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Asymmetric Synthesis of Tetrahydrofurans through Palladium(0)-Catalyzed [3 + 2]-Cycloaddition of Vinylcyclopropanes with Ketenes

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ABSTRACT: In this article we describe a new asymmetric synthesis of highly substituted tetrahydrofurans through a Pd(PPh₃)₄-catalyzed formal [3 + 2]-cycloaddition of donor-acceptor cyclopropanes and ketenes. The desired structural motif was formed in moderate to excellent yields (42-84% for 16 examples), with excellent Z:E isomer diastereoselectivity (≥19:1 for 16 examples), and with good to excellent enantioselectivity in all cases examined (83-97% ee for 6 examples). The synthetic utility of the products was illustrated by a number of diastereoselective transformations into reduced tetrahydrofurans and spirocyclic tetrahydrofuran-barbiturate derivatives.

Introduction

The importance of highly substituted tetrahydrofurans is indicated by the existence of numerous examples of pharmaceutically and biologically interesting tetrahydrofurans/tetrahydrofuran-containing complex molecules, including escitalopram, isosorbide mononitrate, naloxone, and sylvone – all of which possess at least one chiral center.
During the 1980s Tsuji's group had shown that a \( \pi \)-allyl palladium species could be generated through treatment of vinylcyclopropanes with a \( \text{Pd}_2\text{dba}_3\cdot\text{CHCl}_3 \) catalyst in HMPA. Under those conditions vinylcyclopropanes could undergo formal [3 + 2] cycloadditions with a variety of electrophiles, such as isocyanates to afford \( \gamma \)-lactams. A single example with diphenylketene to give a racemic cyclopentanone product was also reported, albeit without any structural characterization provided. In 2005 Johnson’s group showed that Lewis acid-catalyzed [3 + 2] cycloadditions of donor-acceptor (DA) cyclopropanes with aldehydes could facilitate a stereoselective synthesis of tetrahydrofurans. The use of enantioenriched DA cyclopropanes as starting materials enabled an asymmetric synthesis of the desired enantioenriched tetrahydrofurans. The same group also showed that transition metal catalysis (Pd(0) or Ni(0) catalysis) could be utilized to convert DA cyclopropanes to tetrahydrofurans, albeit with maintenance of stereochemical fidelity being dependent upon the metal complex used. In the Pd(0)-catalyzed reactions, transfer of chirality from starting DA cyclopropane to tetrahydrofuran was not observed. As part of our program of studies on the development of new stereoselective reactions of ketenes, we were interested in developing an asymmetric synthesis of highly substituted tetrahydrofurans from ketenes and donor-acceptor cyclopropanes (Scheme 1).

We anticipated that vinylcyclopropane 1a would undergo oxidative addition in the presence of an appropriate Pd(0) catalyst. Subsequent reaction of \( \pi \)-allyl palladium anion A with ketene 2a would lead to reactive enolate intermediate B (Scheme 2). We postulated that enolate intermediate B would undergo rapid cyclization (\( O \)-allylation), and that loss of stereochemistry would be minimized in the formation of the desired highly substituted tetrahydrofuran 3.
Results and Discussion

Our studies began with an examination of palladium(0) catalysis (Pd(dba)_2) as a means of promoting the desired reaction. Donor-acceptor cyclopropanes and ketenes were pre-prepared and isolated as previously described. At the outset, we anticipated that there would be competition between O-enolate allylation of B, to afford tetrahydrofuran 3 (EWG = CN), and C-enolate allylation, to provide highly substituted cyclopentanone 4 (EWG = CN) (Scheme 2). However, surprisingly, highly substituted tetrahydrofuran 3 (EWG = CN) was formed as the only product, due to a cyclization involving O-enolate allylation rather than C-enolate allylation (Table 1, entries 1 and 2). Employment of a variety of Pd precatalysts, ligands, and reaction conditions, invariably provided tetrahydrofuran 3 as the major product (Table 1 entries 2-13). Best conditions for tetrahydrofuran formation from 1a involved the use of the alkaloid derivative (DHQ)_2PHAL as an additive for the Pd(PPh_3)_4 system (Table 1 entry 11). In its absence, polymerization of the dicyano-substituted cyclopropane 1a was noted (entry 12). We speculate that the role of (DHQ)_2PHAL is to decrease the amount of reactive PdL_2 available (where L = PPh_3 or alkaloid), and hence the concentration of intermediate A (Scheme 2), leading to less polymerization of 1a. However, the alkaloid additive was found to be unnecessary in the case of Pd(PPh_3)_2-catalyzed reactions of gem-dimethoxycarbonylcyclopropane 1b (Table 1 entries 14-16), with high conversion to tetrahydrofuran 3 observed. For all subsequent studies, we focused on developing the chemistry of dialkoxy carbonylcyclopropanes 1b-1c (EWG = CO_2Me and CO_2Et) using the conditions developed in entry 14, Table 1.

Table 1. Optimization of Pd(0)-catalyzed formal [3 + 2]-cycloadditions.
For most tetrahydrofuran examples investigated in our study (Table 2), the isolated yield of 3 after flash column chromatography was found to be in the range of 50-84%. The exploration of ketene structure variation revealed that aryl substituents (both electron withdrawing and electron donating) were tolerated. Even ortho-substitution (X = F) on the ketene aryl ring could be incorporated albeit very sensitive to steric size of the substituent; When X was methyl, the reaction failed (entry 6 vs entry 7). Ethyl-substituted ketene and diphenylketene also worked well, albeit with the corresponding tetrahydrofurans afforded in lower yields (ca. 40-50%, entries 11 and 18). However, dialkylketenes (e.g. diethylketene and c-hexylmethylketene) were found to be incompatible under the optimized reaction conditions (e.g. entry 12). In the latter reactions, cyclopropane was recovered unreacted but the ketene had undergone dimerization. We surmise that free triphenylphosphine ligand caused dimerization of the dialkylketenes.7b In addition, DA cyclopropanes substituted with cinnamyl group at C2 failed to undergo the desired reaction (entry 19). When i-Pr was the ester alkyl group (in EWG) no reaction occurred, presumably due to increased steric interactions in the formation of the palladium(II)-allyl intermediate or in reaction with incoming ketene. gem-Dicyanofuran 3a could only be formed when (DHQ)2PHAL (5 mol%) was used as an additive. Under the standard reaction conditions, no desired product was formed, as the starting vinylcyclopropane...
underwent polymerization.

\[ (\pm)-1a' \quad EWG = CN; \quad R^3 = H \]
\[ (\pm)-1b' \quad EWG = COOEt; \quad R^3 = Ph \]
\[ (S),1b' \quad EWG = COOMe; \quad R^3 = H (99\% ee) \]
\[ (S),1c' \quad EWG = COEt; \quad R^3 = H (97\% ee) \]
\[ (\pm)-1d' \quad EWG = COOMe; \quad R^3 = Ph \]

**Table 2.** Substrate scope of Pd(PPh₃)₄-catalyzed stereoselective synthesis of highly substituted tetrahydrofurans.

<table>
<thead>
<tr>
<th>entry</th>
<th>1</th>
<th>R¹</th>
<th>R²</th>
<th>% yield</th>
<th>Z:E</th>
<th>% ee</th>
<th>product</th>
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<td>Ph</td>
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<td>3b</td>
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<tr>
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<td>&gt;99:1</td>
<td>nd</td>
<td>3c</td>
</tr>
<tr>
<td>4</td>
<td>(±)-1b</td>
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<td>4-MeOC₆H₄</td>
<td>54</td>
<td>&gt;99:1</td>
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<td>3d</td>
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<tr>
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<td>Me</td>
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<td>Ph</td>
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* (DHQ)₂PHAL (5 mol%) was used as additive for formation of 3a. * Yield is isolated yield after flash column chromatography on silica. * Z:E ratio determined by GC-MS and corroborated by ¹H NMR analysis. * ee for major diastereomer determined by chiral HPLC analysis.

