Published in final edited form as:

Isr J Chem. 2020 March ; 60(3-4): 452–460. doi:10.1002/ijch.201900077.

Enantioselective Synthesis of Alkyl Allyl Ethers via Palladium-Catalyzed Redox-Relay Heck Alkenylation of *O*-Alkyl Enol Ethers

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Abstract

Herein we report a transformation that generates an array of enantiomerically enriched, alkyl allyl ethers. Cyclic, acyclic, and heteroatom-bearing alkenyl triflates undergo an enantioselective, palladium-catalyzed C–C bond formation with diverse acyclic *O*-alkyl enol ethers in good yields and excellent enantioselectivities.

Keywords

Asymmetric Catalysis; C–C Coupling; Heck Reaction

1. Introduction

Enantioenriched alkyl allyl ethers are present in a variety of biologically relevant and active molecules.^[1] Therefore, efforts have been reported in the development of new methods to synthesize this class of compounds. Traditionally, chiral allylic ethers have been prepared via the reaction of symmetric π -allyl complexes of Ir,^[2] Rh,^[3] and Pd^[4] with exogenous alcohol nucleophiles, or by enantioselective catalytic S_N2' reactions with allylic trichloroacetimidates.^[5] Alternatively, chiral allylic ethers have been synthesized via phosphine-catalyzed γ -oxidation of alkynoates.^[6] Despite noteworthy progress, the scope of these transformations has remained limited due to the nature of suitable electrophiles.

Recently, we have reported an alternative approach to allylic ethers through the use of enantioselective, redox-relay Heck reaction of *O*-aryl enol ethers (**B**) and alkenyl triflates (Scheme 1A).^[7]

The redox-relay Heck reaction differs from the traditional Heck reaction in that the unsaturation of the olefin is relayed along the carbon chain toward a redox acceptor, such as an alcohol, resulting in oxidation and yielding a carbonyl product.^[8] By using an enol ether, it was hypothesized that the oxygen of the alkene would significantly polarize it such that the migratory insertion would occur regioselectively, forming a bond between a cross coupling partner and the proximal alkenyl carbon with respect to the ether (See intermediate C, Scheme 1A). During the course of this work, we noted that *O*-aryl enol ethers effectively

participated in the reaction. However, when employing *O*-alkyl enol ethers of type **D**; E1cB products (**E**) were formed when submitted to our standard reaction conditions (Scheme 1B). We hypothesized that the increased basicity of the alkyl ether compared to aryl ethers may stabilize a six-membered-ring enol intermediate (**F**), which would ultimately lead to undesired product **E**. To overcome this challenge, we envisioned adding an additional methylene unit between the alcohol moiety and the ether, thus circumventing the E1cB pathway (Scheme 1C). Herein we disclose the expansion of our alkenylation protocol to the use of *O*-alkyl enol ethers bearing homoallylic and longer chain alcohols to provide enantiomerically enriched alkyl allylic ether products.

2. Results and Discussion

To begin our study, we subjected *O*-methyl enol ether **2a** to our previously reported reaction conditions developed for the alkenylation of *O*-aryl enol ethers. However, under these conditions, the redox-relay Heck product was not observed (Scheme 2A) but instead the conjugated diene **H** was observed in 10% yield by ¹H NMR with no further reaction of the starting materials observed. This suggests, after migratory insertion, Pd^{II}-alkyl intermediate **G** undergoes β-oxy elimination to give **H** (Path A) instead of β-hydride elimination occurring away from the newly generated stereocenter toward the formation of product **3** (Path B). One possible explanation for this is that due to the small size of the methyl substituent, β-oxy elimination preferentially transpires generating **H**, which may inhibit further catalysis (Scheme 2B).^[8b] As a result, we reasoned that increasing the size of the ether substituent could curtail β-oxy elimination and promote β-hydride elimination toward the remote alcohol. To test this, benzyl enol ether **2b** was selected and excitingly, provided 80% conversion to the desired product **3b** by ¹H NMR analysis, while suppressing the amount of the β-oxy elimination product observed. To further support the hypothesis that the substituent size was important in guiding the catalyst in producing the desired product, **2c** was prepared containing an *O*-cyclohexylmethyl enol ether and subjected to the reaction. Good conversion of this substrate to the Heck chain walking product was observed.

On the basis of these preliminary studies, we examined the efficiency and selectivity of the transformation for a variety of electron-deficient alkenyl triflates with benzyl enol ether **2b** (Table 1). Vinylogous lactone triflate **1a** provided **3b** in 78% yield and >99:1 enantiomeric ratio. An acyclic alkenyl triflate delivered allylic ether **3d** in 62% yield and 98:2 er, whereas the benzyl analog gave product **3e** in diminished yield (49%) and enantiomeric ratio (87:13). An alkenyl triflate containing a remote protected amine produced product **3f** in moderate yield and 90:10 er. An alkenyl triflate containing an alkenyl fluoride was tolerated under the reaction conditions and delivered **3g** in 38% yield and 98:2 er. A 5-membered cyclic alkenyl triflate gave product **3h** in 56% yield and >99:1 er. Lastly, this method can also be used with enol ether **2d**, a substrate that contains a secondary alcohol, to form products bearing a methyl ketone (**3i**, **3j**, and **3k**).

The scope of the *O*-alkyl substituent was then examined using enol triflate **1a** as the standard coupling partner (Table 2). Both electron-rich and electron-poor benzyl ethers were well-tolerated under the reaction conditions (**3l** and **3m**). This suggests that perturbing the electronics of the enol ether has a limited effect on the outcome of the reaction.

Trifluoroethyl enol ether provided **3n** in 76% yield. Homobenzyl ether reacted in moderate yield to generate product **3o**. A Boc-protected amino alcohol derivative delivered product **3p** in 49% yield, displaying a method of derivatizing amino alcohols. An enol ether bearing a styrenyl moiety also reacted in 42% yield, which indicates that enol ethers react significantly faster than styrenes with Pd^{II}-alkenyl complexes. All of these reactions proceed in high enantioselectivity. These results further support the hypothesis that the size of the ether substituent is an important attribute.

To test if enantiomerically enriched substrates impacted the reaction outcome, both enol ethers **2h** and **2i** were subjected to the reaction conditions. These enantiomeric substrates performed similarly giving diastereomeric products in high dr. This demonstrates a catalyst controlled, enantioselective bond-forming event, which is confirmed by the use of a racemic mixture resulting in a 1:1 mixture of diastereomers, **3r** and **3s**. This indicates that the migratory insertion in this case is not sensitive to the adjacent chiral center.

The redox-relay Heck reaction can be used to set remote stereocenters if the Pd-catalyst can effectively migrate towards the alcohol functional group as a result of sequential β -hydride elimination/migratory insertion events. In order to examine the efficiency of this relay process, a bis-homoallylic alcohol substrate was subjected to the reaction conditions and gave δ -alkoxy carbonyl product **4a** in 51% yield and 95:5 er (Table 3). Additionally, an *O*-alkyl enol ether with two additional methylene units (**2l**) also reacted to give ζ -alkoxy carbonyl product **4b** in 54% yield and >99:1 er.

To further explore the scope of this disconnection strategy, we explored the use of aryl coupling partners. It was found that aryl diazonium nucleophiles with enol ether **2b** generated the corresponding arylated products in modest yield (**6**, Table 4). Both electron rich and electron poor aryl diazonium salts were tolerated. However, these reactions gave low levels of enantioselectivity under various conditions with the best enantioselectivity being that of **6c**. Control reactions demonstrated that a non-catalytic, background reaction was occurring between the aryl diazonium and enol ether (see supplementary information).

