CHAPTER 1

Enantioselective Construction of α-Quaternary Cyclobutanones by Catalytic Asymmetric Allylic Alkylation[1]

1.1 INTRODUCTION

1.1.1 Palladium catalyzed allylic alkylation

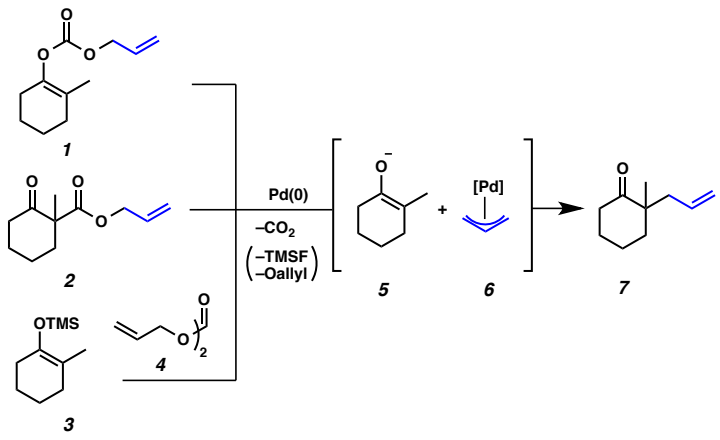
The synthesis of stereogenic all-carbon quaternary centers remains a formidable challenge, notwithstanding the strides made by modern organic chemistry in this regard.[1] Contemporary advances in enolate alkylation have made it a fundamental strategy for the construction of C–C bonds.[2] Allylic alkylation of tetrasubstituted enolates to give rise to α-quaternary carbonyl compounds has emerged as an efficient solution to this problem.[3] The Tsuji research group was among the first to study this class of transformations and pioneering investigations undertaken nearly three decades ago by, which culminated in a series of disclosures describing novel decarboxylative entry into the palladium-catalyzed allylic alkylation of cyclic ketones (Scheme 1.1.1.1).[4]

A simple mechanistic framework for the transformation begins with the oxidative addition of Pd^0 into the allyl group of an allyl enol carbonate (**1**), allyl β-ketoesters (**2**) or

[1] This work was performed in collaboration with Christian Eidamshaus and Jimin Kim, postdoctoral researchers in the Stoltz group. This work has been published. See: Reeves, C. M, Eidamshaus, C.; Kim, J.; Stoltz, B. M. *Angew. Chem. Int. Ed.* **2013**, *52*, 6718.

silyl enol ethers (**3**) in the presence of an allyl source (**4**), and gives a palladium π-allyl species (**6**), and the corresponding free carboxylate species. Spontaneous decarboxylation of the free carboxylate yields a tetrasubstituted enolate (**5**) that may enter into a catalytic cycle and furnish α-quaternary ketones (**7**). This method of enolate formation is particularly attractive in that the so-called "thermodynamic" enolate can be selectively generated *in situ*, in the absence of exogenous base under kinetic control. Furthermore, excellent positional fidelity is observed between the site of enolization and the site of allylic alkylation.

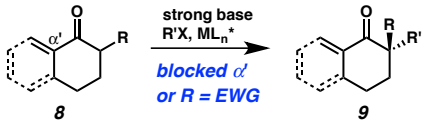
Scheme 1.1.1.1 *Palladium catalyzed allylic alkylation pioneered by Tsuji and coworkers*



Although methods for the alkylation of a number of enolate types (e.g., ester, ketone, amide, etc.) with a variety of alkylating agents exist, catalytic enantioselective variants of these transformations are relatively rare.[5] Of the catalytic asymmetric methods available, there have been few examples of general techniques for the asymmetric alkylation of carbocyclic systems, and still fewer that have the capacity to

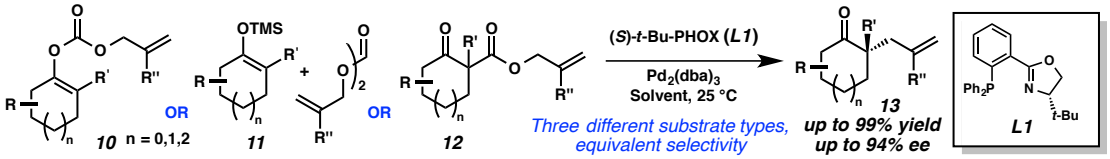
deliver all-carbon quaternary stereocenters.[6] While the Merck phase transfer methylation, and Koga alkylation of 2-alkyltetralone-derived silyl enol ethers represent notable exceptions,[4] the breadth of application and utility of these reactions has been limited. In fact, at the outset of investigations by the Stoltz group in this area, there were no examples of catalytic enantioselective alkylations of monocyclic 2-substituted cycloalkanone enolates in the absence of either α'-blocking groups or α-enolate stabilizing groups (e.g., **8**, R = aryl, ester, etc., Figure 1.1.1.2).

Scheme 1.1.1.2. *State of the art in asymmetric alkylation of prochiral enolates, 2003.*



In 2003, we initiated a program for the catalytic enantioselective synthesis of all-carbon quaternary stereocenters by allylic alkylation of prochiral cyclic ketone enolates. We adapted a protocol originally developed by Tsuji[7] to incorporate a chiral ligand scaffold, and found that the phosphinooxazoline (PHOX) ligands (e.g., **L1,** Scheme 1.1.1.3)[8] were optimal for both chemical yields and enantioselectivity.[9] The allylic alkylation protocol developed in the Stoltz laboratory is robust enough to prevail upon several different enolate precursor classes, namely allyl enol carbonates (**10**), enol silanes (**11**), and β-ketoesters (**12**) to deliver the desired α-quaternary cyclic ketone products (**13**) in good to excellent yields and enantioselectivies.[9,10]

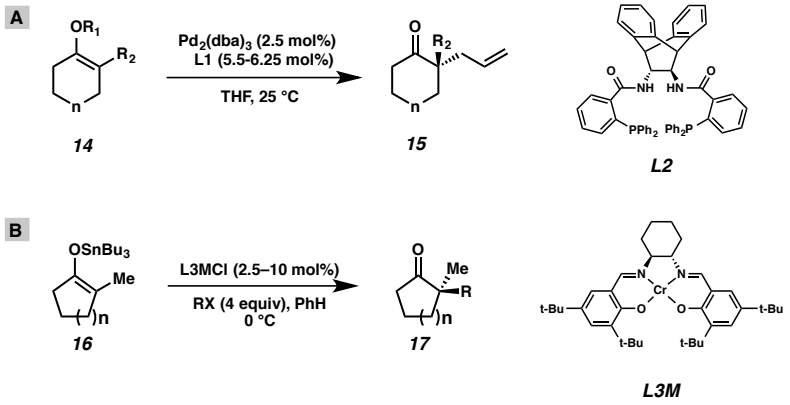
Scheme 1.1.1.3. *Stoltz and coworkers' approach to asymmetric allylic alkylation*



In addition, the reaction is highly tolerant of a broad range of functionality and substitution on both the enolate precursors and allyl fragments. Enolates derived from cyclic ketones,[9] enones,[10] vinylogous esters,[11] vinylogous thioesters,[12] tetralones,[10] and dioxanones[13] function with similar levels of selectivity in the catalytic asymmetric chemistry. We have also developed a scale-up protocol employing 2.5 mol % Pd that allows access to >10 g of enantioenriched material in excellent yields.[14]

Concurrent to our work in this area,[10,15] Trost and coworkers have published a series of papers that complement our studies in asymmetric alkylation, and which employ symmetric bidentate C-2 symmetric bisphosphine ligands (**L2**, Scheme 1.1.1.4a).[16] Shortly after this report, Jacobsen and coworkers, as well, have revealed a unique enantioselective method involving the chromium-catalyzed reaction of tin-enolates (**16**) with a variety of non-activated alkyl halides (Scheme 1.1.1.4b).[6]

Scheme 1.1.1.4. *Asymmetric allylic alkylation by Trost (A) and Jacobsen (B)*

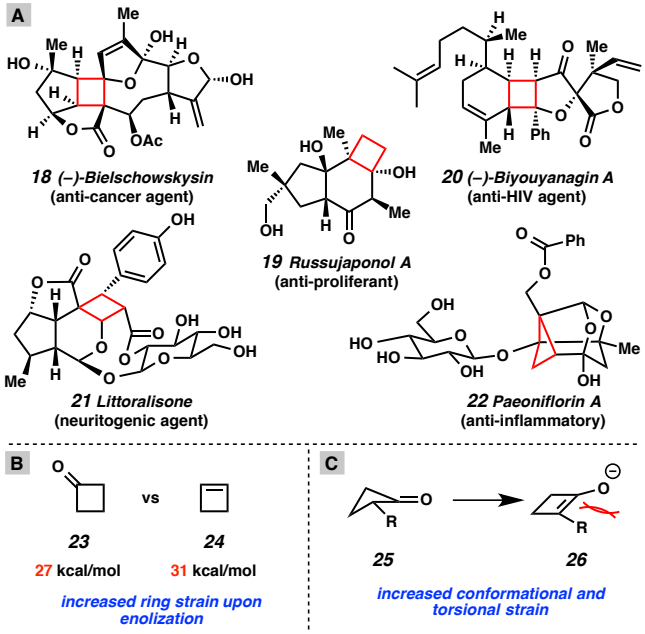


1.1.2 Palladium-catalyzed allylic alkylation of cyclobutanones

In the domain of asymmetric allylic alkylation, cyclobutanones have received far less attention relative to their five-, six- and seven-membered congeners, despite the fact that these compounds and their derivatives are prevalent in important biologically-active natural products[17] (**18**–**22**, Figure 1.1.2.1A). Additionally, cyclobutanes have been shown to serve as highly valuable synthetic intermediates for a variety of transformations.[18] The dearth of reports describing the asymmetric alkylation of cyclobutanones may be attributed to the fact that these compounds possess an estimated 26–28.6 kcal/mol of ring-strain[19] and, in turn, exhibit enhanced carbonyl electrophilicity.[20] The propensity of cyclobutanones to alleviate this strain via electrophilic ring opening is often a limiting challenge during their manipulation. Moreover, the energetic requirements for enolization of cyclobutanones (**23**) are compounded by a concomitant increase in ring-strain to 31–34 kcal/mol (calculated for cyclobutene **24**, Figure 1.1.2.1B)[18] as well as enforced deviation from the more favorable puckered conformation (**25**→**26**, Figure 1.1.2.1C).[21] In the case of α-substituted cyclobutanones, enolization is further impeded

by the development of torsional strain between the putative enolate substituents (**26**, Figure 1.1.2.1C).[22]

