction was removed from the ice bath, equipped with a reflux condenser, and heated in an oil bath to reflux (50 °C) for 2 h. The reaction was then cooled to 0 °C again and quenched with ice and cold water slowly (100 mL) and then 10% H_2SO_4 (100 mL). The reaction was then extracted with diethyl ether three times, dried over Na_2SO_4, and concentrated under reduced pressure on ice to yield diene alcohol **23** as a colorless liquid (1.7 g, 97% yield, 78% over two steps). TLC: silica gel (10% ethyl acetate/hexane) R_f = 0.09. ^{1}H NMR (500 MHz, CDCl$_3$): δ 6.39 (ddd, J = 17.4, 10.7, 0.7 Hz, 1H), 5.68 (t, J = 7.0 Hz, 1H), 5.22 (d, J = 17.4 Hz, 1H), 5.07 (d, J = 10.7 Hz, 1H), 4.30 (d, J = 6.8 Hz, 2H), 1.79 (d, J = 1.1 Hz, 3H), 1.33 (br s, 1H). ^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$): δ 140.8, 136.5, 130.5, 113.3, 59.5, 12.0.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

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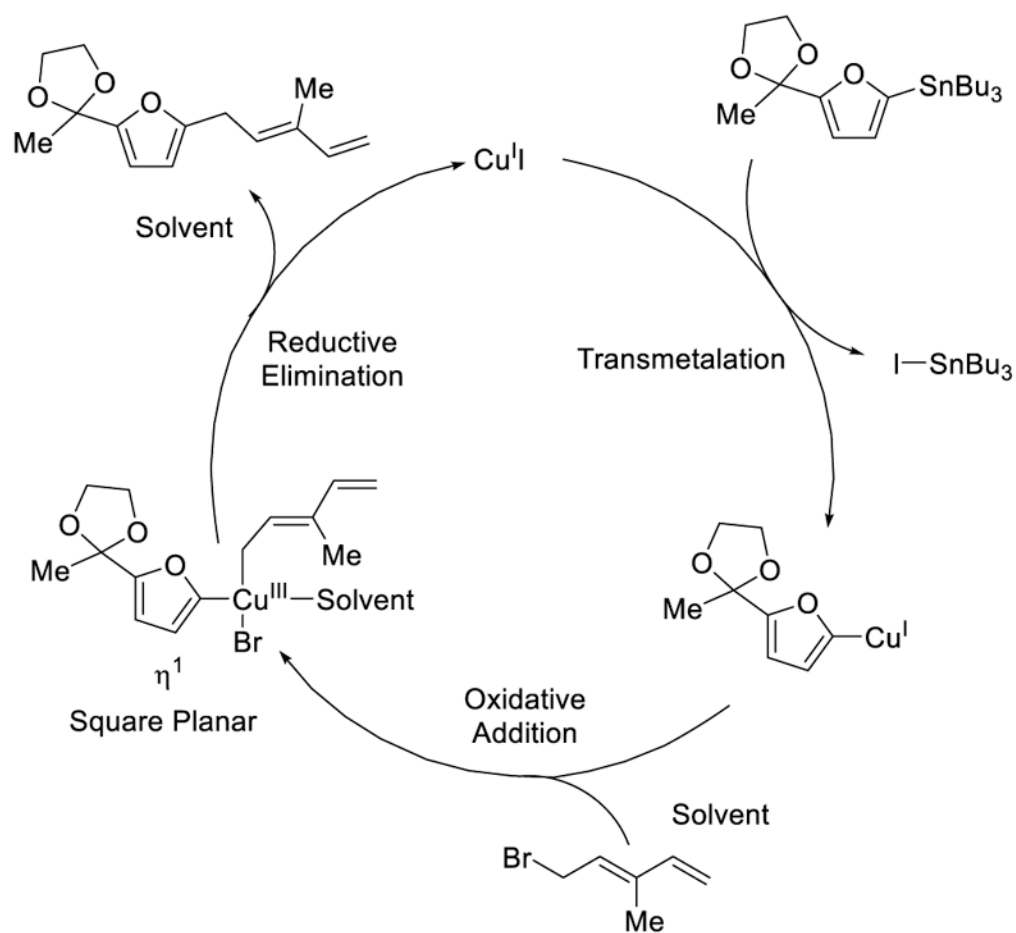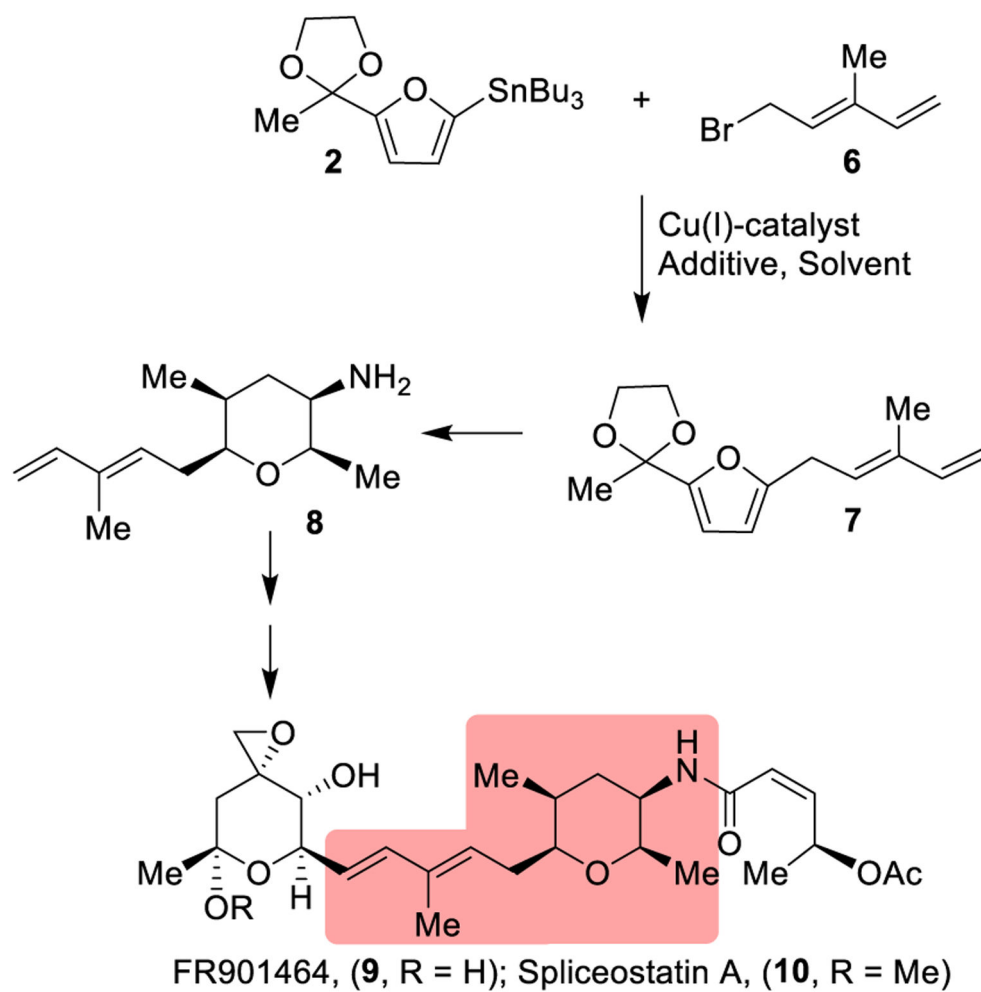
Figure 1.
Plausible mechanism for the solvent coordination and *E*-selective Cu-catalyzed Stille cross-coupling reaction.