3. Conclusion

In summary, we have expanded the redox-relay Heck reaction to the use of *O*-alkyl enol ethers as a coupling partner. The majority of the products have been generated in good yields and excellent enantioselectivities. The use of enantiomerically enriched substrates allowed us to determine that the enantioselectivity is under complete catalyst control. Unfortunately, arylation of *O*-alkyl enol ethers occurred in moderate yields and poor enantioselectivities.

4. Experimental

4.1 General

All reactions were performed using oven-dried or flame-dried glassware equipped with a magnetic stir bar under an atmosphere of nitrogen unless otherwise noted.

Tris(dibenzylideneacetone)dipalladium(0)-chloroform adduct (Pd₂dba₃·CHCl₃) was prepared according to the reported literature procedure.^[9] All reagents were purchased from

commercial suppliers and used without further purification. Dichloromethane, tetrahydrofuran (THF), dimethylformamide (DMF), and acetonitrile were passed through a column of activated alumina immediately prior to use. ^1H NMR spectra were obtained in CDCl_3 or C_6D_6 at 500 MHz. Chemical shifts are reported in ppm and referenced to the CHCl_3 singlet at 7.26 ppm or C_6H_6 singlet at 7.15 ppm. ^{13}C NMR spectra were obtained in CDCl_3 or C_6D_6 125 MHz and referenced to the center peak of the CDCl_3 triplet at 77.0 ppm or C_6D_6 triplet at 128.6 ppm. The abbreviations s, d, t, quint, sext, sept, dd, ddd, dddd, dqd dt, and m stand for the resonance multiplicities singlet, doublet, triplet, quintet, sextet, septet, doublet of doublets, doublet of doublet of doublets, doublet of doublet of doublet of doublets, doublet of quartet of doublets, doublet of triplets, and multiplet, respectively. Thin-layer chromatography was performed with EMD silica gel 60 F254 plates eluting with solvents indicated, visualized by a 254 nm UV lamp and stained with phosphomolybdic acid (PMA). Flash chromatography was performed using EM reagent silica 60 (230–400 mesh). IR spectra were recorded using a Thermo Nicolet FT-IR. HRMS data were obtained on a Waters LCP Premier XE instrument by ESI/TOF. SFC (supercritical fluid chromatography) analysis was performed at 40 °C, using a waters UPC² instrument fitted with AD-H, OZ-H, CEL1, CEL2, AMY1, AY-H, AS-H, OJ-H and OD columns.

4.2 General Procedure A

To a dry 6-dram vial, equipped with a stir bar, was added $\text{Pd}_2\text{dba}_3\cdot\text{CHCl}_3$ (21 mg, 0.020 mmol, 5.0 mol %), ligand (15 mg, 0.06 mmol, 12 mol %), 3 Å MS (200 mg, 50 mg/mmol 1) and sealed using a rubber septum. The reaction vial was evacuated and refilled with N_2 three times. To this, DMF (4 mL) was added under nitrogen and the resulting mixture was stirred for 10 min at room temperature. Next, the substrate alkenol (**2**) (0.4 mmol) and alkenyl triflate **1** (0.4 mmol) were added sequentially, via micro-syringe. The resulting mixture was stirred at room temperature for 12 h. The mixture was then diluted with EtOAc (150 mL) and washed with H_2O (2×30 mL) and brine (30 mL). The combined aqueous layers were back extracted using EtOAc (30 mL) and the organic layers were combined, dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified using silica gel chromatography.

4.3 Product Synthesis

(Z)-4-(benzyloxy)-5-(2-oxodihydrofuran-3(2H)-ylidene)hexanal (3b): The general procedure A was followed using (*E*)-4-(benzyloxy)but-3-en-1-ol (**2b**, 71 mg, 0.40 mmol) and (*Z*)-1-(2-oxodihydrofuran-3(2H)-ylidene)ethyl trifluoromethanesulfonate (**1a**, 110 mg, 0.40 mmol). Purification of this material by chromatography on silica gel (gradient elution: 5→10% EtOAc/hexanes) afforded product **3a** as a colorless oil (92 mg, 78% yield): R_f = 0.14 (30% EtOAc/hexanes); ^1H NMR (500 MHz, CDCl_3) δ 9.75 (t, J = 1.9 Hz, 1H), 7.36 – 7.27 (m, 5H), 5.62 (dd, J = 9.0, 4.3 Hz, 1H), 4.41 – 4.31 (m, 4H), 2.90 – 2.84 (m, 2H), 2.65 (m, 1H), 2.48 (m, 1H), 2.02 (m, 1H), 1.87 (s, 3H), 1.80 – 1.73 (m, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 202.09, 169.58, 153.60, 137.98, 128.33, 127.88, 127.72, 121.99, 74.41, 71.70, 64.89, 40.55, 27.79, 26.82, 15.65; IR (neat) 2922, 1723, 1672, 1653, 1602, 1532, 1454, 1154, 1024 cm^{-1} ; HRMS (ESI-TOF) m/z calcd for $\text{C}_{17}\text{H}_{20}\text{O}_4\text{Na}$ ($\text{M}+\text{Na}$)⁺: 311.1259, found 311.1260; $[\alpha]_D^{20}$ = –2.4 (c = 0.4, CHCl_3).

(Z)-4-(cyclohexylmethoxy)-5-(2-oxodihydrofuran-3(2H)-ylidene)hexanal

(3c): The general procedure A was followed using (*E*)-4-(cyclohexylmethoxy)but-3-en-1-ol (**2c**, 74 mg, 0.40 mmol) and (*Z*)-1-(2-oxodihydrofuran-3(2H)-ylidene)ethyl trifluoromethanesulfonate (**1a**, 110 mg, 0.40 mmol). Purification of this material by chromatography on silica gel (gradient elution: 5→10% EtOAc/hexanes) afforded product **3c** as a colorless oil (79 mg, 67% yield): R_f = 0.18 (30% EtOAc/hexanes); $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 9.76 (t, J = 1.8 Hz, 1H), 5.38 (dd, J = 9.2, 4.6 Hz, 1H), 4.36 (ddd, J = 8.4, 6.6, 2.2 Hz, 2H), 3.05 (qd, J = 9.0, 6.3 Hz, 2H), 2.97 – 2.83 (m, 2H), 2.63 (dddd, J = 17.1, 8.4, 6.5, 1.9 Hz, 1H), 2.47 (dddd, J = 17.6, 8.0, 6.0, 1.5 Hz, 1H), 1.95 (dddd, J = 20.4, 14.6, 8.8, 6.6 Hz, 1H), 1.82 (t, J = 1.8 Hz, 3H), 1.71 (dddd, J = 16.7, 14.5, 5.5, 2.8 Hz, 7H), 1.21 (t, J = 7.1 Hz, 2H), 1.14 (tt, J = 11.9, 2.7 Hz, 1H), 0.90 (ddt, J = 13.4, 9.5, 7.0 Hz, 2H). $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 202.31, 169.61, 154.61, 121.51, 75.29, 74.58, 64.88, 40.64, 38.19, 30.21, 30.03, 27.78, 27.02, 26.96, 26.56, 25.84, 15.46. **IR** (neat) 2974, 2924, 1740, 1654, 1456, 1374, 1265, 1189, 1087, 1035 cm^{-1} . **HRMS** (ESI-TOF) m/z calcd for $\text{C}_{17}\text{H}_{26}\text{O}_4\text{Na}$ ($\text{M}+\text{Na}$) $^+$: 317.1723, found 317.1726; $[\alpha]_{\text{D}}^{20}$ = –8 (c = 0.2, CHCl_3).