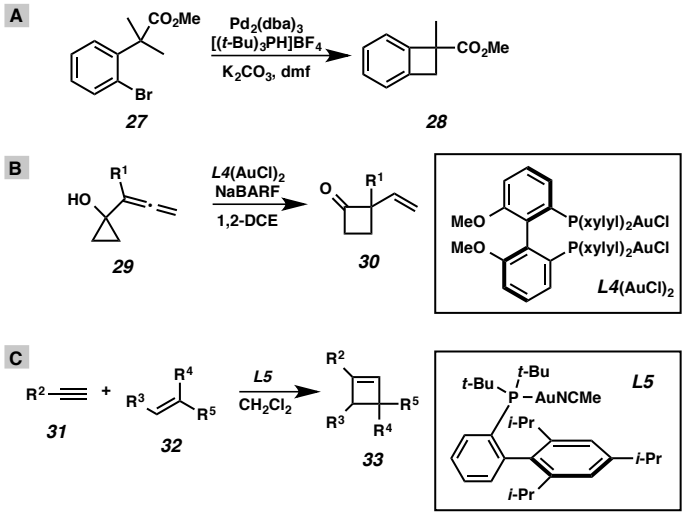
Figure 1.1.2.1. *(A) Representative cycbutanoid natural products; (B) ring, conformational and torsional strain in cyclobutanone enolates*



Given these data, it is not surprising that previous methods for the preparation of enantioenriched cyclobutanes have relied primarily on either [2+2] cycloaddition reactions[23] or ring expansion from various cyclopropane derivatives.[24] Recent reports from Baudoin on annulating C–H activation[25] (Scheme 1.1.2.1A) as well as disclosures from Toste[26] (Scheme 1.1.2.1B) and Echavarren[27] (Scheme 1.1.2.1C) that employ gold(I) catalysis to affect cyclopropanoid rearrangements have emerged as significant new methods for the construction of cyclobutanes, and show the power of transition metals in this regard. Organocatalytic approaches to cyclobutanone synthesis have also gained

traction recently.[28] Despite these advances, transformations that produce chiral cyclobutanones remain limited in scope, and very few methods exist for the catalytic construction of chiral cyclobutanones from achiral starting materials.[9b,29] In order to address these limitations and to further develop the nucleophilic chemistry of these unusually reactive compounds, we report herein the first direct transition metal-catalyzed asymmetric α-alkylation of cyclobutanones to form all-carbon quaternary centers.

Scheme 1.1.2.1. *Selected modern methods for the synthesis of cycbutanoids according to (A) Baudoin, (B) Toste, and (C) Echavarren*



1.2 PREPARATION OF CYCLOBUTANONE β-KETOESTER SUBSTRATES AND REACTION OPTIMIZATION

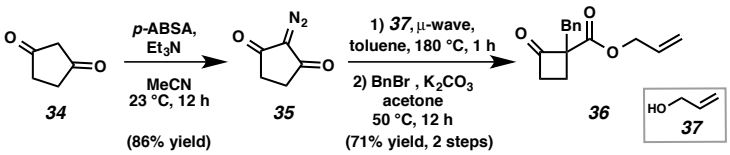
1.2.1 Cyclobutanone β-ketoester substrate synthesis

A longstanding interest of our research group has been the transition metal-catalyzed asymmetric α-functionalization of carbonyl compounds to form all-carbon

quaternary centers.[30] In the course of our studies, we have developed a series of phosphinooxazoline (PHOX) ligands with varied steric and electronic properties that exhibit a range of reactivity and selectivity. We have found that the use of electron deficient ligands (e.g. **L6** and **L7**) often results in superior asymmetric induction in certain cases where electron-rich or electron-neutral ligands perform poorly.[31] Examination of ligand electronic effects would, therefore, help to inform our development of a method for the asymmetric allylic alkylation of cyclobutanones.

We first established a simple and efficient reaction sequence to access allyl 1-alkyl-2-oxocyclobutanecarboxylate substrates (**36**) (Scheme 1). Diazotization of commercially available 1,3-cyclopentane dione (**34**) with *para*-acetamidobenzenesulfonyl azide (*p*-ABSA)[32] delivered the corresponding diazodiketone (**35**) in consistently good yields. Microwave-promoted Wolff rearrangement of diketone **35** in the presence of an allylic alcohol[33] (e.g., allyl alcohol, **37**), followed by alkylation with an alkyl halide (e.g., benzyl bromide) furnished the allyl 1-alkyl-2-oxocyclobutanecarboxylates in good yields over two steps. With a quick and efficient method to access the desired substrates at hand, we next examined reaction parameters to identify optimal conditions for reactivity and enantioselectivity.

Figure 1.2.1.1 *Construction of allyl 1-benzyl-2-oxocyclobutane-carboxylate (**36**)*



1.2.2 Optimization of cyclobutanone allylic alkylation

Our initial experiments revealed that treatment of allyl 1-benzyl-2-oxocyclobutanecarboxylate (**36**) with catalytic $Pd_2(pmdba)_3$ in the presence of (*S*)-*t*-BuPHOX (**L1**) in THF delivered the desired α-quaternary (*S*)-2-allyl-2-benzylcyclobutanone (**38**)[34] in 90% yield, albeit in moderate enantioselectivity (Figure 1.2.2.1, Table 1.2.2.1, Entry 1). The use of electron-deficient ligands **L6** or **L7** resulted in considerably improved enantioinduction (Table 1.2.2.1, Entries 2 and 5). Although the reaction proceeds well in a number of solvents, toluene was identified as optimal for inducing asymmetry. This solvent effect is likely due to an enhanced binding between the enolate and the electrophilic sigma-allyl-Pd(II) center in the catalytic cycle, which may reinforce a tight ion pair and lead to an inner-sphere mechanism.[35] Finally, at temperatures just below ambient, the reaction was found to proceed at a reasonable rate and with high enantioselectivity.

Figure 1.2.2.1. *General initial reaction parameters and select ligands*

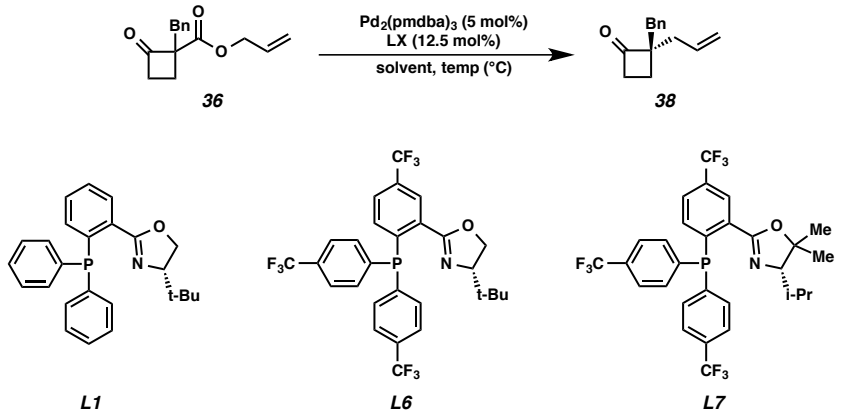


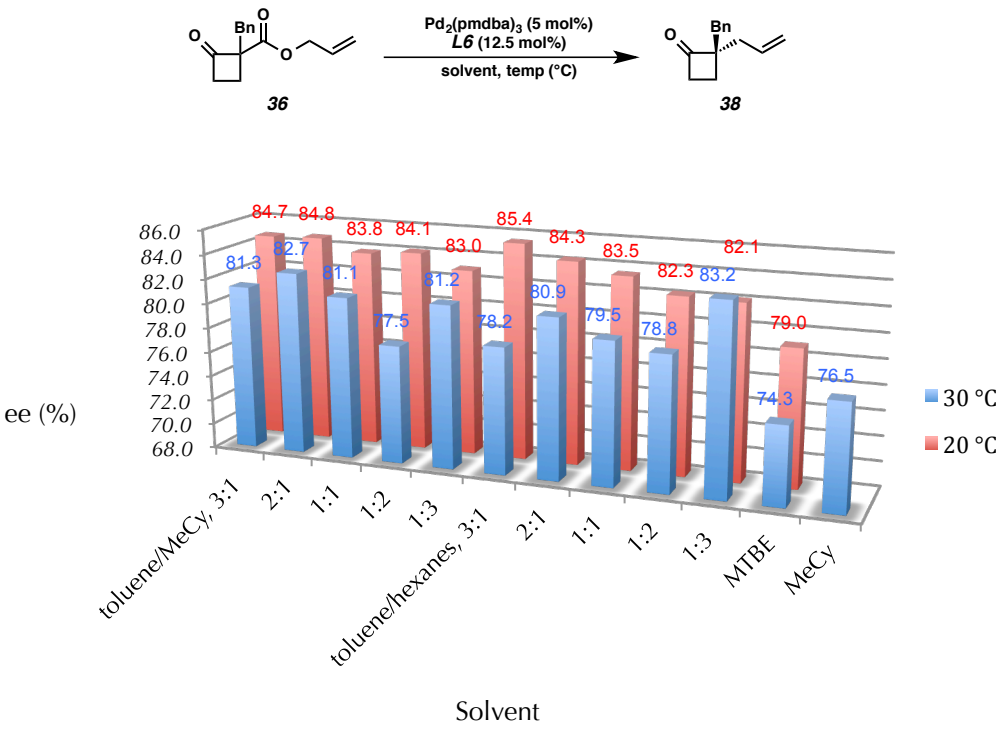
Table 1.2.2.1. *Initial optimization of the palladium-catalyzed allylic alkylation reaction*