**Reaction Mechanism.** Significantly, moderately high to excellent transfer of chirality was observed in tetrahydrofuran formation (83-97% ee from DA cyclopropane (S)-1b with 99% ee). Therefore, there was no need to use a chiral catalyst/chiral
ligands to effect the transformation in order to deliver enantioenriched tetrahydofurans. In addition, retention of configuration was confirmed by X-ray crystallographic analysis of 6k, a barbiturate derivative of tetrahydofuran 3k (Scheme 4 and see cif 6k). We propose that overall retention of configuration is observed as a result of two sequential steps involving inversion of configuration as has been previously postulated for other palladium-catalyzed allylic alkylations. Firstly, (Ph3P)2Pd(0) attack on the vinylcyclopropane results in ring-opening and inversion of the configuration at the chiral center on the DA cyclopropane to form intermediate A (Scheme 3). Secondly, intramolecular O-enolate attack on the Pd(II)-π-allyl moiety in intermediate B results in, once again, inversion of configuration, with overall retention of configuration (i.e. (S)-DA cyclopropane 1 → (S)-tetrahydofuran 3). Intramolecular C-enolate attack on the pendant Pd(II)-π-allyl moiety is disfavored due to steric interactions with the highly substituted C-end of the enolate. The mild conditions utilized in the method prevent significant stereochemical erosion from occurring. It is also clear that an achiral intermediate was not involved as chirality was transferred efficiently (Table 2, 83-97% ee for 6 examples).

Scheme 3. Proposed mechanism for tetrahydofuran formation.

**Synthetic Utility.** Finally, the synthetic utility of products was investigated by subjecting (±)-3b and (−)-3k to catalytic hydrogenation to afford reduced tetrahydofurans (±)-5b and enantioenriched (−)-5k, respectively (Scheme 4). Significantly, excellent diastereoselectivity (dr >99:1), favoring the syn,syn-isomer, was observed in the formation of tetrahydofuran products.
bearing three stereocenters. In addition, good retention of chirality was observed as \((-\)-5k) was obtained with 89% ee from \((-\)-3k) with 94% ee. The slight loss of stereochemical integrity may be due to reversible insertion of Pd(0) into the allyl ether of the tetrahydrofuran ring. The tetrahydrofurans \((-\)-3k) and \((\pm\)-5b) could also be subjected to reaction with urea under basic conditions to form structurally interesting spirocyclic tetrahydrofuran-barbiturate derivatives \((+\)-6k) and \((\pm\)-7b), respectively. X-ray crystallographic analysis was performed on the latter crystalline derivatives formed in this manner, enabling the determination of absolute and relative stereochemistry of the tetrahydrofuran products (see SI).13 The exocyclic olefin stereochemistry of \((+\)-6k) (derived from 3k) was determined to be of Z-geometry, and so all tetrahydrofurans 3a-3o were assigned the Z-stereochemistry by analogy. The absolute stereochemistry of \((+\)-6k) was determined to be the \((S\)-configuration, and so all tetrahydrofurans 3k-3p were assigned the \((S\)-configuration by analogy.

**Scheme 4. Transformations of tetrahydrofurans.**

\[ \text{Scheme 4. Transformations of tetrahydrofurans.} \]

\[ \text{Scheme 4. Transformations of tetrahydrofurans.} \]

**Conclusion**
In conclusion, we report a Pd(PPh$_3$)$_4$-catalyzed method for the stereoselective synthesis of highly substituted tetrahydrofurans from ester substituted vinylcyclopropanes and disubstituted ketenes. Importantly, it was observed that the reactions proceed with very good to excellent transfer of chirality with overall retention of configuration at C2 on the donor-acceptor cyclopropane (6 examples with ee of 83-97%). A key advantage of the reported method is the commercial availability of the catalyst and the avoidance of expensive ligands. The olefin-substituted tetrahydrofuran products undergo highly diastereoselective catalytic hydrogenation, providing access to reduced tetrahydrofuran products bearing three chiral centers. Structurally interesting spirocyclic barbiturate-tetrahydrofuran derivatives were also prepared. Future studies will further explore transition metal catalysis in the context of formal cycloadditions of donor-acceptor substrates with cumulenes and heterocumulenes.

Experimental Section

General

All reactions were carried out in flame-dried glassware under a nitrogen atmosphere using standard inert atmosphere techniques unless otherwise stated. THF was freshly distilled from benzophenone ketyl radical under nitrogen prior to use, while Hüning's base (diisopropylethylamine) was distilled from calcium hydride.$^{14}$ Anhydrous dichloromethane was obtained by distillation from standard still over calcium hydride. All chemicals were purchased and used as received from suppliers without further purification unless mentioned otherwise. All ketenes were synthesized according to reported literature procedures.$^{10}$ Silica gel and TLC plates (UV254, 250μM) were used as received. Both racemic and enantioenriched cyclopropanes 1a-1d were prepared according to known literature procedures.$^9$

\[ \text{(±)-1a} \quad \text{(±)-1b} \quad \text{(S)-1b} \quad \text{(±)-1c} \quad \text{(S)-1c} \]

NMR spectra were recorded on a 200 MHz spectrometer (200 MHz for $^1$H and 50 MHz for $^{13}$C) and on a 400 MHz spectrometer (400 MHz for $^1$H and 100 MHz for $^{13}$C). NMR chemical shifts were reported relative to TMS (0 ppm) for $^1$H and to CDCl$_3$ (77.23 ppm) for $^{13}$C spectra. High resolution mass spectra were recorded on an Accurate Mass Q-TOF LC-MS instrument with ESI as ionization method at Oakland University. Low resolution mass spectra were recorded on a GC-MS instrument equipped with a mass selective detector, and using a GC column (30 m, 0.25 mm ID). IR spectra were recorded on an IR spectrometer. Optical rotations were measured on an automatic polarimeter in dichloromethane at 598 nm.
Diastereoselectivity for tetrahydrofuran formation was determined by GC-MS analysis of the crude product and corroborated by 1H NMR analysis. Chiral high-performance liquid chromatography analysis (chiral HPLC) was performed using AD, AD-H, AS, AS-H, OD and OD-H (25 × 0.46 cm) on a HPLC instrument attached with diode array detector (deuterium lamp, 190-600 nm) with HPLC-grade isopropanol and hexanes as the eluting solvents. Enantiomeric excesses were determined at $\lambda = 254$ or 225 nm (details given for each compound).

**General procedure for tetrahydrofuran synthesis:**

To a stirring suspension of tetrakis(triphenylphosphine)palladium(0) (0.015 mmol) in dichloromethane (1.0 mL) at –25 °C, a solution of cyclopropane (0.3 mmol) in dichloromethane (1.0 mL) was added. To this stirring reaction mixture, a solution of ketene (0.45 mmol) in dichloromethane (1.0 mL) was added over a period of 6 h via syringe pump. The reaction was stirred at this temperature for another 10 h and then poured into ice cold water (20 mL) and extracted with dichloromethane (25 mL × 2). The combined organic layers were washed with water (30 mL), brine (30 mL), and dried over sodium sulfate. 

$E/Z$ ratio was determined by GC-MS analysis of the crude product after workup. Removal of the solvent under reduced pressure followed by regular silica gel column chromatographic purification using a mixture of ethyl acetate and hexanes (details mentioned below) afforded the desired product in ≥95% purity.