ethyl (Z)-4-(benzyloxy)-2,3-dimethyl-7-oxohept-2-enoate (3d): The general procedure A was followed using (*E*)-4-(benzyloxy)but-3-en-1-ol (**2b**, 74 mg, 0.40 mmol) and ethyl (*Z*)-2-methyl-3-(((trifluoromethyl)sulfonyl)oxy)but-2-enoate (**1b**, 110 mg, 0.40 mmol). Purification of this material by chromatography on silica gel (gradient elution: 0→10% EtOAc/hexanes) afforded product **3d** as a colorless oil (75 mg, 62% yield): R_f = 0.21 (30% EtOAc/hexanes); $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 9.76 (d, J = 1.6 Hz, 1H), 7.37 – 7.28 (m, 5H), 4.57 (dd, J = 9.0, 4.8 Hz, 1H), 4.40 (d, J = 11.7 Hz, 1H), 4.21 (d, J = 11.7 Hz, 1H), 4.19 – 4.12 (m, 2H), 2.65 – 2.56 (m, 1H), 2.50 – 2.42 (m, 1H), 2.09 – 2.00 (m, 1H), 1.93 (s, 3H), 1.89 – 1.80 (m, 1H), 1.79 (s, 3H), 1.27 (t, J = 7.1 Hz, 3H); $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 202.34, 169.12, 143.75, 138.12, 128.26, 127.79, 127.54, 127.25, 77.68, 70.58, 60.49, 40.54, 26.49, 16.04, 14.17, 12.89; **IR** (neat) 2924, 2853, 1716, 1706, 1684, 1457, 1274, 1097 cm^{-1} ; **HRMS** (ESI-TOF) m/z calcd for $\text{C}_{18}\text{H}_{24}\text{O}_4\text{Na}$ ($\text{M}+\text{Na}$) $^+$: 327.1572, found 327.1576; $[\alpha]_{\text{D}}^{20}$ = –16.2 (c = 0.4, CHCl_3).

ethyl (Z)-2-benzyl-4-(benzyloxy)-3-methyl-7-oxohept-2-enoate (3e): The general procedure A was followed using (*E*)-4-(benzyloxy)but-3-en-1-ol (**2b**, 74 mg, 0.40 mmol) and ethyl (*Z*)-2-benzyl-3-(((trifluoromethyl)sulfonyl)oxy)but-2-enoate (**1c**, 140 mg, 0.40 mmol). Purification of this material by chromatography on silica gel (gradient elution: 0→10% EtOAc/hexanes) afforded product **3e** as a colorless oil (75 mg, 49% yield): R_f = 0.24 (30% EtOAc/hexanes); $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 9.75 (t, J = 1.5 Hz, 1H), 7.38 – 7.26 (m, 7H), 7.23 – 7.14 (m, 3H), 4.59 (dd, J = 9.0, 4.7 Hz, 1H), 4.43 (d, J = 11.7 Hz, 1H), 4.24 (d, J = 11.7 Hz, 1H), 4.05 (qd, J = 7.1, 1.7 Hz, 2H), 3.75 (s, 2H), 2.68 – 2.55 (m, 1H), 2.52 – 2.39 (m, 1H), 2.12 – 2.02 (m, 1H), 1.96 – 1.87 (m, 1H), 1.85 (s, 2H), 1.12 (t, J = 7.1 Hz, 2H); $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 202.21, 168.44, 145.24, 138.76, 138.05, 131.05, 128.41, 128.31, 128.12, 127.86, 127.62, 126.17, 77.97, 70.77, 60.52, 40.59, 35.91, 26.65, 14.03, 13.03; **IR** (neat) 2924, 2851, 1708, 1652, 1495, 1454, 1265, 1206, 1076 cm^{-1} ; **HRMS** (ESI-TOF) m/z calcd for $\text{C}_{24}\text{H}_{28}\text{O}_4\text{Na}$ ($\text{M}+\text{Na}$) $^+$: 403.1885, found 403.1892. $[\alpha]_{\text{D}}^{20}$ = –13.8 (c = 0.5, CHCl_3).

ethyl (Z)-4-(benzyloxy)-2-(3-(1,3-dioxoisindolin-2-yl)propyl)-3-methyl-7-oxohept-2-enoate (3f): The general procedure A was followed using (*E*)-4-(benzyloxy)but-3-en-1-ol (**2b**, 74 mg, 0.40 mmol) and ethyl (*Z*)-5-(1,3-dioxoisindolin-2-yl)-2-(1-(((trifluoromethyl)sulfonyl)oxy)ethylidene)pentanoate (**1d**, 180 mg, 0.40 mmol). Purification of this material by chromatography on silica gel (gradient elution: 0→10% EtOAc/hexanes) afforded product **3f** as a colorless oil (78 mg, 41% yield): R_f = 0.16 (30% EtOAc/hexanes); $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 9.72 (t, J = 1.7 Hz, 1H), 7.84 (dd, J = 3.1, 2.4 Hz, 2H), 7.71 (dd, J = 3.1, 2.4 Hz, 2H), 7.34 – 7.28 (m, 2H), 7.27 – 7.23 (m, 3H), 4.42 (dd, J = 7.6, 3.8 Hz, 1H), 4.37 (d, J = 11.7 Hz, 1H), 4.18 (d, J = 11.9 Hz, 1H), 4.15 – 4.07 (m, 2H), 3.72 (t, J = 7.3 Hz, 2H), 2.54 (dddd, J = 16.7, 8.3, 6.9, 1.9 Hz, 1H), 2.46 – 2.33 (m, 3H), 2.01 (ddt, J = 14.2, 8.7, 7.3 Hz, 1H), 1.86 – 1.78 (m, 2H), 1.76 (s, 3H), 1.20 (t, J = 7.1 Hz, 3H). $^{13}\text{C NMR}$ (125 MHz, cdCl_3) δ 202.12, 168.72, 168.28, 143.40, 138.14, 133.93, 132.10, 131.37, 128.28, 127.85, 127.56, 123.19, 78.01, 70.63, 60.58, 40.46, 37.74, 27.71, 27.25, 26.49, 14.11, 12.38. **IR** 3031, 2931, 2361, 2338, 1772, 1706, 1652, 1437, 1395, 1206, 1037 cm^{-1} . **HRMS** (ESI-TOF) m/z calcd for $\text{C}_{28}\text{H}_{31}\text{NO}_6\text{Na}$ ($\text{M}+\text{Na}^+$): 500.2049, found: 500.2049. $[\alpha]_D^{20}$ = –14.2 (c = 0.4, CHCl_3).

ethyl (E)-4-(benzyloxy)-2-fluoro-3-methyl-7-oxohept-2-enoate (3g): The general procedure A was followed using (*E*)-4-(benzyloxy)but-3-en-1-ol (**2b**, 72 mg, 0.40 mmol) and ethyl (*E*)-2-fluoro-3-(((trifluoromethyl)sulfonyl)oxy)but-2-enoate (**1e**, 110 mg, 0.40 mmol). Purification of this material by chromatography on silica gel (gradient elution: 0→8% Et_2O /hexanes) afforded product **3g** as a colorless oil (47 mg, 38% yield): R_f = 0.42 (30% EtOAc/hexanes); $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 9.75 (t, J = 1.6 Hz, 1H), 7.37 – 7.25 (m, 5H), 5.10 (ddd, J = 9.1, 4.6, 2.0 Hz, 1H), 4.41 (d, J = 11.5 Hz, 1H), 4.31 – 4.21 (m, 3H), 2.60 (dtd, J = 17.2, 8.1, 6.5, 1.6 Hz, 1H), 2.47 (dddd, J = 17.8, 7.8, 6.3, 1.1 Hz, 1H), 2.14 – 2.00 (m, 1H), 1.87 (d, J = 4.6 Hz, 3H), 1.84 – 1.74 (m, 1H), 1.32 (t, J = 7.2 Hz, 3H). $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 201.77, 160.70 (d, J = 35.0 Hz), 137.75, 132.73 (d, J = 9.8 Hz), 128.43, 127.88, 127.85, 74.22 (d, J = 4.2 Hz), 71.14, 61.54, 40.40, 29.71, 26.68, 26.65, 9.66 (d, J = 8.5 Hz), 74.22 (d, J = 4.2 Hz), 9.66 (d, J = 8.5 Hz). $^{19}\text{F NMR}$ (471 MHz, CDCl_3) δ –120.4 (m). **IR** (neat) 2924, 2854, 1709, 1696, 1645, 1453, 1375, 1266, 1147, 1046 cm^{-1} . **HRMS** (ESI-TOF) m/z calcd for $\text{C}_{17}\text{H}_{21}\text{O}_4\text{NaF}$ ($\text{M}+\text{Na}^+$) 331.1322, found: 331.1321. $[\alpha]_D^{20}$ = –8.0 (c = 0.1, CHCl_3).