Entry	Ligand	Solvent	T [°C]	ee [%]
1	L1	THF	25	58
2	L6	THF	25	75
3	L6	*p*-dioxane	25	84
4	L6	benzene	25	84
5	L7	toluene	25	84
6	L6	toluene	25	85

In order to fully explore the effects of solvent on the reactions selectivity, we made use of the reaction automation system in the Caltech Center for Catalysis and Chemical Synthesis. A Symyx systems robot was employed to expedite a panel of experiments that varied solvent and temperature, while holding constant reaction variables that were found be to optimal during preliminary screening (i.e., ligand **L6** and relatively non-polar solvent).[36] These studies illustrated that while the reaction was most

selective when carried out in relatively non-polar solvent, a number of different non-polar solvents or solvent combinations could be employed without significant detriment to the reaction selectivity (Figure 1.2.2.2). Finally, these studies revealed that, in most cases, decreasing the temperature at which the reaction was carried out resulted in an increase in selectivity.

Figure 1.2.2.2. *Solvent and temperature optimization of the palladium catalyzed allylic alkylation reaction*



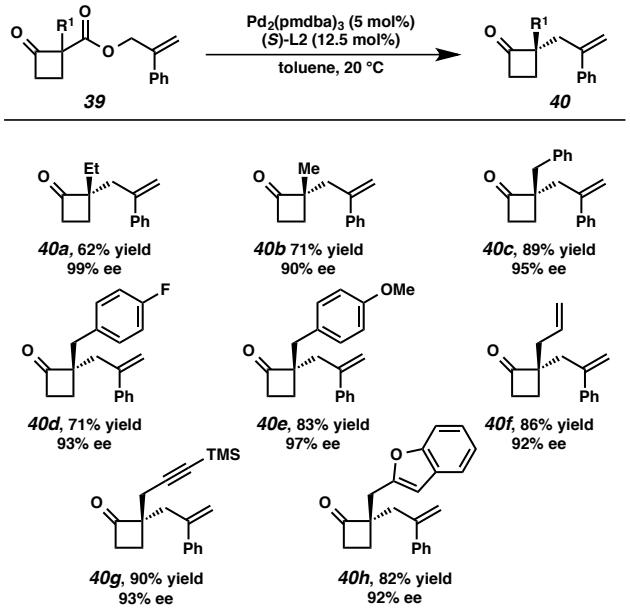
1.3 EXPLORATION OF THE REACTION SCOPE

1.3.1 Reaction scope with respect to enolate α-substitution

With these optimized conditions identified, we next explored the influence of different α-substituents (R^1, Figure 1.3.1.1) on the efficacy of the allylic alkylation

process. To aid in the isolation of these highly volatile products, we chose coupling fragments of higher molecular weights, bearing substitution at both the α-position and allyl fragment (i.e. 2-phenylallyl and 1-alkyl-2-oxocyclobutanecarboxylate). We were pleased to find that α-alkyl substituents were well tolerated with enantiomeric excess up to 99% (Figure 1.3.1.1, **40a**–**40b**). α-Benzyl substituents were found to give the respective α-quaternary cyclobutanones with uniformly excellent enantioselectivity regardless of the electronic nature of the benzyl moiety (compounds **40c**–**40e**). In addition to alkyl- and benzyl- substituents, allyl-, TMS-protected propargyl and heteroaryl substituted 2-carboxyallyl cyclobutanones proved to be eligible substrates in the asymmetric allylic alkylation reaction providing cyclobutanones **40f**–**40h** in high yields and enantiomeric excess.

Figure 1.3.1.1. *Reaction scope with respect to α-quaternary substitution (R^1)*

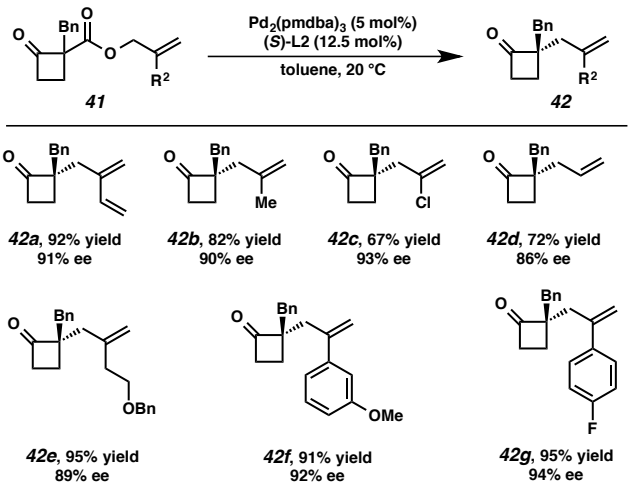


1.3.2 Reaction scope with respect to allyl coupling partner substitution

Having surveyed the scope of the process with respect to various substituents at the quaternary center, we were poised to investigate the influence of different allyl substitution on the process (R^2, Figure 1.3.2.1). In accord with previous studies on the palladium-catalyzed asymmetric allylic alkylation, the catalytic system was found to be relatively inactive when terminally-substituted or cyclic allyl fragments were employed.[15] As such, we limited our survey to carboxyallyl fragments bearing substituents at the 2-allyl position. Gratifyingly, diverse substituents were well tolerated (Figure 1.3.2.1). All α-quaternary cyclobutanones were obtained in moderate to high yield and with outstanding enantiopurity. Particularly interesting are compounds **42a**, **42c**, and **42d** featuring a butadiene, a vinyl chloro and a benzyl ether moiety, respectively. Each of these diverse functional groups may potentially serve as handles for various

derivatization reactions (e.g., cycloaddition, annulation or transition metal-catalyzed cross-coupling).

Figure 1.3.2.1. *Reaction scope with respect to allyl substitution (R^2)*

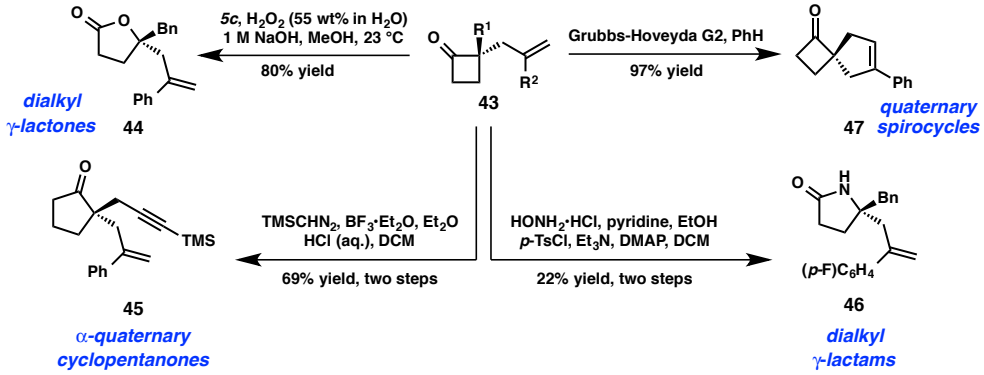


1.4 DERIVATIZATION OF REACTION PRODUCTS

Myriad studies have shown cyclobutanoids to be highly valuable synthetic intermediates, allowing access to enantioenriched oxazepines, [37] piperidines, [38] tetrahydropyrans,[39] α- and β-quaternary cyclopentanones,[17] benzannulated polycycles[40] as well as β-quaternary linear ketones.[17] Cyclobutanones may participate directly in a variety of robust classical transformations, such as Baeyer-Villiger oxidation and Beckmann rearrangement,[17] as well as transition metal-catalyzed ring expansion,[41] ring contraction[42] and ring-opening processes.[43] To demonstrate the utility of our asymmetric synthesis of cyclobutanones within this domain, we carried out a number of transformations on the chiral cyclobutanones generated in this study. Ring expansion by

Baeyer-Villiger oxidation, treatment with trimethylsilyldiazomethane and Beckmann rearrangement all proceeded smoothly to deliver dialkyl γ-lactone **44**, α-quaternary cyclopentanone **45** and dialkyl γ-lactam **46**, respectively. Additionally, ring-closing metathesis of diallyl-substituted cyclobutanone **40f** cleanly furnished quaternary [4.5]-spirocycle **47**.

Figure 1.4.1. *Derivatization of α-quaternary cyclobutanones*



1.5 CONCLUDING REMARKS

In summary, we have developed the first transition metal-catalyzed enantioselective α-alkylation of cyclobutanones. This method employs palladium catalysis and an electron-deficient PHOX type ligand to afford α-quaternary cyclobutanones in good to excellent yields and enantioselectivities. A wide variety of substituents are tolerated at both the α-keto and 2-allyl positions. The mild nature of our method is reflected in its compatibility with otherwise highly electrophilic cyclobutanones. We have further demonstrated the utility of chiral cyclobutanones as synthetic building blocks to access a variety of enantioenriched derivative compounds

including dialkyl γ-lactams, dialkyl γ-lactones, α-quaternary cyclopentanones and quaternary [4.5]-spirocycles. We believe that this novel synthetic method will enable the expeditious synthesis of complex bioactive natural products and pharmaceutical components by providing unique access to previously unknown and inaccessible enantioenriched α-quaternary cyclobutanones. Efforts toward this end are currently underway in our laboratory.