**(Z)-2-(1-Phenylethylidene)-5-vinylidihydrofuran-3,3(2H)-dicarbonitrile (3a):** Following general procedure, cyclopropane (±)-1a (60 mg, 0.51 mmol) solution in dichloromethane (1.5 mL) was added to a stirring suspension of Pd(PPh3)4 (29 mg, 0.025 mmol) and (DHQ)2PHAL (19 mg, 0.025 mmol) in dichloromethane (2.0 mL) at –25 °C. A solution of methylphenylketene (87 mg, 0.66 mmol) in dichloromethane (1.5 ml) was added over 6 h to the reaction mixture at –25 °C. Elution with 4% EtOAc/hexanes through regular silica gel column afforded 3a as a colorless gum (76 mg, 60%). $Z/E = 19:1$ (by crude GC-MS analysis); IR (thin film) 2961, 2927, 2249, 1760, 1664, 1591, 1443, 1154, 1102, 764 cm⁻¹; 1H NMR (400 MHz, CDCl₃, TMS): δ 7.51-7.46 (m, 2H), 7.39-7.33 (m, 2H), 7.30-7.28 (m, 1H), 5.87 (ddd, $J = 17.0, 10.6 & 6.5$ Hz, 1H), 5.42 (d, $J = 17.0$ Hz, 1H), 5.36 (d, $J = 10.6$ Hz, 1H), 4.88-4.81 (m, 1H), 3.08 (dd, $J = 13.1 & 5.5$ Hz, 1H), 2.69 (dd, $J = 13.1 & 8.6$ Hz, 1H), 2.30 (s, 3H); 13C{1H} NMR (100 MHz, CDCl₃): δ 141.5, 138.3, 133.2, 128.4, 128.1, 127.7, 120.3, 113.6, 113.54, 113.48, 80.7, 44.5, 35.3, 18.5; HRMS (ESI-TOF) m/z: [M + H]+ Calcd for (C₁₆H₁₅N₂O)+: 251.1184; Found: 251.1182.

**Dimethyl (Z)-2-(1-phenylethylidene)-5-vinylidihydrofuran-3,3(2H)-dicarboxylate (3b):** Following general procedure, cyclopropane (±)-1b (56 mg, 0.30 mmol) solution in dichloromethane (1.0 mL) was added to a stirring suspension of Pd(PPh3)4 (17 mg, 0.015 mmol) in dichloromethane (1.0 mL) at –25 °C. A solution of methylphenylketene (68 mg, 0.46 mmol) in dichloromethane (1.0 ml) was added over 6 h to the reaction mixture at –25 °C. Elution with 4% EtOAc/hexanes through regular silica gel column afforded 3b as a colorless gum (77 mg, 80%). $Z/E = >>99:1$ (by crude GC-MS analysis); IR (thin film) 3006, 2954, 2934, 1434, 1258, 1162, 1084, 978, 698 cm⁻¹; 1H NMR (400 MHz, CDCl₃, TMS): δ 7.56-7.50 (m, 2H), 7.34-7.27 (m, 2H), 7.20-
7.13 (m, 1H), 5.85 (dd, $J = 17.0$, 10.6 & 6.5 Hz, 1H), 5.31 (dt, $J = 17.0$ & 1.2 Hz, 1H), 5.18 (dt, $J = 10.6$ & 1.2 Hz, 1H), 4.74—4.65 (m, 1H), 3.83 (s, 3H), 3.81 (s, 3H), 2.99 (dd, $J = 12.4$ & 5.8 Hz, 1H), 2.43 (dd, $J = 12.4$ & 9.0 Hz, 1H), 1.93 (s, 3H); $^{13}$C{H} NMR (100 MHz, CDCl$_3$): $\delta$ 170.2, 169.8, 148.1, 140.8, 136.4, 128.4, 127.9, 126.3, 117.6, 109.5, 80.5, 63.1, 53.4, 53.3, 42.7, 18.3; HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for (C$_{18}$H$_{21}$O$_5$)$^+$: 317.1389; Found: 317.1389.

**Diethyl (Z)-2-(1-phenylethylidene)-5-vinylidihydrofuran-3,3(2H)-dicarboxylate (3c):** Following general procedure, cyclopropane (S)-1c (70 mg, 0.33 mmol) solution in dichloromethane (1.0 mL) was added to a stirring suspension of Pd(PPh$_3$)$_4$ (19 mg, 0.017 mmol) in dichloromethane (1.3 mL) at $-25$ °C. A solution of ketene (65 mg, 0.50 mmol) in dichloromethane (1.0 ml) was added over 6 h to the reaction mixture at $-25$ °C. Elution with 4% EtOAc/hexanes through regular silica gel column afforded 3c as a colorless gum (57 mg, 50%). $Z:E = >99:1$ (by crude GC-MS analysis); $[\alpha]^{24}_D = -3$ (c = 1.2, CH$_2$Cl$_2$); IR (thin film) 2964, 2936, 2873, 1730, 1444, 1368, 1259, 1019, 698 cm$^{-1}$; 1H NMR (400 MHz, CDCl$_3$, TMS): $\delta$ 7.55—7.49 (m, 2H), 7.37—7.27 (m, 2H), 7.20—7.14 (m, 1H), 5.85 (ddd, $J = 17.0$, 10.5 & 6.4 Hz, 1H), 5.32 (dt, $J = 17.0$ & 1.2 Hz, 1H), 5.18 (dt, $J = 10.5$ & 1.2 Hz, 1H), 4.73—4.64 (m, 1H), 4.35—4.23 (m, 4H), 2.99 (dd, $J = 12.3$ & 5.7 Hz, 1H), 2.41 (dd, $J = 12.3$ & 8.9 Hz, 1H), 1.96 (s, 3H), 1.35—1.28 (m, 6H); $^{13}$C{H} NMR (100 MHz, CDCl$_3$): $\delta$ 169.7, 169.3, 148.3, 141.1, 136.5, 128.4, 128.0, 126.2, 117.5, 109.4, 80.5, 63.3, 62.5, 62.4, 42.7, 18.7, 14.2 (2-carbons); HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for (C$_{20}$H$_{25}$O$_5$)$^+$: 345.1702; Found: 345.1701.

**Dimethyl (Z)-2-(1-(4-methoxyphenyl)ethylidene)-5-vinylidihydrofuran-3,3(2H)-dicarboxylate (3d):** Following general procedure, cyclopropane (±)-1b (80 mg, 0.44 mmol) solution in dichloromethane (1.0 mL) was added to a stirring suspension of Pd(PPh$_3$)$_4$ (25 mg, 0.022 mmol) in dichloromethane (1.4 mL) at $-25$ °C. A solution of methyl(4-methoxyphenyl)ketene (106 mg, 0.65 mmol) in dichloromethane (1.0 ml) was added over 6 h to the reaction mixture at $-25$ °C. Elution with 7% EtOAc/hexanes through regular silica gel column afforded 3d as a colorless gum (81 mg, 54%). $Z:E = >99:1$ (by crude GC-MS analysis); IR (thin film) 2955, 2838, 1731, 1511, 1246, 1028, 832 cm$^{-1}$; 1H NMR (400 MHz, CDCl$_3$, TMS): $\delta$ 7.49 (d, $J = 9.0$ Hz, 2H), 6.85 (d, $J = 9.0$ Hz, 2H), 5.85 (ddd, $J = 17.0$, 10.5 & 6.5 Hz, 1H), 5.32 (dt, $J = 17.0$ & 1.2 Hz, 1H), 5.18 (dt, $J = 10.5$ & 1.2 Hz, 1H), 4.74—4.65 (m, 1H), 3.83 (s, 3H), 3.80 (s, 3H), 3.79 (s, 3H), 2.99 (dd, $J = 12.4$ & 5.7 Hz, 1H), 2.42 (dd, $J = 12.4$ & 9.0 Hz, 1H), 1.91 (s, 3H); $^{13}$C{H} NMR (100 MHz, CDCl$_3$): $\delta$ 169.7, 169.3, 148.3, 141.1, 136.5, 128.4, 128.0, 126.2, 117.5, 109.4, 80.5, 63.3, 62.5, 62.4, 42.7, 18.7, 14.2 (2-carbons); HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for (C$_{20}$H$_{25}$O$_6$)$^+$: 347.1495; Found: 347.1495.