methyl 2-(1-(benzyloxy)-4-oxobutyl)cyclopent-1-ene-1-carboxylate (3h): The general procedure A was followed using (*E*)-4-(benzyloxy)but-3-en-1-ol (**2b**, 72 mg, 0.40 mmol) and methyl 2-(((trifluoromethyl)sulfonyl)oxy)cyclopent-1-ene-1-carboxylate (**1f**, 110 mg, 0.40 mmol). Purification of this material by chromatography on silica gel (gradient elution: 0→10% EtOAc/hexanes) afforded product **3h** as a colorless oil (47 mg, 38% yield): R_f = 0.26 (30% EtOAc/hexanes); $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 9.75 (t, J = 1.6 Hz, 1H), 7.39 – 7.26 (m, 5H), 5.04 (dd, J = 8.9, 4.9 Hz, 1H), 4.42 (d, J = 11.6 Hz, 1H), 4.32 (d, J = 11.6 Hz, 1H), 3.72 (s, 3H), 2.72 (dtt, J = 15.3, 7.6, 2.4 Hz, 1H), 2.61 (dtt, J = 24.0, 8.6, 7.4, 2.6 Hz, 3H), 2.47 (dddd, J = 17.6, 7.9, 6.3, 1.5 Hz, 1H), 2.06 (dddd, J = 14.3, 8.9, 7.9, 6.7 Hz, 1H), 1.85 (dq, J = 15.6, 7.8 Hz, 4H). $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 202.05, 165.89, 158.76, 138.11, 130.95, 128.30, 127.79, 127.63, 126.93, 74.65, 71.36, 51.20, 40.48, 33.83, 32.86, 26.69, 21.48. **IR** (neat) 2951, 1706, 1638, 1454, 1435, 1353, 1264, 1097 cm^{-1} .

HRMS (ESI-TOF) m/z calcd for $C_{18}H_{22}O_4Na$ ($M+Na$)⁺: 325.1416, found: 325.1421. $[\alpha]_D^{20} = -20.6$ ($c = 0.2$, $CHCl_3$).

(Z)-3-(3-(benzyloxy)-6-oxoheptan-2-ylidene)dihydrofuran-2(3H)-one (3i): The general procedure A was followed using (*E*)-4-(benzyloxy)pent-4-en-2-ol (**2d**, 77 mg, 0.40 mmol) and (*Z*)-1-(2-oxodihydrofuran-3(2H)-ylidene)ethyl trifluoromethanesulfonate (**1a**, 110 mg, 0.40 mmol). Purification of this material by chromatography on silica gel (gradient elution: 0→10% EtOAc/hexanes) afforded product **3i** as a colorless oil (86 mg, 71% yield): $R_f = 0.15$ (30% EtOAc/hexanes); 1H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.24 (m, 5H), 5.57 (dd, $J = 8.9, 5.0$ Hz, 1H), 4.38 – 4.31 (m, 4H), 2.85 (t, $J = 7.3$ Hz, 2H), 2.65 (ddd, $J = 17.6, 9.7, 5.6$ Hz, 1H), 2.44 (ddd, $J = 17.6, 9.6, 5.6$ Hz, 1H), 2.09 (s, 3H), 2.00 – 1.91 (m, 1H), 1.85 (t, $J = 1.8$ Hz, 3H), 1.74 – 1.65 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.33, 169.57, 153.88, 138.18, 128.24, 127.75, 127.58, 121.72, 74.36, 71.54, 64.81, 40.03, 29.86, 28.10, 27.74, 15.56. **IR** (neat) 2919, 2361, 2338, 1737, 1711, 1658, 1372, 1188, 1026 cm^{-1} . **HRMS** (ESI-TOF) m/z calcd for $C_{18}H_{22}O_4Na$ ($M+Na$)⁺: 325.1416, found: 325.1421. $[\alpha]_D^{20} = -14.0$ ($c = 0.8$, $CHCl_3$).

ethyl (Z)-4-(benzyloxy)-2,3-dimethyl-7-oxooct-2-enoate (3j): The general procedure A was followed using (*E*)-4-(benzyloxy)pent-4-en-2-ol (**2d**, 77 mg, 0.40 mmol) and ethyl (*Z*)-2-methyl-3-(((trifluoromethyl)sulfonyl)oxy)but-2-enoate (**1b**, 110 mg, 0.40 mmol). Purification of this product by silica gel chromatography gave a clear, colorless oil (67 mg, 53% yield). $R_f = 0.34$ (20% EtOAc/Hexanes) 1H NMR (500 MHz, $CDCl_3$) δ 7.35 – 7.26 (m, 5H), 4.53 (dd, $J = 8.7, 5.2$ Hz, 1H), 4.38 (d, $J = 11.7$ Hz, 1H), 4.20 (d, $J = 11.7$ Hz, 1H), 4.19 – 4.08 (m, 1H), 2.59 (ddd, $J = 17.3, 8.9, 6.1$ Hz, 1H), 2.41 (ddd, $J = 17.3, 8.7, 5.9$ Hz, 1H), 2.10 (s, 3H), 1.99 – 1.89 (m, 1H), 1.90 (s, 3H), 1.80 – 1.74 (m, 1H), 1.75 (s, 3H) 1.25 (t, $J = 7.0$ Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.47, 169.29, 143.64, 138.42, 128.24, 127.71, 127.45, 127.12, 77.79, 70.51, 60.44, 40.01, 29.86, 27.74, 16.04, 14.19, 12.83. **IR** (neat) 2928, 1710, 1453, 1365, 1276, 1212, 1164, 1093, 1067 cm^{-1} . **HRMS** (ESI-TOF) m/z calcd for $C_{19}H_{26}O_4Na$ ($M+Na$)⁺: 341.1729, found: 341.1736. $[\alpha]_D^{20} = -8.1$ ($c = 1.0$, $CHCl_3$).

methyl 2-(1-(benzyloxy)-4-oxopentyl)cyclopent-1-ene-1-carboxylate (3k): The general procedure A was followed using (*E*)-4-(benzyloxy)pent-4-en-2-ol (**2d**, 77 mg, 0.40 mmol) and methyl 2-(((trifluoromethyl)sulfonyl)oxy)cyclopent-1-ene-1-carboxylate (**1f**, 110 mg, 0.40 mmol). Purification of this product by silica gel chromatography gave a clear, colorless oil (60 mg, 47% yield). $R_f = 0.36$ (20% EtOAc/Hexanes) 1H NMR (500 MHz, $CDCl_3$) δ 7.38 – 7.30 (m, 5H), 5.05 (d, $J = 2.3$ Hz, 1H), 4.74 (d, $J = 11.9$ Hz, 1H), 4.48 (d, $J = 12.1$ Hz, 1H), 3.72 (d, $J = 2.2$ Hz, 3H), 2.66 – 2.56 (m, 2H), 2.58 – 2.45 (m, 1H), 2.45 – 2.32 (m, 1H), 2.14 – 2.03 (m, 1H), 2.00 – 1.91 (m, 1H), 1.88 – 1.74 (m, 4H), 1.32 (d, $J = 6.0$ Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.00, 138.30, 128.80, 128.27, 127.78, 127.62, 106.25, 74.25, 69.11, 51.13, 46.77, 38.72, 37.24, 35.18, 34.51, 33.66, 20.10. **IR** (neat) 2959, 2934, 2360, 2336, 1739, 1717, 1653, 1558, 1270, 1114 cm^{-1} . **HRMS** (ESI-TOF) m/z calcd for $C_{19}H_{24}O_4Na$ ($M+Na$)⁺: 339.1572, found: 339.1574. $[\alpha]_D^{20} = +64$ ($c = 0.2$, $CHCl_3$).