1.6 EXPERIMENTAL SECTION

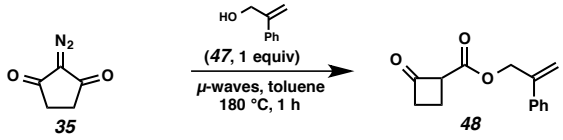
1.6.1 Materials and Methods

Unless otherwise stated, reactions were performed in flame-dried glassware under an inert atmosphere of argon or nitrogen using dry, deoxygenated solvents. Reaction progress was monitored by thin-layer chromatography (TLC). THF, Et_2O, CH_2Cl_2, toluene, benzene, CH_3CN, and dioxane were dried by passage through an activated alumina column under argon. Triethylamine was distilled over CaH_2 prior to use. Brine solutions are saturated aqueous solutions of sodium chloride. 1,3-Cyclopentanedione was purchased from AK Scientific, Inc., reagent grade acetone was purchased from Aldrich and distilled from anhydrous Ca_2SO_4 and stored over molecular sieves (3 Å) under an atmosphere of argon. *para*-Acetamidobenzenesulfonyl azide (*p*-ABSA) was prepared following a procedure by Davies *et al*. [44] 2-Phenylprop-2-en-1-ol, 2-(4-methoxyphenyl)prop-2-en-1-ol and 2-(3-fluorophenyl)prop-2-en-1-ol were prepared according to the method by Gouverneur and Brown.[45] 2-Diazocyclopentane-1,3-dione was prepared through diazotization of 1,3-cyclopentanedione with *p*-ABSA following a procedure by Coquerel and Rodriguez.[46] Phosphinooxazoline (PHOX) ligands were

prepared by methods described in our previous work.[9, 47] Tris(4,4'-methoxydibenzylideneacetone)dipalladium(0) ($Pd_2(pmdba)_3$) was prepared according to the method of Ibers[48] or Fairlamb.[49] All other reagents were purchased from Sigma-Aldrich, Acros Organics, Strem, or Alfa Aesar and used as received unless otherwise stated. Reaction temperatures were controlled by an IKAmag temperature modulator unless otherwise indicated. Stirring was accomplished with Teflon® coated magnetic stir bars. Microwave-assisted reactions were performed in a Biotage Initiator 2.5 microwave reactor. Glove box manipulations were performed under a N_2 atmosphere. TLC was performed using E. Merck silica gel 60 F254 precoated glass plates (0.25 mm) and visualized by UV fluorescence quenching, *p*-anisaldehyde, or $KMnO_4$ staining. Silicycle Silia*Flash* P60 Academic Silica gel (particle size 0.040-0.063 mm) was used for flash column chromatography. ^{1}H NMR spectra were recorded on a Varian Inova 500 MHz spectrometer and are reported relative to residual $CHCl_3$ (δ 7.26 ppm), C_6H_6 (δ 7.16 ppm), or CH_2Cl_2 (δ 5.32 ppm). ^{13}C NMR spectra were recorded on a Varian Inova 500 MHz (126 MHz) or Varian Mercury 300 MHz (75 MHz) spectrometer and are reported relative to $CHCl_3$ (δ 77.16 ppm) or C_6H_6 (δ 128.06 ppm). Data for ^{1}H NMR are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, h = heptet, m = multiplet, br s = broad singlet, br d = broad doublet, app = apparent. Data for ^{13}C are reported in terms of chemical shifts (δ ppm). IR spectra were obtained using a Perkin Elmer Spectrum BXII spectrometer using thin films deposited on NaCl plates and reported in frequency of absorption (cm^{-1}). Optical rotations were measured with a Jasco P-2000 polarimeter operating on the sodium D-line (589 nm)

using a 100 mm path-length cell and are reported as: $[\alpha]_D^T$ (concentration in g/100 mL, solvent, ee). Analytical UHPLC-LCMS was performed with an Agilent 1290 Infinity Series UHPLC/Agilent 6140 Quadrupole LCMS utilizing an Agilent Eclipse Plus C18 RRHD 1.8 μm column (2.1 x 50 mm), part number 959757-902. High-resolution mass spectra (HRMS) were obtained from the Caltech Mass Spectral Facility (EI+ or FAB+) or on an Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI), atmospheric pressure chemical ionization (APCI), or mixed (MM: ESI-APCI) ionization mode.

1.6.2 Representative procedure for the preparation of 2-oxocyclobutanecarboxylates

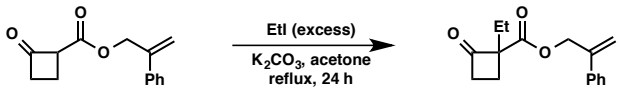


2-Phenylallyl 2-oxocyclobutanecarboxylate. To a 20 mL microwave vial charged with a magnetic stir bar were added 2-diazocyclopentane-1,3-dione (**35**, 500 mg, 4.03 mmol), toluene (13.5 mL) and 2-phenylprop-2-en-1-ol (**47**, 540 mg, 4.03 mmol). The vial was sealed with a microwave crimp cap and heated to 180 °C for one hour using a Biotage Initiator microwave reactor (sensitivity set to low; reaction mixture heated gradually over first 2 min by increasing the temperature in 20 °C increments). After 30 min of stirring, the mixture was cooled to ambient temperature and the pressure was released by puncture of the crimp cap with a needle. The reaction vessel was then subsequently irradiated at 180 °C for an additional 30 min. The vessel was then cooled to ambient temperature, the

vial uncapped and mixture directly loaded onto a silica gel column followed by elution with hexanes to 20% EtOAc in hexanes to afford of **48** (635 mg, 68% yield) as a colorless oil. R_f = 0.2 (20% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44–7.30 (m, 5H), 5.57–5.55 (m, 1H), 5.40–5.39 (m, 1H), 5.06–5.05 (m, 2H), 4.26–4.20 (m, 1H), 3.20–3.15 (m, 2H), 2.48–2.34 (m, 1H), 2.29–2.16 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.5, 166.5, 142.0, 137.8, 128.5, 128.1, 126.0, 115.4, 66.5, 64.5, 47.1, 13.6; IR (Neat Film, NaCl) 3448, 3084, 3057, 3024, 2970, 1956, 1790, 1732, 1633, 1600, 1574, 1497, 1445, 1387, 1310, 1177, 1046, 915, 780 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{14}H_{15}O_3$ $[M+H]^+$: 231.1016; found 231.1018.

*With the exception of compound **48**, all 2-carboxyallylcyclobutanone derivatives were directly used in the following steps without rigorous characterization due to their instability.*

1.6.3 Representative procedure for the alkylation of 2-H-2-oxocyclobutanecarboxylates



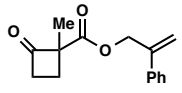
48 *39a*

2-Phenylallyl 1-ethyl-2-oxocyclobutanecarboxylate (39a). To a solution of **48** (233 mg, 1.01 mmol) in acetone (14 mL) were added K_2CO_3 (224 mg, 1.62 mmol) and freshly distilled EtI (787 mg, 5.05 mmol). The mixture was heated to reflux until full consumption of the starting material was indicated by TLC analysis (alkylation reaction

times typically ranged from 12 to 24 hours). Upon completion, the mixture was cooled to 25 °C, the solids were removed by filtration through filter paper and the mixture was concentrated *in vacuo*. The crude material was purified by flash column chromatography (SiO_2, hexanes to 10% EtOAc in hexanes to 20% EtOAc in hexanes) to provide **39a** (105 mg, 40% yield) as a colorless oil. R_f = 0.3 (20% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42–7.28 (m, 5H), 5.55 (s, 1H), 5.38 (s, 1H), 5.06 (dd, *J* = 9.0, 1.0 Hz, 2H), 2.56–2.17 (m, 3H), 1.88-1.63 (m, 3H), 0.69 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.4, 171.5, 142.2, 137.8, 128.5, 128.1, 126.1, 116.5, 66.5, 63.7, 35.5, 30.4, 27.1, 8.6; IR (Neat Film, NaCl) 3084, 2972, 2880, 1738, 1709, 1460, 1444, 1231, 1207, 1138 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{16}H_{19}O_3$ $[M+H]^+$: 259.1334; found 259.1326.

1.6.4 Spectroscopic data for novel cyclobutanone β-ketoester substrates

2-Phenylallyl 1-methyl-2-oxocyclobutanecarboxylate (39b)

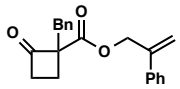


39b

Compound **39b** was isolated by flash column chromatography (SiO_2, hexanes to 10% EtOAc in hexanes) as a colorless oil. 32% yield. R_f = 0.5 (20% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40–7.29 (m, 5H), 5.54–553 (m, 1H), 5.35–5.34 (m, 1H), 5.06 (dq, *J* = 11.2, 1.0 Hz, 1H), 3.20 (ddd, *J* = 18.3, 11.3, 7.6 Hz, 1H), 3.10 (ddd, *J* = 18.3, 9.9, 6.3 Hz, 1H), 2.53 (td, *J* = 11.3, 6.3 Hz, 1H), 1.84 (ddd, *J* = 11.5, 9.9, 7.6 Hz, 1H), 1.45 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 204.3, 170.0, 142.3, 137.9, 128.5, 128.1, 126.0, 115.2, 69.4, 66.5, 45.3, 23.1, 18.4; IR (Neat Film, NaCl) 2970, 2930, 1788,

1729, 1452, 1274, 1145, 1049 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{15}H_{16}O_3$ $[M]^+$: 244.1100; found 244.1103.