Previous work

Present work

Scheme 1.
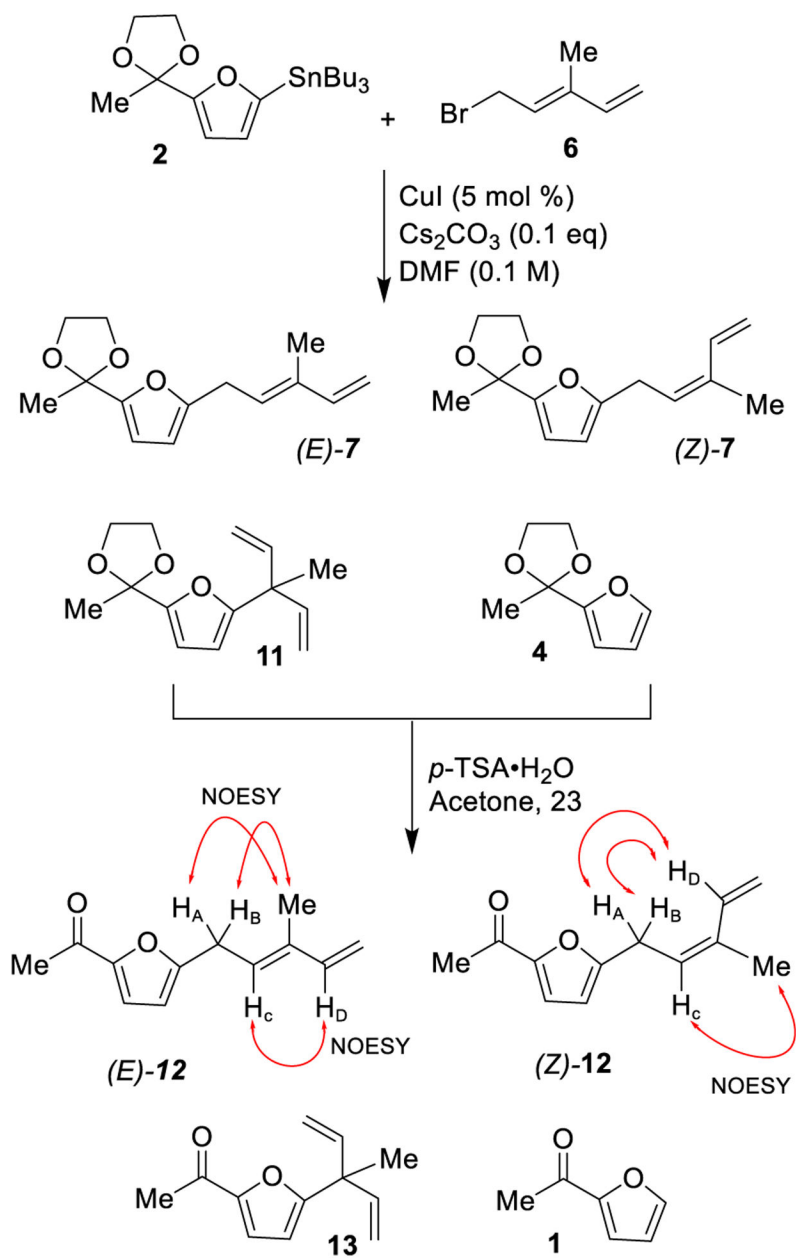Selected Prior Cu-Catalyzed Stille Reactions and Present Work