(Z)-5-(2-oxodihydrofuran-3(2H)-ylidene)-4-((4-

(trifluoromethyl)benzyl)oxy)hexanal (3l): The general procedure A was followed using (*E*)-4-((4-(trifluoromethyl)benzyl)oxy)but-3-en-1-ol (**2e**, 98 mg, 0.40 mmol) and (*Z*)-1-(2-oxodihydrofuran-3(2H)-ylidene)ethyl trifluoromethanesulfonate (**1a**, 110 mg, 0.40 mmol). Purification of this product by silica gel chromatography gel (gradient elution: 0→18% EtOAc/hexanes) gave a clear, colorless oil (81 mg, 57% yield); $R_f = 0.33$ (50% EtOAc/Hexanes) $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 9.76 (t, $J = 1.6$ Hz, 1H), 7.59 (d, $J = 8.1$ Hz, 2H), 7.41 (d, $J = 7.9$ Hz, 2H), 5.65 (dd, $J = 8.9, 4.9$ Hz, 1H), 4.42 (q, $J = 11.2, 10.2$ Hz, 2H), 4.36 (q, $J = 7.2$ Hz, 2H), 2.88 (td, $J = 7.5, 1.9$ Hz, 2H), 2.64 (dddd, $J = 16.9, 8.4, 6.5, 1.8$ Hz, 1H), 2.48 (dddd, $J = 17.7, 7.8, 6.1, 1.4$ Hz, 1H), 2.06 (ddd, $J = 20.7, 8.6, 6.6$ Hz, 1H), 1.87 (t, $J = 1.8$ Hz, 3H), 1.79 (ddt, $J = 11.1, 8.4, 6.2, 5.0$ Hz, 1H). $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 201.74, 169.55, 152.80, 142.11, 129.4 (q, $J = 64$ Hz), 127.70, 125.27 (q, $J = 3.8$ Hz), 74.62, 70.72, 64.87, 40.48, 29.69, 27.79, 26.68, 15.54. **HRMS** (ESI-TOF) m/z calcd for $\text{C}_{18}\text{H}_{19}\text{O}_4\text{NaF}_3$ ($\text{M}+\text{Na}^+$) 379.1133, found: 379.1136. $[\alpha]_D^{20} = -9.2$ ($c = 0.5$, CHCl_3).

(Z)-4-((4-methoxybenzyl)oxy)-5-(2-oxodihydrofuran-3(2H)-ylidene)hexanal

(3m): The general procedure A was followed using (*E*)-4-((4-methoxybenzyl)oxy)but-3-en-1-ol (**2f**, 83 mg, 0.40 mmol) and (*Z*)-1-(2-oxodihydrofuran-3(2H)-ylidene)ethyl trifluoromethanesulfonate (**1a**, 110 mg, 0.40 mmol). Purification of this product by silica gel chromatography gel (gradient elution: 0→18% EtOAc/hexanes) gave a clear, colorless oil (78 mg, 61% yield); $R_f = 0.31$ (50% EtOAc/Hexanes) $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 9.73 (t, $J = 1.7$ Hz, 1H), 7.21 (d, $J = 8.2$ Hz, 2H), 6.86 (d, $J = 8.3$ Hz, 2H), 5.58 (dd, $J = 9.2, 4.7$ Hz, 1H), 4.40 – 4.31 (m, 2H), 4.28 (s, 2H), 3.80 (s, 3H), 2.86 (t, $J = 7.9$ Hz, 2H), 2.61 (ddt, $J = 17.2, 6.4, 4.1$ Hz, 1H), 2.45 (ddd, $J = 17.3, 8.0, 6.3$ Hz, 1H), 2.00 (tt, $J = 15.6, 7.0$ Hz, 2H), 1.85 (t, $J = 1.8$ Hz, 3H), 1.74 (ddt, $J = 19.6, 8.9, 4.7$ Hz, 1H). $^{13}\text{C NMR}$ (125 MHz, cdcl_3) δ 202.22, 169.70, 153.93, 130.29, 129.72, 121.93, 113.84, 74.28, 71.54, 65.00, 55.39, 40.70, 29.82, 27.93, 27.02, 15.80. **IR** (neat) 2916, 2849, 1737, 1653, 1612, 1513, 1246, 1180, 1026 cm^{-1} **HRMS** (ESI-TOF) m/z calcd for $\text{C}_{19}\text{H}_{24}\text{O}_4\text{Na}$ ($\text{M}+\text{Na}^+$) 341.1378, found: 341.1372. $[\alpha]_D^{20} = +11$ ($c = 0.2$, CHCl_3).

(Z)-5-(2-oxodihydrofuran-3(2H)-ylidene)-4-(2,2,2-trifluoroethoxy)hexanal

(3n): The general procedure A was followed using (*E*)-4-(2,2,2-trifluoroethoxy)but-3-en-1-ol (**2g**, 77 mg, 0.40 mmol) and (*Z*)-1-(2-oxodihydrofuran-3(2H)-ylidene)ethyl trifluoromethanesulfonate (**1a**, 110 mg, 0.40 mmol). Purification of this product by silica gel chromatography gave a clear, colorless oil (85 mg, 76% yield). $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 9.73 (t, $J = 1.4$ Hz, 1H), 5.61 (dd, $J = 9.1, 4.7$ Hz, 1H), 4.34 (t, $J = 7.5$ Hz, 2H), 3.75 – 3.57 (m, 2H), 2.94 – 2.81 (m, 3H), 2.63 (dddd, $J = 18.0, 8.4, 6.3, 1.5$ Hz, 1H), 2.48 (dddd, $J = 18.0, 8.5, 6.0, 1.2$ Hz, 1H), 2.00 (dtd, $J = 14.9, 8.9, 6.2$ Hz, 1H), 1.82 (t, $J = 1.8$ Hz, 3H), 1.72 (ddt, $J = 14.1, 8.7, 5.8, 4.6$ Hz, 1H). $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 201.36, 169.47, 150.94, 127.80 (q, $J = 201.2$ Hz), 123.19, 76.12, 66.82 (q, $J = 32.2$ Hz), 64.94, 40.24, 27.79, 26.34, 15.28. **IR** (neat) 2931, 1739, 1713, 1660, 1437, 1378, 1270, 1157, 1111, 1035 cm^{-1} . **HRMS** (ESI-TOF) m/z calcd for $\text{C}_{12}\text{H}_{15}\text{O}_4\text{NaF}_3$ ($\text{M}+\text{Na}^+$) 303.0820, found: 303.0825. $[\alpha]_D^{20} = +8$ ($c = 0.1$, CHCl_3).