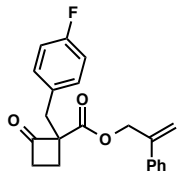
2-Phenylallyl 1-benzyl-2-oxocyclobutanecarboxylate (39c)



39c

Compound **39c** was isolated by flash column chromatography (SiO_2, hexanes to 10% EtOAc in hexanes) as a colorless oil. 37% yield. R_f = 0.4 (10% EtOAc in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ7.33–7.14 (m, 8H), 7.04–7.02 (m, 2H), 5.47 (s, 1H), 5.28–5.27 (m, 1H), 5.01–4.95 (m, 2H), 3.12, 3.10 (AB system, J_{AB} = 14.2 Hz, 2H), 2.95 (ddd, *J* = 18.3, 11.1, 7.3 Hz, 1H), 2.62 (ddd, *J* = 18.3, 10.3, 6.3 Hz, 1H), 2.39 (ddd, *J* = 11.9, 11.1, 6.3 Hz, 1H), 1.93 (ddd, *J* = 11.9, 10.3, 7.3 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 203.7, 168.7, 142.1, 137.8, 135.9, 129.7, 128.51, 128.49, 128.1, 126.9, 126.0, 115.5, 75.0, 66.7, 45.2, 37.9, 19.2; IR (Neat Film, NaCl) 3029, 2924, 1788, 1725, 1496, 1270, 1191, 1046 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{42}H_{40}NaO_6$ $[2M+Na]^+$: 663.2717; found 663.2692.

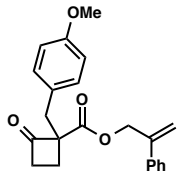
2-Phenylallyl 1-(4-fluorobenzyl)-2-oxocyclobutanecarboxylate (39d)



39d

Compound **39d** was isolated by flash column chromatography (SiO_2, 3% EtOAc in hexanes to 6% EtOAc in hexanes) as a colorless oil. 22% yield. R_f = 0.4 (20% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40–7.29 (m, 5H), 7.08–7.04 (m, 2H), 6.95–6.91 (m, 2H), 5.54 (s, 1H), 5.34 (d, J = 0.9 Hz, 1H), 5.05 (s, 2H), 3.18, 3.16 (AB system, J_{AB} = 14.3 Hz, 2H), 3.05 (ddd, J = 18.4, 11.2, 7.4 Hz, 1H), 2.73 (ddd, J = 18.4, 10.2, 6.2 Hz, 1H), 2.46 (ddd, J = 11.8, 11.2, 6.2 Hz, 1H), 1.97 (ddd, J = 11.8, 10.2, 7.4 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 203.4, 168.6, 161.9 (d, $^1J_{CF}$ = 245.6 Hz), 142.1, 137.8, 131.6 (d, $^4J_{CF}$ = 3.7 Hz), 131.2 (d, $^3J_{CF}$ = 8.0 Hz), 128.5, 128.1, 126.0, 115.7, 115.3 (d, $^2J_{CF}$ = 21.2 Hz), 75.0, 66.8, 45.2, 37.0, 19.3; IR (Neat Film, NaCl) 3052, 2968, 2928, 1784, 1717, 1506, 1219, 1186, 1042, 912 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{21}H_{20}{}^{19}FO_3$ $[M+H]^+$: 339.1391; found 339.1387.

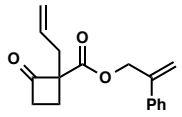
2-Phenylallyl 1-(4-methoxybenzyl)-2-oxocyclobutanecarboxylate (39e)



39e

To a solution of NaI (1.88 g, 12.54 mmol) in acetone (20 mL) was added 4-methoxybenzyl chloride (1.55 mL, 11.38 mmol). The mixture was stirred at 25 °C for 2 hours before K_2CO_3 (504 mg, 3.65 mmol) and **48** (524 mg, 2.28 mmol) were added. The resulting mixture was heated to reflux for 16 hours until full conversion of the starting material was indicated by TLC analysis. The mixture was cooled to room temperature, the solids removed by filtration and concentrated *in vacuo*. The crude material was purified by flash column chromatography (SiO_2, hexanes to 10% EtOAc in hexanes to 20% EtOAc in hexanes) to provide **39e** (506 mg, 63% yield) as a colorless oil. R_f = 0.5 (20% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41–7.39 (m, 2H), 7.36–7.29 (m, 3H), 7.04–7.01 (m, 2H), 6.80–6.77 (m, 2H), 5.54 (s, 1H), 5.36–5.35 (m, 1H), 5.08–5.02 (m, 2H), 3.77 (s, 3H), 3.13 (s, 2H), 3.00 (ddd, *J* = 18.3, 11.1, 7.2 Hz, 1H), 2.68 (ddd, *J* = 18.3, 10.3, 6.4 Hz, 1H), 2.45 (ddd, *J* = 11.8, 11.1, 6.4 Hz, 1H), 2.00 (ddd, *J* = 11.8, 10.3, 7.2 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 203.9, 168.8, 158.5, 142.1, 137.8, 130.7, 128.5, 128.1, 127.8, 126.0, 115.5, 113.9, 75.2, 66.7, 55.2, 45.0, 37.1, 19.1; IR (Neat Film, NaCl) 2957, 2933, 2836, 1788, 1725, 1513, 1248, 1179, 1037 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{22}H_{23}O_4$ $[M+H]^+$: 351.1596; found 351.1601.

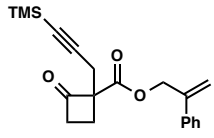
2-Phenylallyl 1-allyl-2-oxocyclobutanecarboxylate (39f)



39f

Compound **39f** was isolated by flash column chromatography (SiO_2, 3% EtOAc in hexanes to 4% EtOAc in hexanes) as a colorless oil. 68% yield. R_f = 0.2 (10% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49–7.27 (m, 5H), 5.64 (ddt, *J* = 17.5, 9.7, 7.1 Hz, 1H), 5.56 (q, *J* = 0.8 Hz, 1H), 5.38 (q, *J* = 1.2 Hz, 1H), 5.12–5.08 (m, 2H), 5.07 (dd, *J* = 1.4, 0.7 Hz, 2H), 3.14 (ddd, *J* = 18.4, 11.0, 7.4 Hz, 1H), 3.02 (ddd, *J* = 18.4, 10.1, 6.4 Hz, 1H), 2.70 (ddt, *J* = 14.3, 7.1, 1.2 Hz, 1H), 2.59–2.44 (m, 2H), 1.99 (ddd, *J* = 11.9, 10.1, 7.4 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 203.4, 168.6, 142.3, 137.9, 131.9, 128.5, 128.1, 126.1, 119.2, 115.5, 73.6, 66.6, 45.0, 36.7, 19.5; IR (Neat Film, NaCl) 3072, 2967, 1786, 1725, 1638, 1497, 1440, 1387, 1193, 1142, 1043, 919, 779 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{17}H_{19}O_3$ $[M+H]^+$: 271.1329; found 271.1330.

2-Phenylallyl 2-oxo-1-(3-(trimethylsilyl)prop-2-yn-1-yl)cyclobutanecarboxylate (39g)

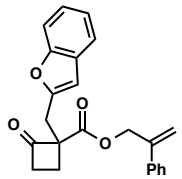


39g

Compound **39g** was isolated by flash column chromatography (SiO_2, 3% EtOAc in hexanes to 7% EtOAc in hexanes) as a colorless oil. 63% yield. R_f = 0.3 (10% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42–7.27 (m, 5H), 5.54 (q, *J* = 0.7 Hz, 1H),

5.35 (td, *J* = 1.3, 0.7 Hz, 1H), 5.10–4.98 (m, 2H), 3.18 (ddd, *J* = 18.4, 11.0, 7.4 Hz, 1H), 3.06 (ddd, *J* = 18.4, 10.4, 6.5 Hz, 1H), 2.82 (d, *J* = 17.3 Hz, 1H), 2.69 (d, *J* = 17.3 Hz, 1H), 2.48 (ddd, *J* = 11.8, 11.0, 6.5 Hz, 1H), 2.27 (ddd, *J* = 11.8, 10.4, 7.4 Hz, 1H), 0.13 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 201.9, 168.1, 142.1, 137.8, 128.5, 128.1, 126.0, 115.4, 100.9, 87.9, 72.1, 66.8, 46.3, 22.8, 19.7, -0.1; IR (Neat Film, NaCl) 3058, 2959, 2177, 1949, 1794, 1732, 1634, 1575, 1496, 1444, 1422, 1315, 1250, 1194, 1161, 1116, 1028, 906, 843, 778, 760, 708 cm^{-1}; HRMS (APCI) *m/z* calc'd for $C_{20}H_{25}O_3Si$ $[M+H]^+$: 341.1567; found 341.1582.