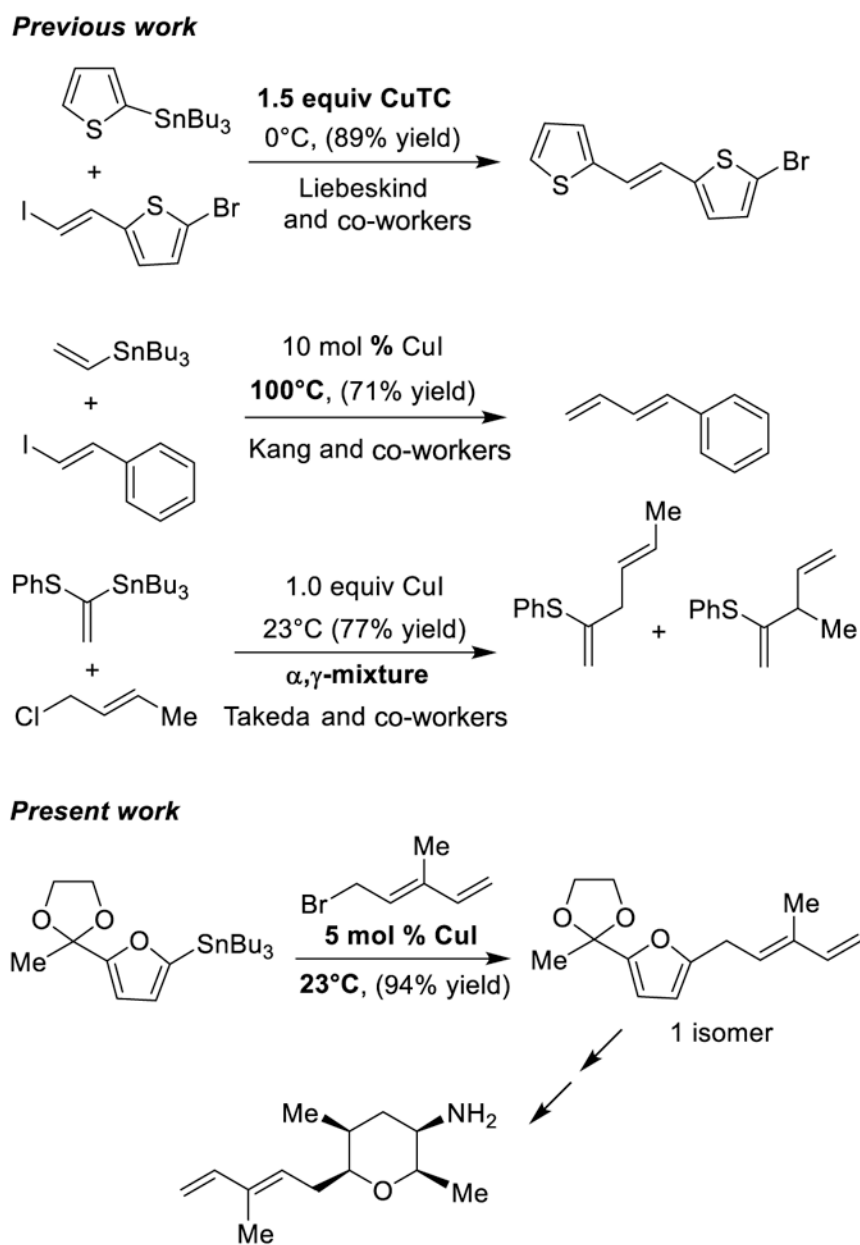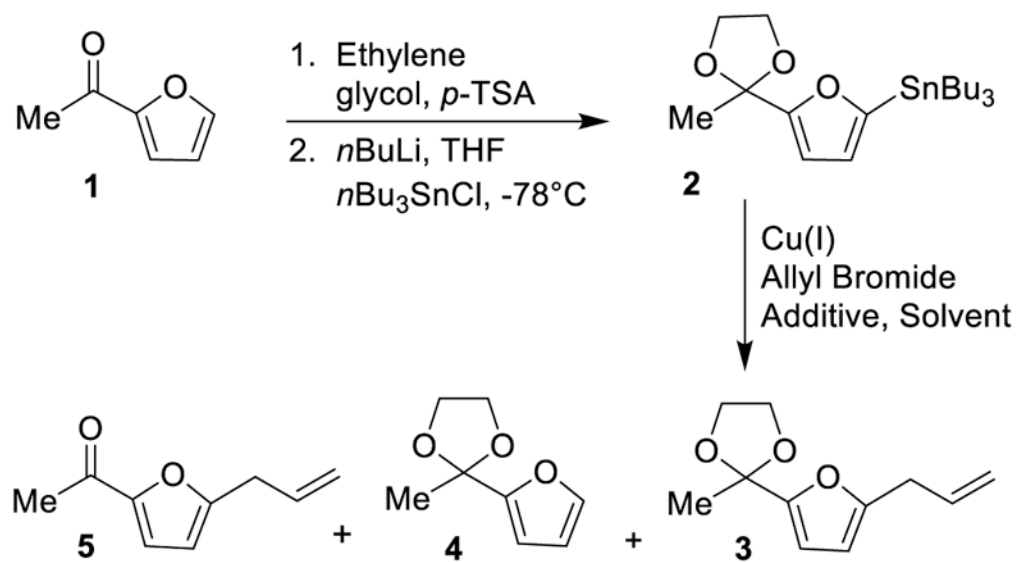
Scheme 2.
Cu-Catalyzed Stille Cross-Coupling Reactions of Organnostannane and Allyl Bromide