(Z)-5-(2-oxodihydrofuran-3(2H)-ylidene)-4-phenethoxyhexanal (3o): The general procedure A was followed using (*E*)-4-phenethoxybut-3-en-1-ol (**2g**, 83 mg, 0.40 mmol) and (*Z*)-1-(2-oxodihydrofuran-3(2H)-ylidene)ethyl trifluoromethanesulfonate (**1a**, 110 mg, 0.40 mmol). Purification of this product by silica gel chromatography gel (gradient elution: 0→18% EtOAc/hexanes) gave a clear, colorless oil (52 mg, 43% yield); $R_f = 0.34$ (50% EtOAc/Hexanes) $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 9.71 (t, $J = 1.5$ Hz, 1H), 7.31 – 7.26 (m, 2H), 7.20 (t, $J = 6.8$ Hz, 3H), 5.46 (dd, $J = 9.1, 4.7$ Hz, 1H), 4.35 (dd, $J = 5.8, 2.7$ Hz, 1H), 4.33 (dd, $J = 5.8, 2.3$ Hz, 1H), 3.56 – 3.43 (m, 2H), 2.84 (m, 4H), 2.55 (dddd, $J = 16.8, 8.5, 6.7, 1.8$ Hz, 1H), 2.42 (dddd, $J = 17.7, 7.8, 6.1, 1.3$ Hz, 1H), 1.94 (dtd, $J = 17.3, 9.0, 8.3, 6.7$ Hz, 1H), 1.71 (t, $J = 1.6$ Hz, 4H). $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 202.14, 169.60, 153.99, 138.90, 128.97, 128.26, 126.19, 121.72, 74.48, 70.24, 64.84, 40.54, 36.33, 27.75, 26.82, 15.36. **IR** (neat) 2923, 2854, 1739, 1717, 1653, 1455, 1376, 1267, 1194, 1091 cm^{-1} **HRMS** (ESI-TOF) m/z calcd for $\text{C}_{18}\text{H}_{22}\text{O}_4\text{Na}$ ($\text{M}+\text{Na}$) $^+$: 325.1416, found: 325.1422. $[\alpha]_D^{20} = -6$ ($c = 0.1$, CHCl_3).

tert-butyl (Z)-methyl(2-((6-oxo-2-(2-oxodihydrofuran-3(2H)-ylidene)hexan-3-yl)oxy)ethyl)carbamate (3p): The general procedure A was followed using tert-butyl (*E*)-(2-((4-hydroxybut-1-en-1-yl)oxy)ethyl)(methyl)carbamate (**2h**, 98 mg, 0.40 mmol) and (*Z*)-1-(2-oxodihydrofuran-3(2H)-ylidene)ethyl trifluoromethanesulfonate (**1a**, 110 mg, 0.40 mmol). Purification of this product by silica gel chromatography gel (gradient elution: 0→18% EtOAc/hexanes) gave a clear, colorless oil (70 mg, 49% yield); $R_f = 0.21$ (50% EtOAc/Hexanes) $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 9.75 (t, $J = 1.6$ Hz, 1H), 5.44 (dd, $J = 8.7, 4.9$ Hz, 1H), 4.35 (td, $J = 6.3, 1.7$ Hz, 2H), 3.49 – 3.26 (m, 5H), 2.91 – 2.86 (m, 1H, overlapping peaks) 2.89 (s, 3H), 2.61 (dtd, $J = 17.5, 10.2, 6.7, 1.7$ Hz, 1H), 2.47 (dddd, $J = 16.3, 9.3, 6.2, 1.1$ Hz, 1H), 1.96 (dtd, $J = 17.0, 8.4, 6.6$ Hz, 1H), 1.82 (t, $J = 1.7$ Hz, 3H), 1.74 (dtd, $J = 14.0, 8.3, 6.1, 5.0$ Hz, 1H), 1.45 (s, 9H). $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 201.82, 169.54, 155.76, 153.56, 148.16, 122.12, 79.36, 74.76, 67.64, 64.87, 49.48, 40.52, 28.44, 27.80, 26.83, 15.29. **IR** (neat) 2997, 2924, 1762, 1740, 1692, 1423, 1389, 1202, 1159, 1140, 1098 cm^{-1} **HRMS** (ESI-TOF) m/z calcd for $\text{C}_{18}\text{H}_{29}\text{NO}_6\text{Na}$ ($\text{M}+\text{Na}$) $^+$: 378.1893, found: 378.1897. $[\alpha]_D^{20} = -4.5$ ($c = 0.5$, CHCl_3).

(Z)-4-(cinnamyloxy)-5-(2-oxodihydrofuran-3(2H)-ylidene)hexanal (3q): The general procedure A was followed using tert-butyl (*E*)-4-(cinnamyloxy)but-3-en-1-ol (**2i**, 82 mg, 0.40 mmol) and (*Z*)-1-(2-oxodihydrofuran-3(2H)-ylidene)ethyl trifluoromethanesulfonate (**1a**, 110 mg, 0.40 mmol). Purification of this product by silica gel chromatography gel (gradient elution: 0→18% EtOAc/hexanes) gave a clear, colorless oil (53 mg, 42% yield); $R_f = 0.21$ (50% EtOAc/Hexanes) $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 9.77 (t, $J = 1.5$ Hz, 1H), 7.42 – 7.34 (m, 2H), 7.34 – 7.26 (m, 2H), 7.23 (tt, $J = 7.2, 1.3$ Hz, 1H), 6.56 (d, $J = 15.9$ Hz, 1H), 6.23 (dt, $J = 15.9, 6.1$ Hz, 1H), 5.57 (dd, $J = 8.9, 4.9$ Hz, 1H), 4.38 (t, $J = 7.3$ Hz, 2H), 4.00 (dddd, $J = 18.8, 12.4, 6.0, 1.3$ Hz, 2H), 2.66 (dddd, $J = 16.8, 8.3, 6.5, 1.7$ Hz, 1H), 2.50 (dddd, $J = 17.6, 9.7, 6.3, 1.7$ Hz, 1H), 2.07 – 1.96 (m, 2H), 1.88 (t, $J = 1.6$ Hz, 3H), 1.82 – 1.71 (m, 2H). $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 202.02, 169.58, 153.70, 149.60, 132.56, 128.51, 127.70, 126.47, 125.53, 74.26, 70.14, 64.86, 64.33, 40.54, 27.80, 26.70, 15.66. **IR** (neat) 3056, 3922, 1739, 1713, 1656, 1375, 1265, 1187, 1035, 968 cm^{-1} .

$[\alpha]_D^{20} = +32.5$ ($c = 0.4$, CHCl_3). **HRMS** (ESI-TOF) m/z calcd for $\text{C}_{19}\text{H}_{22}\text{O}_4\text{Na}$ ($\text{M}+\text{Na}^+$) 337.1416, found: 337.1427.

(Z)-5-(2-oxodihydrofuran-3(2H)-ylidene)-4-((S)-1-phenylethoxy)hexanal

(3r): General procedure A was followed using (*S,E*)-4-(1-phenylethoxy)but-3-en-1-ol (**2j**, 77 mg, 0.40 mmol) and (*Z*)-1-(2-oxodihydrofuran-3(2H)-ylidene)ethyl trifluoromethanesulfonate (**1a**, 110 mg, 0.40 mmol). Purification of this material by silica gel chromatography gave a colorless oil (56 mg, 46% yield) $R_f = 0.21$ (40% EtOAc in Hexanes) **¹H NMR** (500 MHz, CDCl_3) δ 9.65 (t, $J = 1.4$ Hz, 1H), 7.36 – 7.31 (m, 2H), 7.29 – 7.24 (m, 3H), 5.34 (dd, $J = 9.1, 4.8$ Hz, 1H), 4.36 (td, $J = 7.5, 0.7$ Hz, 2H), 4.19 (q, $J = 6.5$ Hz, 1H), 2.95 (ddd, $J = 15.9, 7.6, 1.5$ Hz, 1H), 2.88 (ddd, $J = 15.9, 7.6, 1.5$ Hz, 1H), 2.48 (dddd, $J = 17.8, 8.8, 6.1, 1.7$ Hz, 1H), 2.24 (dddd, $J = 17.8, 8.7, 6.0, 1.3$ Hz, 1H), 1.94 (t, $J = 1.7$ Hz, 3H), 1.89 (ddt, $J = 14.8, 9.0, 6.2$ Hz, 1H), 1.65 (dddd, $J = 14.0, 9.0, 6.1, 5.1$ Hz, 1H), 1.41 (d, $J = 6.6$ Hz, 3H). **¹³C NMR** (125 MHz, CDCl_3) δ 202.2, 169.1, 154.1, 142.9, 128.4, 127.8, 126.6, 121.6, 76.3, 71.7, 64.8, 40.4, 27.9, 26.8, 23.7, 15.9. **IR** (neat) 2972, 2927, 1738, 1719, 1658, 1493, 1452, 1374, 1265, 1187 cm^{-1} . **HRMS** (ESI-TOF) m/z calcd for $\text{C}_{18}\text{H}_{22}\text{O}_4\text{Na}$ ($\text{M}+\text{Na}^+$) 325.1416, found: 325.1423. $[\alpha]_D^{20} = -59^\circ$ ($c = 0.4$, CHCl_3).