2-Phenylallyl 1-(benzofuran-2-ylmethyl)-2-oxocyclobutanecarboxylate (39h)

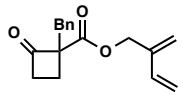


39h

Compound **39h** was isolated by flash column chromatography (SiO_2, 5% EtOAc in hexanes to 10% EtOAc in hexanes) as a colorless oil. 27% yield. R_f = 0.6 (20% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48–7.46 (m, 1H), 7.40–7.38 (m, 3H), 7.33–7.29 (m, 3H), 7.25–7.18 (m, 2H), 6.37 (d, *J* = 0.8 Hz, 1H), 5.55 (m, 1H), 5.37 (m, 1H), 5.09 (s, 2H), 3.43 (d, *J* = 15.6 Hz, 1H), 3.28 (dd, *J* = 15.6, 0.8 Hz, 1H), 3.18 (ddd, *J* = 18.4, 11.2, 7.6 Hz, 1H), 2.97 (ddd, *J* = 18.4, 10.2, 6.1 Hz, 1H), 2.58 (ddd, *J* = 11.9, 11.2, 6.1 Hz, 1H), 2.11 (ddd, *J* = 11.9, 10.2, 7.6 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 202.2, 168.1, 154.8, 153.6, 142.1, 137.7, 128.5, 128.4, 128.1, 126.0, 123.8, 122.7, 120.6, 115.7, 110.9, 104.9, 73.1, 67.0, 45.8, 30.9, 19.9; IR (Neat Film, NaCl) 3582, 3056, 3033,

2963, 2928, 1790, 1726, 1601, 1586, 1455, 1253, 1193, 1045 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{23}H_{21}O_4$ $[M+H]^+$: 361.1434; found 361.1427.

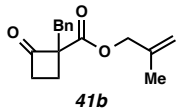
2-Methylenebut-3-en-1-yl 1-benzyl-2-oxocyclobutanecarboxylate (41a)



41a

Compound **41a** was isolated by flash column chromatography (SiO_2, 1% EtOAc in hexanes to 8% EtOAc in hexanes) as a colorless oil. 51% yield. R_f = 0.4 (10% EtOAc in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 7.33–7.20 (m, 3H), 7.19–7.05 (m, 2H), 6.36 (ddd, *J* = 17.9, 11.1, 0.8 Hz, 1H), 5.28–5.09 (m, 4H), 4.89–4.78 (m, 2H), 3.24 (dd, *J* = 18.6, 14.2 Hz, 2H), 3.14 (ddd, *J* = 18.3, 11.0, 7.2 Hz, 1H), 2.75 (ddd, *J* = 18.3, 10.3, 6.4 Hz, 1H), 2.58 (ddd, *J* = 11.8, 11.0, 6.4 Hz, 1H), 2.06 (ddd, *J* = 11.8, 10.3, 7.2 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 203.7, 168.7, 140.0, 136.0, 135.9, 129.7, 128.5, 127.0, 118.4, 114.8, 75.1, 64.6, 45.2, 38.0, 19.2; IR (Neat Film, NaCl) 3987, 3027, 2929, 1789, 1725, 1598, 1495, 1454, 1393, 1266, 1192, 1044, 909, 743 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{17}H_{19}O_3$ $[M+H]^+$: 271.1329; found 271.1330.

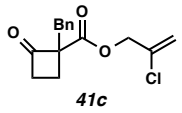
2-Methylallyl 1-benzyl-2-oxocyclobutanecarboxylate (41b)



41b

Compound **41b** was isolated by flash column chromatography (SiO_2, 3% EtOAc in hexanes) as a colorless oil. 44% yield. R_f = 0.4 (10% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32–7.24 (m, 3H), 7.19–7.17 (m, 2H), 4.97 (d, J = 15.1 Hz, 2H), 4.60, 4.56 (AB system, J_{AB} = 13.1 Hz, 2H), 3.28, 3.26 (AB system, J_{AB} = 14.2 Hz, 2H), 3.16 (ddd, J = 18.3, 11.0, 7.2 Hz, 1H), 2.77 (ddd, J = 18.3, 10.4, 6.5 Hz, 1H), 2.61 (ddd, J = 11.8, 11.0, 6.5 Hz, 1H), 2.09 (ddd, J = 11.8, 10.4, 7.2 Hz, 1H) 1.70 (d, J = 0.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 203.9, 168.7, 139.3, 134.0, 129.7, 128.5, 127.0, 113.4, 75.1, 68.7, 45.2, 38.0, 19.4, 19.2; IR (Neat Film, NaCl) 3030, 2974, 2925, 1790, 1727, 1454, 1271, 1193, 1047, 907 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{18}H_{19}O_3$ $[M+H]^+$ 259.1329; found 259.1340.

2-Chloroallyl 1-benzyl-2-oxocyclobutanecarboxylate (41c)

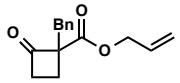


41c

Compound **41c** was isolated by flash column chromatography (SiO_2, 2% EtOAc in hexanes to 5% EtOAc in hexanes) as a colorless oil. 63% yield. R_f = 0.3 (10% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33–7.24 (m, 3H), 7.18–7.16 (m, 2H), 5.44–5.40 (m, 2H), 4.71 (m, 2H), 3.26 (s, 2H), 3.17 (ddd, J = 18.3, 11.0, 7.2 Hz, 1H),

2.77 (ddd, J = 18.3, 10.3, 6.5 Hz, 1H), 2.61 (ddd, J = 11.8, 11.0, 6.5 Hz, 1H), 2.01 (ddd, J = 11.8, 10.3, 7.2 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 203.4, 168.2, 135.7, 135.2, 129.7, 128.6, 127.1, 115.3, 74.9, 66.7, 45.3, 38.0, 19.2; IR (Neat Film, NaCl) 3578, 2918, 1792, 1734, 1637, 1439, 1268, 1191, 1045 cm^{-1}; HRMS (ESI) m/z calc'd for $C_{15}H_{15}ClO_3$ $[M]^+$: 278.0710; found 278.0714.

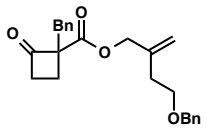
Allyl 1-benzyl-2-oxocyclobutanecarboxylate (36)



36

Compound **36** was isolated by flash column chromatography (SiO_2, 3% EtOAc in hexanes to 6% EtOAc in hexanes) as a colorless oil. 87% yield. R_f = 0.3 (10% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ7.30–7.27 (m, 2H), 7.25–7.22 (m, 1H), 7.17–7.14 (m, 2H), 5.88 (ddt, J = 17.2, 10.5, 5.7 Hz, 1H), 5.31 (dq, J = 17.2, 1.4 Hz, 1H), 5.24 (dq, J = 10.5, 1.4 Hz, 1H), 4.64 (dq, J = 5.7, 1.4 Hz, 2H), 3.26, 3.22 (AB system, J_{AB} = 14.2 Hz, 2H), 3.14 (ddd, J = 18.3, 11.0, 7.2 Hz, 1H), 2.75 (ddd, J = 18.3, 10.3, 6.5 Hz, 1H), 2.59 (ddd, J = 11.8, 11.0, 6.5 Hz, 1H), 2.07 (ddd, J = 11.8, 10.3, 7.2 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 203.9, 168.6, 136.0, 131.5, 129.7, 128.5, 127.0, 118.7, 75.1, 66.1, 45.1, 38.1, 19.3; IR (Neat Film, NaCl) 2916, 2848, 1781, 1715, 1438, 1181, 1040 cm^{-1}; HRMS (MM: ESI-APCI) m/z calc'd for $C_{15}H_{17}O_3$ $[M+H]^+$: 245.1172; found 245.1178.

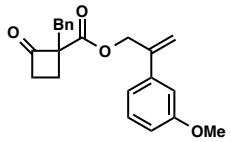
4-(Benzyloxy)-2-methylenebutyl 1-benzyl-2-oxocyclobutanecarboxylate (41d)



41d

Compound **41d** was isolated by flash column chromatography (SiO_2, 1% EtOAc in Hexanes to 3% EtOAc in hexanes) as a colorless oil. 51% yield. R_f = 0.5 (10% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47–7.12 (m, 10H), 5.11 (q, *J* = 1.0 Hz, 1H), 5.04 (h, *J* = 1.1 Hz, 1H), 4.67, 4.61 (AB system, J_{AB} = 13.3 Hz, 2H), 4.53 (s, 2H), 3.60 (t, *J* = 6.6, 2H), 3.26 (s, 2H), 3.14 (ddd, *J* = 18.2, 11.0, 7.2 Hz, 1H), 2.76 (ddd, *J*=18.3, 10.3, 6.4 Hz, 1H), 2.60 (ddd, *J* = 11.8, 11.0, 6.5 Hz, 1H), 2.42–2.33 (m, 2H), 2.08 (ddd, *J* = 11.8, 10.3, 7.2 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 203.9, 168.7, 140.7, 138.2, 136.0, 129.7, 128.6, 128.4, 127.7, 127.6, 127.0, 114.4, 75.1, 73.0, 68.5, 68.0, 45.2, 38.1, 33.5, 19.3; IR (Neat Film, NaCl) 3029, 2920, 2849, 1784, 1717, 1495, 1451, 1360, 1268, 1187, 1095, 904, 732 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{24}H_{27}O_4$ $[M+H]^+$: 379.1904; found 379.1926.

2-(3-Methoxyphenyl)allyl 1-benzyl-2-oxocyclobutanecarboxylate (41e)

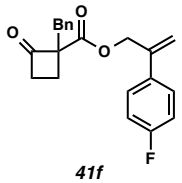


41e

Compound **41e** was isolated by flash column chromatography (SiO_2, 3% EtOAc in Hexanes to 7% EtOAc in Hexanes) as a colorless oil. 79% yield. R_f = 0.35 (10% EtOAc

in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41–7.16 (m, 4H), 7.16–7.09 (m, 2H), 7.05–6.90 (m, 2H), 6.91–6.82 (m, 1H), 5.60–5.53 (m, 1H), 5.37 (q, J = 1.2 Hz, 1H), 5.12–5.01 (m, 2H), 3.84 (s, 3H), 3.24, 3.21 (AB system, J_{AB} = 14.13 Hz, 2H), 3.06 (ddd, J = 18.3, 11.1, 7.3 Hz, 1H), 2.72 (ddd, J = 18.3, 10.2, 6.3 Hz, 1H), 2.51 (ddd, J = 11.9, 11.1, 6.3 Hz, 1H), 2.04 (ddd, J = 11.8, 10.2, 7.3 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 203.7, 168.7, 159.7, 142.1, 139.4, 136.0, 129.7, 129.5, 128.5, 126.9, 118.5, 115.8, 113.6, 111.8, 75.1, 66.8, 55.3, 45.2, 37.9, 19.2; IR (Neat Film, NaCl) 2957, 2833, 1786, 1720, 1575, 1494, 1453, 1387, 1221, 1180, 1039, 783 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{22}H_{23}O_4$ $[M+H]^+$: 351.1591; found 351.1582.