**Dimethyl (Z)-2-(1-(p-tolyl)ethylidene)-5-vinylidihydrofuran-3,3(2H)-dicarboxylate (3e):** Following general procedure, cyclopropane (±)-1b (56 mg, 0.30 mmol) solution in dichloromethane (1.0 mL) was added to a stirring suspension of Pd(PPh$_3$)$_4$ (17 mg, 0.015 mmol) in dichloromethane (1.0 mL) at $-25$ °C. A solution of methyl-p-tolylketene (67 mg, 0.46 mmol) in dichloromethane (1.0 ml) was added over 6 h to the reaction mixture at $-25$ °C. Elution with 5% EtOAc/hexanes through regular silica gel column afforded 3e as a colorless gum (77 mg, 77%). $Z:E = 32:1$ (by crude GC-MS analysis); IR (thin film) 2953, 2924,
1732, 1591, 1511, 1434, 1255, 1212, 1170, 978, 817 cm⁻¹; ¹H NMR (400 MHz, CDCl₃, TMS): δ 7.42 (d, J = 8.3 Hz, 2H), 7.11 (d, J = 8.3 Hz, 2H), 5.84 (ddd, J = 17.0, 10.6 & 6.5 Hz, 1H), 5.31 (dt, J = 17.0 & 1.2 Hz, 1H), 5.18 (dt, J = 10.6 & 1.2 Hz, 1H), 4.73-4.64 (m, 1H), 3.83 (s, 3H), 3.80 (s, 3H), 2.98 (ddd, J = 12.3 & 5.8 Hz, 1H), 2.42 (ddd, J = 12.3 & 9.0 Hz, 1H), 2.32 (s, 3H), 1.91 (s, 3H); ¹³C¹H NMR (100 MHz, CDCl₃): δ 170.3, 169.9, 147.7, 137.8, 136.5, 135.8, 128.7, 128.2, 117.5, 109.4, 80.4, 63.0, 53.4, 53.3, 42.7, 21.3, 18.3; HRMS (ESI-TOF) m/z: [M + H⁺] Calcd for (C₁₉H₂₀ClO₅): 331.1545; Found: 331.1543.

Dimethyl (Z)-2-(1-(2-fluorophenyl)ethylidene)-5-vinylidihydrofuran-3,3(Z)-dicarboxylate (3f): Following general procedure, cyclopropane (±)-1b (56 mg, 0.30 mmol) solution in dichloromethane (1.0 mL) was added to a stirring suspension of Pd(PPh₃)₄ (17 mg, 0.015 mmol) in dichloromethane (1.0 mL) at –25 °C. A solution of (2-fluorophenyl)methylketene (68 mg, 0.46 mmol) in dichloromethane (1.0 mL) was added over 6 h to the reaction mixture at –25 °C. Elution with 4% EtOAc/hexanes through regular silica gel column afforded 3f as a colorless gum (45 mg, ~95% pure by ¹H NMR, 42%). Z:E = >99:1 (by crude GC-MS analysis); IR (thin film) 2956, 2934, 2873, 1732, 1437, 1268, 1212, 1168, 757 cm⁻¹; ¹H NMR (400 MHz, CDCl₃, TMS): δ 7.34-7.27 (m, 1H), 7.22-7.14 (m, 1H), 7.11-6.98 (m, 2H), 5.78 (ddd, J = 17.0, 10.6 & 6.4 Hz, 1H), 5.26 (dt, J = 17.0 & 1.3 Hz, 1H), 5.13 (dt, J = 10.6 & 1.3 Hz, 1H), 4.69-4.59 (m, 1H), 3.86 (s, 3H), 3.83 (s, 3H), 2.99 (ddd, J = 12.4 & 5.9 Hz, 1H), 2.45 (ddd, J = 12.4 & 8.7 Hz, 1H), 1.88 (s, 3H); ¹³C¹H NMR (100 MHz, CDCl₃): δ 170.0, 169.7, 159.9 (d, J = 247 Hz, 1C), 148.8, 136.4, 131.1 (d, J = 4 Hz, 1C), 129.0 (d, J = 16 Hz, 1C), 128.3 (d, J = 8 Hz, 1C), 123.7 (d, J = 3 Hz, 1C), 117.4, 115.8 (d, J = 23 Hz, 1C), 104.9, 80.2, 62.4, 53.5, 53.4, 42.7, 18.1 (d, J = 2 Hz, 1C); HRMS (ESI-TOF) m/z: [M + H⁺] Calcd for (C₁₉H₁₈O₅): 335.1295; Found: 335.1295.

Dimethyl (Z)-2-(1-(3-chlorophenyl)ethylidene)-5-vinylidihydrofuran-3,3(Z)-dicarboxylate (3g): Following general procedure, cyclopropane (±)-1b (56 mg, 0.30 mmol) solution in dichloromethane (1.0 mL) was added to a stirring suspension of Pd(PPh₃)₄ (17 mg, 0.015 mmol) in dichloromethane (1.0 mL) at –25 °C. A solution of (3-chlorophenyl)methylketene (76 mg, 0.46 mmol) in dichloromethane (1.0 mL) was added over 6 h to the reaction mixture at –25 °C. Elution with 5% EtOAc/hexanes through regular silica gel column afforded 3g as a colorless gum (87 mg, 82%). Z:E = >99:1 (by crude GC-MS analysis); IR (thin film) 2954, 2924, 1731, 1474, 1434, 1258, 1212, 1164, 979, 694 cm⁻¹; ¹H NMR (400 MHz, CDCl₃, TMS): δ 7.52 (t, J = 1.8 Hz, 1H), 7.41 (dt, J = 7.9 & 1.8 Hz, 1H), 7.23 (dd, J = 14.9 & 7.9 Hz, 1H), 7.14 (dq, J = 7.9 & 1.1 Hz, 1H), 5.84 (ddd, J = 17.0, 10.6 & 6.4 Hz, 1H), 5.32 (dt, J = 17.0 & 1.2 Hz, 1H), 5.20 (dt, J = 10.6 & 1.2 Hz, 1H), 4.76-4.67 (m, 1H), 3.84 (s, 3H), 3.81 (s, 3H), 3.01 (dd, J = 12.4 & 5.7 Hz, 1H), 2.43 (ddd, J = 12.4 & 9.0 Hz, 1H), 1.91 (s, 3H); ¹³C¹H NMR (100 MHz, CDCl₃): δ 170.0, 169.5, 149.0, 142.6, 136.1, 133.8, 129.1, 128.5, 126.6, 126.3, 117.8, 108.3, 80.7, 63.2, 53.5, 53.4, 42.6, 18.1; HRMS (ESI-TOF) m/z: [M + H⁺] Calcd for (C₁₉H₁₈O₅Cl): 351.0999; Found: 351.0997.