Scheme 3.
Cu-Catalyzed Stille Cross-Coupling and Synthetic Strategy of Tetrahydropyran Derivative 8 for Spliceostatins

Scheme 4.
Cu-Catalyzed Stille Reactions of Organnostannane and Bromo Diene 6

Scheme 5.
Optically Active Synthesis of the Functionalized Tetrahydropyran Derivative 8

Table 1.

Optimization of the Cu-Catalyzed Reaction of Stannane 2 and Allyl Bromide [a,b]

entry	catalyst (mol %)	additive (10 mol %)	% yield 3	ratio[c] 3:4
1	CuI (50)	Na_2CO_3	73	5:1
2	CuI (50)	Na_2CO_3	77	≫20:1
3	CuCN (50)	Na_2CO_3	38	10:1
4	CuI (50)	Na_2CO_3	84	10:1
5	CuBr-DMS (50)	Na_2CO_3	79	ND
6	$Cu(ACN)_4BF_4$ (5)	Na_2CO_3	87	≫20:1
7	CuI (5)	Na_2CO_3	89	>20:1
8	CuCl (5)	None	79	>10:1
9	CuCl (5)	Na_2CO_3	89	>10:1
10	CuCl (5)	Li_2CO_3	85	>15:1
11	CuCl (5)	Cs_2CO_3	83	>20:1
12	CuOAc (5)	Cs_2CO_3	80[d]	>20:1
13	$(CuOTf)_2 \cdot PhH$ (5)	Cs_2CO_3	79[d]	ND
14	Cu_2O (5)	Cs_2CO_3	78	ND
15	CuTC (5)	Cs_2CO_3	43	4:1
16	**CuI (5)**	**Cs_2CO_3**	**90[e]**	**>20:1**

[a]Reaction time of 3–120 h depending on the desired product and scale of reaction.

[b]Solvents used: DMSO/THF (3:1) for entries 1–3, DMF for entries 4–15.

[c]Ratio determined by ^{1}H NMR (400 MHz).

[d]Yield of ketone **5**.

[e]Gram scale; ND = not determined.

Table 2.

Cu-Catalyzed Reaction of Stannane 2 and (*E*)-5-Bromo-3-methyl-penta-1,3-diene 6[a,b]

entry	additive (10 mol %)	solvent	% yield (BRSM)	ratio (*E*)-7:(*Z*)-7:11:4[b]
1	Cs$_2$CO$_3$	DMF	72	10:3:2:4
2	Cs$_2$CO$_3$	DMSO/THF (3:1)	69[c]	>20:8:2:1
3[d]	Cs$_2$CO$_3$	DMF	77	10:4:1:4
4	Cs$_2$CO$_3$	THF	63 (87)	>20:1:1:2
5	Cs$_2$CO$_3$[e]	DMF/THF (1:3)	90	>20:1:1:4
6	Cs$_2$CO$_3$[e]	MeCN	94[f]	>20:1:1:1
7	Cs$_2$CO$_3$[e]	MeCN	85[g]	>20:1:1:1

[a] Reaction time of 24–96 h depending on the desired product and scale of reaction.

[b] Ratio determined via NMR.

[c] Ketone products formed.

[d] CuI added last.

[e] >0.1 equiv Cs$_2$CO$_3$ added.

[f] Multigram scale.

[g] Yield of ketone (*E*)-**12** over two steps, decagram scale. BRSM = based on the recovered starting material.

Table 3.

Synthesis of Enone 17 and Optimization of Kishi Anomeric Reduction

entry	acid (equiv), Et$_3$SiH (equiv)	temp	yield (4 steps)	ratio 17:16[a]
1	BF$_3$·Et$_2$O (2), Et$_3$SiH (2.5)	−78	28%	10:1
2	BF$_3$·Et$_2$O (1.2), Et$_3$SiH (1.2)	−78	24%	>20:1
3	BF$_3$·Et$_2$O (3), Et$_3$SiH (3)	−78 °C to 0 °C	Degraded	ND
4	TFA (15), Et$_3$SiH (10)	−45 °C	33%	2:1
5	BF$_3$·Et$_2$O (5), Et$_3$SiH (5)	−60 °C to −45 °C	20%	>20:1
6	TFA (2), Et$_3$SiH (6)	−78 °C[b]	ND	1:>20
7	BF$_3$·Et$_2$O (2), Et$_3$SiH (6)	−78 °C[b]	60%	>10:1

[a]Ratio determined via NMR.

[b]Reacted for 7 h. ND = not determined.