2-(4-Fluorophenyl)allyl 1-benzyl-2-oxocyclobutanecarboxylate (41f)



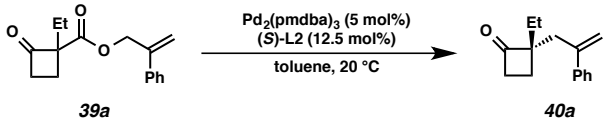
41f

Compound **41f** was isolated by flash column chromatography (SiO_2, 3% EtOAc in hexanes to 6% EtOAc in hexanes) as a colorless oil. 93% yield. R_f = 0.3 (10% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40–7.36 (m, 2H), 7.30–7.23 (m, 3H), 7.14–7.11 (m, 2H), 7.07–7.02 (m, 2H), 5.51 (s, 1H), 5.36 (s, 1H), 5.07–5.01 (m, 2H), 3.23, 3.20 (AB system, J_{AB} = 14.2 Hz, 2H), 3.06 (ddd, J = 18.3, 11.0, 7.3 Hz, 1H), 2.74 (ddd, J = 18.3, 10.3, 6.4 Hz, 1H), 2.51 (ddd, J = 11.9, 11.0, 6.4 Hz, 1H), 2.05 (ddd, J = 11.9, 10.3, 7.3 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 203.5, 168.6, 162.7 (d, $^{1}J_{CF}$ = 247.5 Hz), 141.1, 135.9, 133.9 (d, $^{4}J_{CF}$ = 3.9 Hz), 129.6, 128.5, 127.7 (d, $^{3}J_{CF}$ = 8.6 Hz), 126.9,

115.7, 115.4 (d, $^2J_{CF}$ = 21.4 Hz), 75.0, 66.7, 45.1, 37.8, 19.2; IR (Neat Film, NaCl) 3060, 3029, 2967, 2928, 1790, 1728, 1634, 1602, 1511, 1454, 1386, 1233, 1193, 1162, 1047, 917, 840, 744 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{21}H_{20}{}^{19}FO_3$ $[M+H]^+$: 339.1391; found 339.1397.

1.6.5 Representative procedure for the asymmetric decarboxylative allylic alkylation of 2-oxocyclobutanecarboxylates

(*S*)-2-Ethyl-2-(2-phenylallyl)cyclobutanone (40a)



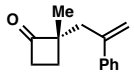
39a *40a*

To a 20 mL scintillation vial with a stir bar were added $Pd_2(pmdba)_3$ (16.4 mg, 0.015 mmol), **L6** (21.9 mg, 0.037 mmol) and toluene (9 mL) in a nitrogen−filled glove box. The dark purple mixture was stirred at ambient glove box temperature (ca. 30 °C) for 35 min at which point the mixture had become red-orange. 2-Carboxyallylcyclobutanone **39a** (80.0 mg, 0.31 mmol) was then added. The resulting yellow-greenish reaction mixture was stirred at 20 °C until full conversion of the starting material was indicated by TLC analysis (reaction times typically ranged from 18 to 36 hours). The vial was removed from the glove box, uncapped and directly purified by flash column chromatography (SiO_2, pentane to 15% Et_2O in pentane) afforded **40a** (41 mg, 62% yield) as colorless oil. R_f = 0.3 (15% Et_2O in pentane); ^1H NMR (300 MHz, $CDCl_3$) δ 7.46–7.25 (m, 5H), 5.55 (d, *J* = 0.9 Hz, 1H), 5.38 (d, *J* = 1.1 Hz, 1H), 5.16–4.92 (m, 2H), 2.51 (ddd, *J* = 14.7,

10.5, 2.0 Hz, 1H), 2.42–2.30 (m, 1H), 2.29–2.14 (m, 1H), 1.93–1.77 (m, 2H), 1.73–1.59 (m, 1H), 0.69 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.1, 145.2, 141.9, 128.3, 127.6, 126.5, 116.5, 63.8, 42.8, 40.6, 23.5, 21.6, 8.4; IR (Neat Film, NaCl) 3078, 2966, 1699, 1464, 1443, 905 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{15}H_{17}O$ $[(M+H)-H_2]^+$: 213.1279; found 213.1274; $[\alpha]_D^{26.0}$ +8.50 (*c* 1.00, $CHCl_3$, 99% ee).

1.6.6 Spectroscopic data for novel α-quaternary cyclobutanone products

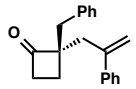
(*S*)-2-Methyl-2-(2-phenylallyl)cyclobutanone (40b)



40b

Cyclobutanone **40b** was isolated by flash column chromatography (SiO_2, 10% Et_2O in pentane) as a colorless oil. 92% yield. R_f = 0.3 (10% Et_2O in pentane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31–7.19 (m, 5H), 5.25 (d, J = 1.5 Hz, 1H), 5.04–5.03 (m, 1H), 2.93–2.66 (m, 3 H), 2.56 (d, J = 14.1 Hz, 1H), 1.82 (ddd, J = 11.4, 10.5, 6.9 Hz, 1H), 1.47 (ddd, J = 11.4, 10.2, 6.6 Hz, 1H), 1.09 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 215.1, 145.2, 141.9, 128.3, 127.6, 126.5, 116.5, 63.8, 42.8, 40.6, 23.5, 21.6; IR (Neat Film, NaCl) 2080, 2865, 1774, 1443, 1059 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{14}H_{17}O$ $[M+H]^+$: 201.1279; found 201.1286; $[\alpha]_D^{26.0}$ –83.9 (*c* 1.00, $CHCl_3$, 90% ee).

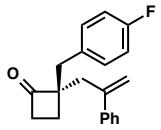
(*R*)-2-Benzyl-2-(2-phenylallyl)cyclobutanone (40c)



40c

Cyclobutanone **40c** was isolated by flash column chromatography (SiO_2, 5% Et_2O in petroleum ether) as a colorless oil. 81% yield. R_f = 0.6 (10% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36–7.26 (m, 8H), 7.13–7.11 (m, 2H), 5.37 (d, *J* = 1.4 Hz, 1H), 5.15–5.14 (m, 1H), 2.94 (t, *J* = 14.9 Hz, 2H), 2.72 (t, *J* = 14.2 Hz, 2H), 2.61 (ddd, *J* = 18.1, 9.6, 7.2 Hz, 1H), 2.32 (ddd, *J* = 18.1, 10.0, 7.5 Hz, 1H), 1.86–1.77 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 214, 145.0, 141.8, 137.3, 130.0, 128.4, 128.3, 127.7, 126.5, 126.4, 116.9, 68.8, 43.7, 41.2, 39.9, 20.0; IR (Neat Film, NaCl) 3028, 2918, 1770, 1494, 1453, 1074, 905 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{20}H_{21}O$ $[M+H]^+$: 277.1587; found 277.1587; $[\alpha]_D^{26.0}$ –2.91 (*c* 1.14, $CHCl_3$, 95% ee).

(*R*)-2-(4-Fluorobenzyl)-2-(2-phenylallyl)cyclobutanone (40d)

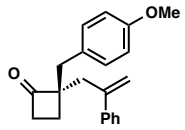


40d

Cyclobutanone **40d** was isolated by flash column chromatography (SiO_2, hexanes to 3% Et_2O in hexanes) as a colorless oil. 71% yield. R_f = 0.3 (25% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ7.36–7.26 (m, 5H), 7.09–7.05 (m, 2H), 6.97–6.93 (m, 2H), 5.37 (d, *J* = 1.4 Hz, 1H), 5.14 (d, *J* = 0.9 Hz, 1H), 2.93–2.89 (m, 2H), 2.74–2.67 (m, 2H), 2.33 (ddd, *J* = 18.1, 10.7, 6.9 Hz, 1H), 2.62 (ddd, *J* = 18.1, 10.4, 6.5 Hz, 1H), 1.83 (ddd, *J*

= 11.7, 10.4, 6.9 Hz, 1H), 1.75 (ddd, *J* = 11.7, 10.7, 6.5 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 214.7, 161.7 (d, $^1J_{CF}$ = 244.8 Hz), 144.9, 141.8, 132.9 (d, $^4J_{CF}$ = 3.8 Hz), 131.5 (d, $^3J_{CF}$ = 8.3 Hz), 128.8, 127.2, 126.4, 117.0, 115.1 (d, $^2J_{CF}$ = 21.1 Hz), 68.7, 43.7, 40.2, 39.9, 19.9; IR (Neat Film, NaCl) 3047, 2918, 2848, 1772, 1599, 1508, 1221, 1158, 1060 836 cm^{-1}; HRMS (MM: ESI-APCI) m/z calc'd for $C_{20}H_{20}{}^{19}FO$ $[M+H]^+$: 294.1420; found 294.1408; $[\alpha]_D^{26.0}$ –9.9 (*c* 0.59, $CHCl_3$, 94% ee).