(Z)-5-(2-oxodihydrofuran-3(2H)-ylidene)-4-((R)-1-phenylethoxy)hexanal

(3s): General procedure A was followed using (*R,E*)-4-(1-phenylethoxy)but-3-en-1-ol (**2k**, 77 mg, 0.40 mmol) and (*Z*)-1-(2-oxodihydrofuran-3(2H)-ylidene)ethyl trifluoromethanesulfonate (**1a**, 110 mg, 0.40 mmol). Purification of this material by silica gel chromatography gave a colorless oil (56 mg, 46% yield) $R_f = 0.21$ (40% EtOAc in Hexanes) **¹H NMR** (500 MHz, CDCl_3) δ 9.80 (t, $J = 1.7$ Hz, 1H), 7.27 – 7.18 (m, 5H), 5.67 (dd, $J = 9.2, 4.7$ Hz, 1H), 4.36 (q, $J = 6.4$ Hz, 1H), 4.23 (td, $J = 9.2, 4.9$ Hz, 1H), 4.10 (td, $J = 8.9, 6.6$ Hz, 1H), 2.64 (ttd, $J = 15.3, 8.9, 6.9, 2.2$ Hz, 2H), 2.49 (dddd, $J = 17.4, 7.6, 6.1, 1.3$ Hz, 2H), 2.01 (dddd, $J = 14.8, 9.1, 8.0, 6.9$ Hz, 1H), 1.69 (ddt, $J = 14.1, 8.1, 6.1, 4.8$ Hz, 1H), 1.61 (t, $J = 1.6$ Hz, 3H), 1.44 (d, $J = 6.5$ Hz, 3H). **¹³C NMR** (125 MHz, CDCl_3) δ 202.18, 169.54, 153.53, 145.03, 143.82, 127.92, 126.53, 78.16, 73.21, 64.67, 40.67, 27.56, 26.95, 25.92, 22.68, 15.96. **IR** (neat) 3387, 2973, 2925, 2853, 1736, 1719, 1656, 1451, 1374, 1451, 1375, 1027 cm^{-1} . **HRMS** (ESI-TOF) m/z calcd for $\text{C}_{18}\text{H}_{22}\text{O}_4\text{Na}$ ($\text{M}+\text{Na}^+$) 325.1416, found: 325.1423. $[\alpha]_D^{20} = +100.3$ ($c = 0.5$, CHCl_3).

(Z)-5-(2-oxodihydrofuran-3(2H)-ylidene)-4-(1-phenylethoxy)hexanal

(3r:3s): General procedure A was followed using (*E*)-4-(1-phenylethoxy)but-3-en-1-ol (**2l**, 77 mg, 0.40 mmol) and (*Z*)-1-(2-oxodihydrofuran-3(2H)-ylidene)ethyl trifluoromethanesulfonate (**1a**, 110 mg, 0.40 mmol). Crude NMR displayed a 1:1 ratio of the two diastereomers (**3r** and **3s**, comparing the peaks at 5.34 and 5.67 ppm respectively). The two diastereomers were separable via slow gradient utilizing silica gel chromatography. (0 $\rightarrow$ 30% Et_2O /Hexanes). Data matched the respective diastereomers (**3r** and **3s**). Combined isolated yield of 65 mg (54% yield).

(Z)-5-(benzyloxy)-6-(2-oxodihydrofuran-3(2H)-ylidene)heptanal (6a): General procedure A was followed using (*E*)-5-(benzyloxy)pent-4-en-1-ol (**2m**, 77 mg, 0.40 mmol) and (*Z*)-1-(2-oxodihydrofuran-3(2H)-ylidene)ethyl trifluoromethanesulfonate (**1a**, 110 mg,

0.40 mmol). Purification of this material by silica gel chromatography gave a colorless oil (56 mg, 46% yield) R_f = 0.14 (30% EtOAc in Hexanes) $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 9.71 (t, J = 1.6 Hz, 1H), 7.34 – 7.24 (m, 5H), 5.64 (dd, J = 8.0, 5.0 Hz, 1H), 4.37 – 4.31 (m, 4H), 2.86 (td, J = 7.6, 7.2, 1.8 Hz, 2H), 2.50 – 2.36 (m, 2H), 1.85 (t, J = 1.7 Hz, 3H), 1.81 – 1.62 (m, 3H). $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 202.41, 169.56, 154.06, 138.27, 128.25, 127.85, 127.59, 121.64, 74.22, 71.59, 64.77, 43.33, 33.38, 27.75, 18.10, 15.55. **IR** (neat) 2921, 2853, 1736, 1717, 1658, 1453, 1261, 1189, 1026 cm^{-1} **HRMS** (ESI-TOF) m/z calcd for $\text{C}_{18}\text{H}_{22}\text{O}_4\text{Na}$ ($\text{M}+\text{Na}^+$) 325.1416, found: 325.1420. $[\alpha]_D^{20}$ = +13.2 (c = 1.0, CHCl_3).

(Z)-7-(benzyloxy)-8-(2-oxodihydrofuran-3(2H)-ylidene)nonanal (6b): General procedure A was followed using (*E*)-7-(benzyloxy)hept-6-en-1-ol (**2n**, 88 mg, 0.40 mmol) and (*Z*)-1-(2-oxodihydrofuran-3(2H)-ylidene)ethyl trifluoromethanesulfonate (**1a**, 110 mg, 0.40 mmol). Purification of this material by silica gel chromatography gave a colorless oil (71mg, 54% yield) R_f = 0.15 (30% EtOAc in Hexanes) $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 9.73 (t, J = 1.8 Hz, 1H), 7.35 – 7.22 (m, 5H), 5.63 (dd, J = 8.3, 4.6 Hz, 1H), 4.38 – 4.30 (m, 4H), 2.86 (td, J = 7.6, 1.9 Hz, 2H), 2.39 (td, J = 7.4, 1.8 Hz, 2H), 1.84 (t, J = 1.7 Hz, 3H), 1.73 – 1.65 (m, 1H), 1.64 – 1.56 (m, 2H), 1.49 – 1.38 (m, 2H), 1.36 – 1.28 (m, 3H). $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 202.76, 169.55, 154.44, 138.49, 128.23, 127.84, 127.52, 121.36, 74.75, 71.61, 64.70, 43.77, 33.83, 28.83, 27.80, 25.23, 21.91, 15.59. **IR** (neat) 2929, 2858, 2361, 1739, 1723, 1658, 1454, 1188, 1038 cm^{-1} **HRMS** (ESI-TOF) m/z calcd for $\text{C}_{20}\text{H}_{26}\text{O}_4\text{Na}$ ($\text{M}+\text{Na}^+$) 353.1729, found: 353.1738. $[\alpha]_D^{20}$ = +12.7 (c = 1.0, CHCl_3).