Dimethyl (Z)-2-(1-(4-chlorophenyl)ethylidene)-5-vinylidihydrofuran-3,3(Z)-dicarboxylate (3h): Following general procedure, cyclopropane (±)-1b (56 mg, 0.30 mmol) solution in dichloromethane (1.0 mL) was added to a stirring suspension of
Pd(PPh₃)₄ (17 mg, 0.015 mmol) in dichloromethane (1.0 mL) at −25 °C. A solution of (4-chlorophenyl)methylketene (76 mg, 0.46 mmol) in dichloromethane (1.0 ml) was added over 6 h to the reaction mixture at −25 °C. Elution with 5% EtOAc/hexanes through regular silica gel column afforded 3h as a colorless gum (90 mg, ~95% pure by ¹H NMR, 80%). Z:E = >99:1 (by crude GC-MS analysis); IR (thin film) 2954, 1731, 1492, 1434, 1258, 1162, 1082, 831 cm⁻¹; ¹H NMR (400 MHz, CDCl₃, TMS): δ 7.47 (dt, J = 8.7 & 2.0 Hz, 2H), 7.26 (dt, J = 8.7 & 2.0 Hz, 2H), 5.84 (ddd, J = 17.0, 10.6 & 6.5 Hz, 1H), 5.31 (dt, J = 17.0 & 1.3 Hz, 1H), 5.20 (dt, J = 10.6 & 1.3 Hz, 1H), 4.75-4.66 (m, 1H), 3.84 (s, 3H), 3.81 (s, 3H), 3.00 (dd, J = 12.4 & 5.7 Hz, 1H), 2.42 (dd, J = 12.4 & 9.0 Hz, 1H), 1.91 (s, 3H); ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 170.0, 169.6, 148.6, 139.2, 136.1, 131.8, 129.8, 128.0, 117.9, 108.3, 80.7, 63.1, 53.5, 53.4, 42.6, 18.1; HRMS (ESI-TOF) m/z: [M + H]+ Calcd for (C₁₈H₂₁ClO₅)+: 351.0999; Found: 351.0998.

Dimethyl (Z)-2-(1-(4-(trifluoromethyl)phenyl)ethylidene)-5-vinyldihydrofuran-3,3(2H)-dicarboxylate (3i): Following general procedure, cyclopropane (±)-1b (56 mg, 0.30 mmol) solution in dichloromethane (1.0 mL) was added to a stirring suspension of Pd(PPh₃)₄ (17 mg, 0.015 mmol) in dichloromethane (1.0 mL) at −25 °C. A solution of methyl(4-(trifluoromethyl)phenyl)ketene (91 mg, 0.46 mmol) in dichloromethane (1.0 ml) was added over 6 h to the reaction mixture at −25 °C. Elution with 6% EtOAc/hexanes through regular silica gel column afforded 3i as a colorless gum (103 mg, ~95% pure by ¹H NMR, 84%). Z:E = >99:1 (by crude GC-MS analysis); IR (thin film) 2956, 2930, 2873, 1733, 1614, 1436, 1324, 1261, 1162, 1119, 1063, 980, 843 cm⁻¹; ¹H NMR (400 MHz, CDCl₃, TMS): δ 7.64 (d, J = 8.2 Hz, 2H), 7.54 (d, J = 8.2 Hz, 2H), 5.84 (ddd, J = 17.0, 10.6 & 6.5 Hz, 1H), 5.32 (dt, J = 17.0 & 1.2 Hz, 1H), 5.21 (dt, J = 10.6 & 1.2 Hz, 1H), 4.77-4.68 (m, 1H), 3.85 (s, 3H), 3.82 (s, 3H), 3.02 (dd, J = 12.4 & 5.7 Hz, 1H), 2.44 (dd, J = 12.4 & 9.1 Hz, 1H), 1.94 (s, 3H); ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 169.9, 169.5, 149.5, 144.5, 136.0, 128.6, 128.1 (d, J = 32 Hz, 1C), 124.8 (q, J = 4 Hz, 1C), 124.6 (q, J = 272 Hz, 1C), 124.6 (q, J = 272 Hz, 1C), 118.0, 108.3, 80.9, 63.3, 53.5, 53.47, 42.6, 18.0; HRMS (ESI-TOF) m/z: [M + H]+ Calcd for (C₁₉H₂₀F₃O₅)+: 385.1263; Found: 385.1262.
Dimethyl \((S,Z)\)-2-(1-phenylethylidene)-5-vinylidihydrofuran-3,3(2H)-dicarboxylate \((3k)\): Following general procedure, \((S)\)-1b (56 mg, 0.30 mmol) solution in dichloromethane (1.0 mL) was added to a stirring suspension of Pd(PPh₃)₄ (17 mg, 0.015 mmol) in dichloromethane (1.0 mL) at −25 °C. A solution of methylphenylketene (68 mg, 0.46 mmol) in dichloromethane (1.0 mL) was added over 6 h to the reaction mixture at −25 °C. Elution with 4% EtOAc/hexanes through regular silica gel column afforded 3k as a colorless gum (76 mg, 79%). \(Z:E = >99:1\) (by crude GC-MS analysis); HPLC analysis: 94% ee [OD-H column; 1.0 mL/min; solvent system: 1% isopropanol in hexane; retention times: 10.8 min (minor), 11.3 min (major)]; \([\alpha]_{D}^{24} = -13 \ (c \ 2.4, \text{CH}_2\text{Cl}_2); \) IR (thin film) 3006, 2953, 1730, 1434, 1259, 1162, 1084, 978, 698 cm⁻¹; \(^1\)H NMR (400 MHz, CDCl₃, TMS): \(\delta 7.56-7.50 \ (m, 2\text{H}), 7.34-7.27 \ (m, 2\text{H}), 7.20-7.13 \ (m, 1\text{H}), 5.85 \ (ddd, \ J = 17.0, 10.6 \ & 6.5 \ Hz, 1\text{H}), 5.31 \ (dt, \ J = 17.0 \ & 1.2 \ Hz, 1\text{H}), 5.18 \ (dt, \ J = 10.6 \ & 1.2 \ Hz, 1\text{H}), 4.74-4.65 \ (m, 1\text{H}), 3.83 \ (s, 3\text{H}), 3.81 \ (s, 3\text{H}), 2.99 \ (dd, \ J = 12.4 \ & 5.8 \ Hz, 1\text{H}), 2.43 \ (dd, \ J = 12.4 \ & 9.0 \ Hz, 1\text{H}), 1.93 \ (s, 3\text{H}); \) \(^{13}\)C{¹H} NMR (100 MHz, CDCl₃): \(\delta 170.2, 169.8, 148.1, 140.8, 136.4, 128.4, 128.0, 126.3, 117.6, 109.5, 80.5, 63.1, 53.40, 53.35, 42.7, 18.3; \) HRMS (ESI-TOF) m/z: \([M + H]^+\) Calcd for \((\text{C}_{17}\text{H}_{20}\text{O}_5)^+\): 317.1389; Found: 317.1387.

Dimethyl \((S,Z)\)-2-(1-(p-tolyl)ethylidene)-5-vinylidihydrofuran-3,3(2H)-dicarboxylate \((3l)\): Following general procedure, \((S)\)-1b (56 mg, 0.30 mmol) solution in dichloromethane (1.0 mL) was added to a stirring suspension of Pd(PPh₃)₄ (17 mg, 0.015 mmol) in dichloromethane (1.0 mL) at −25 °C. A solution of methyl-p-tolylketene (67 mg, 0.46 mmol) in dichloromethane (1.0 mL) was added over 6 h to the reaction mixture at −25 °C. Elution with 5% EtOAc/hexanes through regular silica gel column afforded 3l as a colorless gum (75 mg, 75%). \(Z:E = 32:1\) (by crude GC-MS analysis); HPLC analysis: 92% ee [AD-H column; 1.0 mL/min; solvent system: 1% isopropanol in hexane; retention times: 11.6 min (minor), 12.7 min (major)]; \([\alpha]_{D}^{24} = -6 \ (c \ 2.7, \text{CH}_2\text{Cl}_2); \) IR (thin film) 2954, 2917, 1733, 1434, 1257, 1213, 1168, 977, 817 cm⁻¹; \(^1\)H NMR (400 MHz, CDCl₃, TMS): \(\delta 7.42 \ (d, \ J = 8.3 \ Hz, 2\text{H}), 7.12 \ (d, \ J = 8.3 \ Hz, 2\text{H}), 5.84 \ (ddd, \ J = 17.0, 10.6 \ & 6.4 \ Hz, 1\text{H}), 5.31 \ (dt, \ J = 17.0 \ & 1.2 \ Hz, 1\text{H}), 5.17 \ (dt, \ J = 10.6 \ & 1.2 \ Hz, 1\text{H}), 4.73-4.64 \ (m, 1\text{H}), 3.83 \ (s, 3\text{H}), 3.80 \ (s, 3\text{H}), 2.98 \ (dd, \ J = 12.3 \ & 5.8 \ Hz, 1\text{H}), 2.42 \ (dd, \ J = 12.3 \ & 9.0 \ Hz, 1\text{H}), 2.32 \ (s, 3\text{H}), 1.91 \ (s, 3\text{H}); \) \(^{13}\)C{¹H} NMR (100 MHz, CDCl₃): \(\delta 170.3, 169.8, 149.1, 140.8, 136.4, 128.4, 128.0, 126.3, 117.6, 109.5, 80.4, 63.0, 53.4, 53.3, 42.7, 21.3, 18.4; \) HRMS (ESI-TOF) m/z: \([M + H]^+\) Calcd for \((\text{C}_{19}\text{H}_{23}\text{O}_5)^+\): 331.1545; Found: 331.1543.