4-(benzyloxy)-4-phenylbutan-1-ol (6a): General procedure A was followed using (*E*)-4-(benzyloxy)but-3-en-1-ol (**2b**, 72 mg, 0.40 mmol, 1.0 equiv), phenyldiazonium tetrafluoroborate (**5a**, 77 mg, 0.40 mmol, 1.0 equiv), and **L2** (13.2 mg, 0.048 mmol, 0.12 equiv). General procedure B was used on the crude material to reduce the resulting aldehyde for purification purposes. Purification of this material by silica gel chromatography (0→26% EtOAc/Hexanes) yielded a clear oil (52 mg, 51% yield) R_f = 0.32 (35% EtOAc/Hexanes) $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.41 – 7.26 (m, 10H), 4.47 (d, J = 11.7 Hz, 1H), 4.36 (dd, J = 8.1, 4.7 Hz, 1H), 4.26 (d, J = 11.7 Hz, 1H), 3.63 (t, J = 6.2 Hz, 2H), 1.91 (dtd, J = 13.5, 8.3, 5.7 Hz, 2H), 1.84 – 1.74 (m, 2H, overlapping peaks), 1.77 – 1.68 (m, 1H, overlapping peaks), 1.61 (dq, J = 7.5, 5.3 Hz, 2H). $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 142.25, 138.22, 128.49, 128.38, 127.88, 127.64, 127.62, 126.71, 81.37, 70.54, 62.84, 35.03, 29.33. **IR** (neat) 3386, 3029, 2925, 2864, 1494, 1452, 1350, 1265, 1056, 1026 cm^{-1} . **HRMS** (ESI-TOF) m/z calcd for $\text{C}_{17}\text{H}_{20}\text{O}_2\text{Na}$ ($\text{M}+\text{Na}^+$) 279.1361, found: 279.1370.

4-(benzyloxy)-4-(4-methoxyphenyl)butan-1-ol (6b): General procedure A was followed using (*E*)-4-(benzyloxy)but-3-en-1-ol (**2b**, 72 mg, 0.40 mmol, 1.0 equiv), 4-methoxyphenyldiazonium tetrafluoroborate (**5b**, 89 mg, 0.40 mmol, 1.0 equiv), and **L2** (13.2 mg, 0.048 mmol, 0.12 equiv). General procedure B was used on the crude material to reduce the resulting aldehyde for purification purposes. Purification of this material by silica gel chromatography (0→28% EtOAc/Hexanes) yielded a clear oil (52 mg, 51% yield) R_f = 0.28 (35% EtOAc/Hexanes) $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.32 (d, J = 7.4 Hz, 2H), 7.31 – 7.24 (m, 5H), 6.91 (d, J = 8.5 Hz, 2H), 4.44 (d, J = 11.7 Hz, 1H), 4.30 (dd, J = 8.0, 4.9 Hz, 1H), 4.24 (d, J = 11.7 Hz, 1H), 3.82 (s, 3H), 3.62 (t, J = 6.2 Hz, 2H), 1.91 (tt, J = 14.0, 8.4, 5.9

Hz, 1H), 1.81 – 1.66 (m, 3H), 1.59 (dtd, $J = 13.7, 6.7, 4.0$ Hz, 2H). ^{13}C NMR (125 MHz, CDCl_3) δ 158.92, 140.29, 135.10, 128.43, 127.99, 127.96, 127.65, 113.91, 80.94, 70.32, 62.94, 55.33, 35.06, 29.45. IR (neat) 3382, 3031, 2926, 2858, 1610, 1510, 1453, 1302, 1243, 1127, 1028 cm^{-1} . HRMS (ESI-TOF) m/z calcd for $\text{C}_{18}\text{H}_{22}\text{O}_3\text{Na}$ ($\text{M}+\text{Na}^+$) 309.1467, found: 309.1477.

4-(benzyloxy)-4-(4-bromophenyl)butan-1-ol (6c): General procedure A was followed using (E)-4-(benzyloxy)but-3-en-1-ol (**2b**, 72 mg, 0.40 mmol, 1.0 equiv), 4-bromophenyldiazonium tetrafluoroborate (**5b**, 89 mg, 0.40 mmol, 1.0 equiv), and **L2** (13.2 mg, 0.048 mmol, 0.12 equiv). General procedure B was used on the crude material to reduce the resulting aldehyde for purification purposes. Purification of this material by silica gel chromatography (0→28% EtOAc/Hexanes) yielded a clear oil (52 mg, 51% yield) $R_f = 0.28$ (35% EtOAc/Hexanes) ^1H NMR (500 MHz, CDCl_3) δ 7.50 (d, $J = 8.3$ Hz, 2H), 7.37 – 7.27 (m, 5H), 7.22 (d, $J = 8.4$ Hz, 2H), 4.45 (d, $J = 11.6$ Hz, 1H), 4.32 (dd, $J = 8.0, 4.6$ Hz, 1H), 4.25 (d, $J = 11.5$ Hz, 1H), 3.63 (t, $J = 6.5$ Hz, 2H), 1.95 – 1.81 (m, 1H), 1.80 – 1.66 (m, 3H, overlapping peaks), 1.64 – 1.53 (m, 2H, overlapping peaks). ^{13}C NMR (126 MHz, CDCl_3) δ 141.30, 137.93, 131.66, 130.45, 128.44, 127.87, 127.75, 121.36, 80.65, 70.64, 62.73, 34.87, 29.14. IR (neat) 3367, 3062, 2926, 2871, 1594, 1489, 1453, 1208, 1072 cm^{-1} . HRMS (ESI-TOF) m/z calcd for $\text{C}_{17}\text{H}_{19}\text{O}_2\text{NaBr}$ ($\text{M}+\text{Na}^+$) 357.0466, found: 357.0470.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

The work was supported by National Institute of Health (NIGMS R01GM063540).

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A. Recent Work with Enol Ethers **B. Alkyl Enol Ethers Bearing Allylic Alcohol** **C. This Work** **Scheme 1.**

A. Recent synthesis of enantiomerically enriched aryl allyl ethers using a redox-relay Heck strategy. **B.** Limitation of previous work. **C.** Proposed synthesis of optically active allylic and benzylic ethers remote from an aldehyde.

A. Initial Reactions **B. Methyl Vs. Benzyl Ether** **Scheme 2.**

A. Early observations, percent conversions by ^1H NMR. **B.** Differing reaction pathways favored based on the substituent on the oxygen.

Table 1.

Alkenyl Triflate Scope

Yields are reported as an average of two parallel experiments. Enantioselectivity determined by SFC equipped with a chiral column. Reactions performed on 0.4 mmol scale. Absolute configuration determined to be (*S*) for **7a** (see SI) arising from the (*E*)-alkene. All other products were assigned by analogy.

Table 2.

Scope of *O*-Alkyl Enol Ethers

Yields are reported as an average of two parallel experiments. Enantioselectivity determined by SFC equipped with a chiral column. Reactions performed on 0.4 mmol scale. Absolute configuration determined to be (*S*) for 7a (see S1) arising from the (*E*)-alkene. All other products were assigned by analogy.

Table 3.

Evaluation of Redox-Relay Process

Yields are reported as an average of two parallel experiments. Enantioselectivity determined by SFC equipped with a chiral column. Reactions performed on 0.4 mmol scale. Absolute configuration determined to be (*S*) for **7a** (see SI) arising from the (*E*)-alkene. All other products were assigned by analogy.

Table 4.

Arylation of *O*-Alkyl Enol Ethers

Yields are reported as an average of two parallel experiments. Enantioselectivity determined by SFC equipped with a chiral column. Reactions performed on 0.4 mmol scale.