Dimethyl \((S,Z)\)-2-(1-(2-fluorophenyl)ethylidene)-5-vinylidihydrofuran-3,3(2H)-dicarboxylate \((3m)\): Following general procedure, \((S)\)-1b (56 mg, 0.30 mmol) solution in dichloromethane (1.0 mL) was added to a stirring suspension of Pd(PPh₃)₄ (17 mg, 0.015 mmol) in dichloromethane (1.0 mL) at −25 °C. A solution of (2-fluorophenyl)methylketene (68 mg, 0.46 mmol) in dichloromethane (1.0 mL) was added over 6 h to the reaction mixture at −25 °C. Elution with 4% EtOAc/hexanes through regular silica gel column afforded 3m as a colorless gum (45 mg, ~95% pure by \(^1\)H NMR, 42%). \(Z:E = >99:1\) (by crude GC-MS analysis); HPLC analysis: 92% ee [AD-H column; 1.0 mL/min; solvent system: 1% isopropanol in hexane; retention times: 8.5 min (minor), 10.4 min (major)]; \([\alpha]_{D}^{24} = -13 \ (c \ 2.4, \text{CH}_2\text{Cl}_2); \) IR (thin film) 3006, 2953, 1730, 1434, 1259, 1162, 1084, 978, 698 cm⁻¹; \(^1\)H NMR (400 MHz, CDCl₃, TMS): \(\delta 7.56-7.50 \ (m, 2\text{H}), 7.34-7.27 \ (m, 2\text{H}), 7.20-7.13 \ (m, 1\text{H}), 5.85 \ (ddd, \ J = 17.0, 10.6 \ & 6.5 \ Hz, 1\text{H}), 5.31 \ (dt, \ J = 17.0 \ & 1.2 \ Hz, 1\text{H}), 5.18 \ (dt, \ J = 10.6 \ & 1.2 \ Hz, 1\text{H}), 4.74-4.65 \ (m, 1\text{H}), 3.83 \ (s, 3\text{H}), 3.81 \ (s, 3\text{H}), 2.99 \ (dd, \ J = 12.4 \ & 5.8 \ Hz, 1\text{H}), 2.43 \ (dd, \ J = 12.4 \ & 9.0 \ Hz, 1\text{H}), 1.93 \ (s, 3\text{H}); \) \(^{13}\)C{¹H} NMR (100 MHz, CDCl₃): \(\delta 170.2, 169.8, 148.1, 140.8, 136.4, 128.4, 128.0, 126.3, 117.6, 109.5, 80.5, 63.1, 53.40, 53.35, 42.7, 18.3; \) HRMS (ESI-TOF) m/z: \([M + H]^+\) Calcd for \((\text{C}_{18}\text{H}_{21}\text{O}_5)^+\): 317.1389; Found: 317.1387.
9.3 min (major)], $[\alpha]_{D}^{24}$ 5 (c 0.4, CH$_2$Cl$_2$); IR (thin film) 2955, 2931, 1436, 1266, 1211, 1168, 787 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$, TMS): δ 7.34–7.27 (m, 1H), 7.22–7.14 (m, 1H), 7.11–6.98 (m, 2H), 5.78 (ddd, J = 17.0, 10.6 & 6.4 Hz, 1H), 5.26 (dt, J = 17.0 & 1.3 Hz, 1H), 5.13 (dt, J = 10.6 & 1.3 Hz, 1H), 4.69–4.59 (m, 1H), 3.86 (s, 3H), 3.83 (s, 3H), 2.99 (dd, J = 12.4 & 5.9 Hz, 1H), 2.45 (dd, J = 12.4 & 8.6 Hz, 1H), 1.88 (s, 3H); $^{13}$C{1H} NMR (100 MHz, CDCl$_3$): δ 170.0, 169.7, 159.9 (d, J = 247 Hz, 1C), 148.8, 136.4, 131.1 (d, J = 4 Hz, 1C), 129.0 (d, J = 16 Hz, 1C), 128.3 (d, J = 8 Hz, 1C), 123.7 (d, J = 3 Hz, 1C), 117.4, 115.8 (d, J = 23 Hz, 1C), 104.9, 80.2, 62.4, 53.5, 53.4, 42.7, 18.1 (d, J = 2 Hz, 1C); HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for (C$_{18}$H$_{20}$FO$_5$)$_{+}$: 335.1295; Found: 335.1296.

Dimethyl (S,Z)-2-(1-(4-chlorophenyl)ethylidene)-5-vinylidihydrofuran-3,3(2H)-dicarboxylate (3n): Following general procedure, (S)-1b (56 mg, 0.30 mmol) solution in dichloromethane (1.0 mL) was added to stirring suspension of Pd(PPh$_3$)$_4$ (17 mg, 0.015 mmol) in dichloromethane (1.0 mL) at –25 °C. A solution of (4-chlorophenyl)methylketene (76 mg, 0.46 mmol) in dichloromethane (1.0 mL) was added over 6 h to the reaction mixture at –25 °C. Elution with 5% EtOAc/hexanes through regular silica gel column afforded 3n as a colorless gum (88 mg, ~95% pure by $^1$H NMR, 79%). Z:E = >99:1 (by crude GC-MS analysis); HPLC analysis: 97% ee [OD-H column; 1.0 mL/min; solvent system: 1% isopropanol in hexane; retention times: 10.2 min (minor), 11.1 min (major)]; $[\alpha]_{D}^{24}$ −5 (c 1.9, CH$_2$Cl$_2$); IR (thin film) 2954, 2918, 2849, 1731, 1492, 1434, 1258, 1162, 1082, 831 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$, TMS): δ 7.47 (dt, J = 8.7 & 2.1 Hz, 2H), 7.26 (dt, J = 8.7 & 2.1 Hz, 2H), 5.84 (ddd, J = 17.0, 10.6 & 6.5 Hz, 1H), 5.31 (dt, J = 17.0 & 1.3 Hz, 1H), 5.20 (dt, J = 10.6 & 1.3 Hz, 1H), 4.75–4.65 (m, 1H), 3.84 (s, 3H), 3.81 (s, 3H), 3.00 (dd, J = 12.4 & 5.7 Hz, 1H), 2.42 (dd, J = 12.4 & 9.0 Hz, 1H), 1.90 (s, 3H); $^{13}$C{1H} NMR (100 MHz, CDCl$_3$): δ 170.0, 169.6, 148.6, 139.2, 136.1, 131.8, 129.8, 128.0, 117.9, 108.4, 80.7, 63.2, 53.5, 53.4, 42.6, 18.1; HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for (C$_{18}$H$_{20}$ClO$_5$)$_{+}$: 351.0999; Found: 351.0999.

Dimethyl (S,Z)-2-(1-(4-(trifluoromethyl)phenyl)ethylidene)-5-vinylidihydrofuran-3,3(2H)-dicarboxylate (3o): Following general procedure, (S)-1b (56 mg, 0.30 mmol) solution in dichloromethane (1.0 mL) was added to stirring suspension of Pd(PPh$_3$)$_4$ (17 mg, 0.015 mmol) in dichloromethane (1.0 mL) at –25 °C. A solution of methyl(4-(trifluoromethyl)phenyl)ketene (91 mg, 0.46 mmol) in dichloromethane (1.0 mL) was added over 6 h to the reaction mixture at –25 °C. Elution with 6% EtOAc/hexanes through regular silica gel column afforded 3o as a colorless gum (101 mg, ~95% pure by $^1$H NMR, 82%). Z:E = >99:1 (by crude GC-MS analysis); HPLC analysis: 83% ee [OD-H column; 1.0 mL/min; solvent system: 1% isopropanol in hexane; retention times: 10.0 min (major), 10.8 min (minor)]; $[\alpha]_{D}^{24}$ −6 (c 4.1, CH$_2$Cl$_2$); IR (thin film) 2956, 2918, 2849, 1733, 1614, 1436, 1324, 1261, 1162, 1119, 1063, 980, 843 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$, TMS): δ 7.64 (d, J = 8.2 Hz, 2H), 7.54 (d, J = 8.2 Hz, 2H), 5.84 (ddd, J = 17.0, 10.6 & 6.5 Hz, 1H), 5.32 (dt, J = 17.0 & 1.2 Hz, 1H), 5.21 (dt, J = 10.6 & 1.2 Hz, 1H), 4.77-4.68 (m, 1H), 3.85 (s, 3H), 3.82
(s, 3H), 3.02 (dd, J = 12.4 & 5.7 Hz, 1H), 2.44 (dd, J = 12.4 & 9.0 Hz, 1H), 1.94 (s, 3H); ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 169.9, 169.4, 149.5, 144.5, 136.0, 128.6, 128.1 (d, J = 32 Hz, 1C), 124.8 (q, J = 4 Hz, 1C), 124.6 (q, J = 272 Hz, 1C), 118.0, 108.3, 80.9, 63.3, 53.52, 53.45, 42.6, 18.0; HRMS (ESI-TOF) m/z: [M + H]+ Calcd for (C₁₉H₂₀F₃O₅)+: 385.1263; Found: 385.1262.

Dimethyl (S)-2-(diphenylmethylene)-5-vinyldihydrofuran-3,3(2H)-dicarboxylate (3p): Following general procedure, (S)-1b (60 mg, 0.33 mmol) solution in dichloromethane (1.0 mL) was added to stirring suspension of Pd(PPh₃)₄ (19 mg, 0.016 mmol) in dichloromethane (1.3 mL) at −25 °C. A solution of diphenylketene (95 mg, 0.49 mmol) in dichloromethane (1.0 ml) was added over 6 h to the reaction mixture at −25 °C. Elution with 6% EtOAc/hexane through regular silica gel column afforded 3p as a colorless gum (52 mg, 42%). HPLC analysis: 88% ee [OD-H column; 1.0 mL/min; solvent system: 1% isopropanol in hexane; retention times: 13.0 min (major), 14.5 min (minor)]; [α]D⁺²⁴ = −114 (c 1.3, CH₂Cl₂); IR (thin film) 2957, 2932, 1735, 1436, 1277, 1247, 1197, 1162, 701 cm⁻¹; ¹H NMR (400 MHz, CDCl₃, TMS): δ 7.40–7.34 (m, 2H), 7.32–7.19 (m, 7H), 7.15–7.09 (m, 1H), 5.94 (ddd, J = 17.0, 10.5 & 6.5 Hz, 1H), 5.38 (dt, J = 17.0 & 1.2 Hz, 1H), 5.27 (dt, J = 10.5 & 1.2 Hz, 1H), 4.74–4.64 (m, 1H), 3.70 (s, 3H), 3.25 (s, 3H), 2.97 (dd, J = 12.5 & 5.7 Hz, 1H), 2.69 (dd, J = 12.5 & 9.3 Hz, 1H); ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 169.6, 168.8, 149.7, 140.3, 138.7, 136.0, 131.9, 129.7, 127.93, 127.90, 127.2, 126.3, 118.2, 116.2, 80.2, 64.2, 53.3, 53.0, 43.8; HRMS (ESI-TOF) m/z: [M + H]+ Calcd for (C₂₃H₂₃O₅)+: 379.1545; Found: 379.1545.

Dimethyl 5-ethyl-2-(1-phenylethyl)dihydrofuran-3,3(2H)-dicarboxylate [(±)-(5b)]: A solution of tetrahydrofuran (±)-3b (70 mg, 0.22 mmol) in methanol (4.4 mL) was added via Pasteur pipette to the pressure device containing the 10 wt.% Pd/C catalyst (12 mg, 0.011 mmol). While the inlet to the pressure device was closed and stirring commenced, minimum vacuum was applied to remove air inside the pressure device through its outlet. Then the outlet was closed, and hydrogen was transferred to the pressure device at 50 psi. Minimum vacuum was applied again to remove hydrogen inside the pressure device through its outlet after the inlet was closed. This hydrogen flushing cycle was repeated twice to make sure that air was removed from the pressure device completely. Then, hydrogen pressure of 225 psi (15 atm) was applied under stirring (1150 rpm) and continued at room temperature for 30 min. After the pressure device was vented, the mixture was diluted with dichloromethane (20 mL), filtered through celite (10 g), and washed with dichloromethane (30 mL). Diastereomeric ratio of crude product was determined by GC-MS analysis. Removal of solvent under reduced pressure afforded pure reduced product (±)-5b as a colorless oil (70 mg, 99%). dr = >99:1 (by crude GC-MS analysis); IR (thin film) 2955, 2935, 1730, 1452, 1434, 1260, 1099, 761, 700 cm⁻¹; ¹H NMR (400 MHz, CDCl₃, TMS): δ 7.29–7.21 (m, 4H), 7.18–7.12 (m, 1H), 4.80 (d, J = 7.7 Hz, 1H), 3.79–3.70 (m, 1H), 3.64 (s, 3H), 3.30 (s, 3H), 3.02 (app quint, J = 7.2 Hz, 1H), 2.51–2.38 (m, 2H), 1.80–1.68 (m, 1H), 1.67–1.55 (m, 1H), 1.25 (d, J = 6.9 Hz, 3H), 0.98 (t, J = 7.5 Hz, 3H); ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 171.6, 169.7, 144.9, 128.4, 128.3, 126.4, 85.4, 79.0, 63.6, 53.0, 52.5, 42.1, 40.5, 28.5, 19.9, 10.5; HRMS (ESI-TOF) m/z: [M + H]+ Calcd for (C₁₉H₂₅O₅)+: 321.1702; Found: 321.1697.
Dimethyl (2S,5R)-5-ethyl-2-((R)-1-phenylethyl)dihydrofuran-3,3(2H)-dicarboxylate [(–)-5k]: A solution of tetrahydrofuran (–)3k (35 mg, 0.11 mmol) in methanol (2.2 mL) was added via Pasteur pipette to the pressure device containing the 10 wt.% Pd/C catalyst (6 mg, 0.005 mmol). While the inlet to the pressure device was closed and stirring commenced, minimum vacuum was applied to remove air inside the pressure device through its outlet. Then the outlet was closed, and hydrogen was transferred to the pressure device at 50 psi. Minimum vacuum was applied again to remove hydrogen inside the pressure device through its outlet after the inlet was closed. This hydrogen flushing cycle was repeated twice to make sure that air was removed from the pressure device completely. Then, hydrogen pressure of 225 psi (15 atm) was applied under stirring (1150 rpm) and continued at room temperature for 30 min. After the pressure device was vented, the mixture was diluted with dichloromethane (15 mL), filtered through celite (10 g), and washed with dichloromethane (25 mL). The diastereomeric ratio was determined by GC-MS analysis. Removal of solvent under reduced pressure afforded pure reduced product (–)5k as a colorless oil (35 mg, 99%). dr = >99:1 (by crude GC-MS analysis); HPLC analysis: 89% ee [AD-H column; 1.0 mL/min; solvent system: 1% isopropanol in hexane; retention times: 6.1 min (major), 8.3 min (minor)]; [α]D24 –52 (c 3.5, CH2Cl2); IR (thin film) 2955, 2930, 1731, 1452, 1434, 1260, 1228, 1098, 762, 700 cm–1; 1H NMR (400 MHz, CDCl3, TMS): δ 7.29-7.21 (m, 4H), 7.18-7.12 (m, 1H), 4.80 (d, J = 7.7 Hz, 1H), 3.79-3.69 (m, 1H), 3.64 (s, 3H), 3.30 (s, 3H), 3.02 (app quint, J = 7.2 Hz, 1H), 2.51-2.38 (m, 2H), 1.80-1.68 (m, 1H), 1.67-1.55 (m, 1H), 1.25 (d, J = 7.0 Hz, 3H), 0.98 (t, J = 7.5 Hz, 3H); 13C{1H} NMR (100 MHz, CDCl3): δ 171.6, 169.7, 144.9, 128.4, 128.3, 126.4, 85.4, 79.0, 63.6, 53.0, 52.5, 42.1, 40.5, 28.5, 19.9, 10.5; HRMS (ESI-TOF) m/z: [M + H]+ Calcd for (C18H25O5)+: 321.1702; Found: 321.1700.

(S,Z)-1-(1-Phenylethylidene)-3-vinyl-2-oxa-7,9-diazaspiro[4.5]decane-6,8,10-trione [(+)–6k]: To an ice cooled stirring suspension of (–)3k (172 mg, 0.54 mmol) and urea (130 mg, 2.18 mmol) in DMSO (2.0 mL), a solution of t-BuOK (1.2 mL, 1.2 mmol) in THF (1.0 M) was added dropwise. After 15 min the ice was removed and the reaction mixture was allowed to warm to room temperature. After stirring at room temperature for 6 h the reaction was quenched with cold water (2.0 mL) and diluted with EtOAc (60 mL). The organic layer was washed with brine (30 mL × 4), dried over sodium sulfate, and concentrated under reduced pressure. Recrystallization of the crude product from a mixture of hexanes and dichloromethane afforded (+)–6k as a colorless crystalline solid (83 mg, 49%). mp 258-259 °C; [α]D24 151 (c 0.6, Acetone); IR (thin film) 3186, 3092, 2922, 2858, 1752, 1725, 1692, 1406, 1351, 1250, 1210, 696 cm–1; 1H NMR (400 MHz, Acetone-d6, TMS): δ 10.53 (bs, 1H), 7.53 (d, J = 8.2 Hz, 2H), 7.29 (t, J = 7.8 Hz, 2H), 7.15 (t, J = 7.4 Hz, 1H), 5.99 (ddd, J = 17.2, 10.3 & 7.1 Hz, 1H), 5.43 (d, J = 17.0 Hz, 1H), 5.25 (d, J = 10.3 Hz, 1H), 5.05-4.96 (m, 1H), 2.96 (dd, J = 12.7 & 5.5 Hz, 1H), 2.44 (dd, J = 12.7 & 10.5 Hz, 1H), 1.80 (s, 3H); 13C{1H} NMR (100 MHz, Acetone-d6): δ 172.0, 171.8, 152.6, 150.5, 141.7, 137.7, 129.6, 129.3, 127.6, 119.4, 107.2, 83.6, 60.9, 47.7, 18.7; HRMS (ESI-TOF) m/z: [M + H]+ Calcd for (C17H17N2O4)+: 313.1188; Found: 313.1185.
3-Ethyl-1-(1-phenylethyl)-2-oxa-7,9-diazaspiro[4.5]decane-6,8,10-trione [(±)-7b]: To an ice cooled stirring suspension of (±)-5a (80 mg, 0.25 mmol) and urea (60 mg, 1.0 mmol) in DMSO (1.0 mL), a solution of t-BuOK (0.55 mL, 0.55 mmol) in THF (1.0 M) was added dropwise. After 15 min the ice was removed and the reaction mixture allowed to warm to room temperature. After stirring at room temperature for 6h the reaction was quenched with cold water (2.0 mL) and diluted with EtOAc (40 mL). The organic layer was washed with brine (30 mL × 4), dried over sodium sulfate and concentrated under reduced pressure. Recrystallization of the crude product from a mixture of hexanes and acetone afforded (±)-7b as a colorless crystalline solid (45 mg, 57%). mp 241-243 °C; IR (thin film) 3199, 3088, 2966, 2874, 1748, 1718, 1686, 1364, 1346, 1242, 1105, 910, 763 cm⁻¹; ¹H NMR (400 MHz, CDCl₃, TMS): δ 7.81 (bs, 1H), 7.50 (bs, 1H), 7.27-7.20 (m, 3H), 7.14-7.08 (m, 2H), 4.55 (d, J = 10.6 Hz, 1H), 4.20-4.11 (m, 1H), 3.15-3.04 (m, 1H), 2.53 (dd, J = 12.5 & 6.6 Hz, 1H), 2.08 (dd, J = 12.5 & 9.0 Hz, 1H), 1.95-1.83 (m, 1H), 1.75-1.63 (m, 1H), 1.41 (d, J = 6.8 Hz, 3H), 1.03 (t, J = 7.5 Hz, 3H); ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 172.4, 171.0, 147.8, 141.4, 129.1, 128.3, 128.1, 94.1, 81.6, 58.6, 46.9, 41.9, 27.5, 22.1, 147.0, 141.4, 10.7; HRMS (ESI-TOF) m/z: [M + H]⁺ Calcd for (C₁₇H₂₁N₂O₄)⁺: 317.1501; Found: 317.1497.

Determination of absolute configuration and Z/E geometry of tetrahydrofurans: The absolute stereochemistry and Z/E geometry of all tetrahydrofurans were determined from the X-ray crystal structure analysis of tetrahydrofuran derivative (+)-6k. (+)-6k was determined to possess (S)-absolute stereochemistry at C3 (and hence at C5 in tetrahydrofuran (-)3k) and so all tetrahydrofurans 3k-3p were assigned (S)-absolute configuration by analogy. The olefin geometry in the major isomer of (+)-6k was determined to be of Z-stereochemistry, and so all tetrahydrofurans 3a-3o were assigned Z-olefin stereochemistry by analogy. See the supporting information for cif-6k and ORTEP diagram of 6k.

Relative stereochemistry of (±)-5b (and hence (-)-5k) was determined from the X-ray crystal structure analysis of cyclic urea derivative (±)-7b, and absolute stereochemistry was determined by comparing with X-ray crystal structure of (+)-6k. See the supporting information for cif-7b and ORTEP diagram of 7b.

Supporting Information Available: Spectroscopic data, X-ray crystallographic data (cifs for 6k and 7b), and chromatograms for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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References:


(c) ref 4b (d) ref 5b.


13. CCDC 1895670 and 1895669 contain the supplementary crystallographic data for 6k and 7b. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.