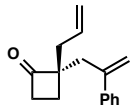
(*R*)-2-(4-Methoxybenzyl)-2-(2-phenylallyl)cyclobutanone (40e)



40e

Cyclobutanone **40e** was isolated by flash column chromatography (SiO_2, 10% EtOAc in hexanes) as a colorless oil. 83% yield. R_f = 0.3 (10% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ7.37–7.26 (m, 5H), 7.06–7.01 (m, 2H), 6.83–6.78 (m, 2H), 5.37 (d, *J* = 1.2 Hz, 1H), 5.14 (s, 1H), 3.78 (s, 3H), 2.91 (dd, *J* = 14.5, 3.1 Hz, 2H), 2.69 (dd, *J* = 14.5, 1.9 Hz, 2H), 2.64–2.53 (m, 1H), 2.37-2.26 (m, 1H) 1.78 (ddd, *J* = 10.1, 7.2, 2.6 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ215.1, 158.2, 145.0, 141.8, 131.0, 129.2, 128.3, 127.6, 126.4, 116.8, 113.6, 68.9, 55.1, 43.6, 40.3, 39.8; IR (Neat Film, NaCl) 3080, 2913, 2835, 1770, 1611, 1513, 1248, 1179, 1035, 907 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{21}H_{22}O_2$ $[M]^+$: 306.1620; found 306.1614; $[\alpha]_D^{26.0}$ –0.60 (*c* 1.00, $CHCl_3$, 95% ee).

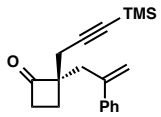
(*R*)-2-Allyl-2-(2-phenylallyl)cyclobutanone (40f)



40f

Cyclobutanone **40f** was isolated by flash column chromatography (SiO_2, 3% EtOAc in hexanes to 4% EtOAc in hexanes) as a colorless oil. 86% yield. R_f = 0.2 (10% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42–7.25 (m, 5H), 5.84–5.71 (m, 1H), 5.37 (d, J = 1.5 Hz, 1H), 5.14 (d, J = 1.0 Hz, 1H), 5.15–5.05 (m, 2H), 2.91, 2.70 (AB system, J_{AB} = 14.4 Hz, 2H), 2.87–2.65 (m, 2H), 2.36 (ddt, J = 13.9, 7.1, 1.2 Hz, 1H), 2.27 (ddt, J = 13.9, 7.6, 1.1 Hz, 1H), 1.85 (ddd, J = 11.7, 10.4, 6.8 Hz, 1H), 1.77–1.64 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 214.5, 145.1, 141.8, 133.3, 128.3, 128.3, 126.5, 118.7, 116.9, 67.5, 43.3, 39.7, 39.1, 20.3; IR (Neat Film, NaCl) 3078, 2921, 1774, 1625, 1493, 1443, 1387, 1059, 1000, 908, 779 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{16}H_{19}O$ $[M+H]^+$: 227.1430; found 227.1418; α_D^{25} –13.98 (*c* 0.51, $CHCl_3$, 92% ee).

(*S*)-2-(2-Phenylallyl)-2-[3-(trimethylsilyl)prop-2-yn-1-yl]cyclobutanone (40g)

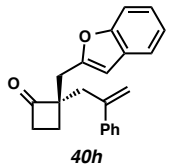


40g

Cyclobutanone **40g** was isolated by flash column chromatography (SiO_2, 1% EtOAc in hexanes to 3% EtOAc in hexanes) as a colorless oil. 90% yield. R_f = 0.2 (10% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51–7.08 (m, 5H), 5.37 (d, J = 1.4 Hz, 1H),

5.13 (d, J = 1.1 Hz, 1H), 2.93–2.86 (m, 2H), 2.82–2.75 (m, 2H), 2.42, 2.37 (AB system, J_{AB} = 17.0 Hz, 2H), 1.96–1.85 (m, 2H) 0.15 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 212.6, 144.5, 141.4, 128.4, 127.7, 126.4, 116.9, 102.7, 87.2, 66.6, 43.9, 38.9, 25.8, 20.9, 0.0; IR (Neat Film, NaCl) 2957, 2169, 1776, 1713, 1444, 1249, 1177, 1061, 1031, 834, 760 cm^{-1}; HRMS (MM: ESI-APCI) m/z calc'd for $C_{19}H_{25}OSi$ $[M+H]^+$: 297.1681; found 297.1683; $[\alpha]_D^{25}$ +10.76 (*c* 0.29, $CHCl_3$, 93% ee).

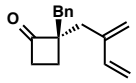
(S)-2-(Benzofuran-2-ylmethyl)-2-(2-phenylallyl)cyclobutanone (40h)



40h

Cyclobutanone **40h** was isolated by flash column chromatography (SiO_2, hexanes to 10% EtOAc in hexanes) as a colorless oil. 82% yield. R_f = 0.5 (10% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50–7.48 (m, 1H), 7.42–7.40 (m, 1H), 7.38–7.36 (m, 2H), 7.33–7.28 (m, 3H), 7.25–7.18 (m, 2H), 6.44 (s, 1H), 5.40 (d, J = 1.34 Hz, 1H), 5.17 (m, 1H), 3.07 (d, J = 15.2 Hz, 1H), 2.98 (dd, J = 14.3, 0.9 Hz, 1H), 2.96 (d, J = 15.0 Hz, 1H), 2.82 (d, J = 14.3 Hz, 1H), 2.79–2.64 (m, 2H), 1.96–1.86 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 213.2, 155.0, 154.7, 144.7, 141.6, 128.5, 128.4, 127.8, 126.4, 123.6, 122.6, 120.5, 117.2, 110.9, 105.0, 67.2, 43.8, 39.6, 33.7, 20.9; IR (Neat Film, NaCl) 3054, 2917, 2849, 1770, 1598, 1585, 1453, 1251, 1104, 1061, 905 cm^{-1}; HRMS (MM ESI-APCI) m/z calc'd for $C_{22}H_{21}O_2$ $[M+H]^+$: 317.1536; found 317.1530; $[\alpha]_D^{26}$ +56.4 (*c* 1.00, $CHCl_3$, 92% ee).

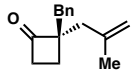
(*S*)-2-Benzyl-2-(2-methylenebut-3-en-1-yl)cyclobutanone (42a)



42a

Cyclobutanone **42a** was isolated by flash column chromatography (SiO_2, hexanes to 5% Et_2O in hexanes) as a colorless oil. 92% yield. R_f = 0.3 (10% EtOAc in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 7.33–7.27 (m, 3H), 7.25–7.20 (m, 2H), 7.19–7.12 (m, 1H), 6.59–6.19 (m, 1H), 5.24–5.06 (m, 2H), 5.05 (s, 2H), 3.01 (d, *J* = 13.6 Hz, 1H), 2.80 (d, *J* = 13.6 Hz, 1H), 2.68 (ddd, *J* = 18.1, 10.3, 6.8 Hz, 1H), 2.57 (dd, *J* = 14.4, 1.0 Hz, 1H), 2.45 (ddd, *J* = 18.1, 10.3, 6.9 Hz, 1H), 2.40 (d, *J* = 14.4 Hz, 1H), 1.95 (qdd, *J* = 11.6, 10.2, 6.8 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 215.2, 142.4, 139.4, 137.3, 130.1, 128.3, 126.6, 119.2, 114.5, 68.6, 43.9, 41.4, 35.5, 20.2; IR (Neat Film, NaCl) 3022, 2921, 2843, 1768, 1590, 1493, 1452, 1384, 1065, 989, 898, 755 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{16}H_{18}O$ $[M+H]^+$: 227.1430; found 227.1433; $[\alpha]_D^{25}$ +0.44 (*c* 1.60, $CHCl_3$, 91% ee).

(*S*)-2-Benzyl-2-(2-methylallyl)cyclobutanone (42b)

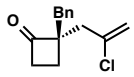


42b

Cyclobutanone **42b** was isolated by flash column chromatography (SiO_2, 2% Et_2O in hexanes to 5% Et_2O in hexanes) as a colorless oil. 82% yield. R_f = 0.3 (10% EtOAc in

hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41–7.12 (m, 5H), 4.91 (t, J = 1.7 Hz, 1H), 4.78 (dd, J = 2.0 Hz, 1.0, 1H), 2.88, 2.65 (AB system, J_{AB} = 13.7 Hz, 2H), 2.77 (ddd, J = 18.1, 9.6, 6.9 Hz, 1H), 2.43–2.33 (m, 1H), 2.33, 2.22 (AB system, J_{AB} = 14.2 Hz, 2H), 1.97 (ddd, J = 9.4, 7.2, 3.1, 2H), 1.80–1.72 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 215.3, 141.8, 137.4, 130.1, 128.3, 126.5, 114.8, 68.2, 43.6, 43.2, 40.6, 24.0, 20.7; IR (Neat Film, NaCl) 3072, 3027, 2964, 2919, 1772, 1322, 1131, 1062, 894 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{15}H_{18}O$ $[M]^+$: 214.1358, found 214.1346; $[\alpha]_D^{26}$ –2.4° (*c* 0.48, $CHCl_3$, 90% ee).

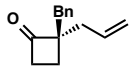
(*R*)-2-Benzyl-2-(2-chloroallyl)cyclobutanone (42c)



42c

Cyclobutanone **42c** was isolated by flash column chromatography (SiO_2, hexanes to 3% EtOAc in hexanes) as a colorless oil. 67% yield. R_f = 0.3 (10% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33–7.21 (m, 3H), 7.18–7.15 (m, 2H), 5.33 (d, J = 1.3 Hz, 1H), 5.22–5.21 (m, 1H), 2.97 (d, J = 13.7 Hz, 1H), 2.90–2.76 (m, 1H), 2.82 (d, J = 13.7 Hz, 1H), 2.74 (dd, J = 14.7, 1.0 Hz, 1H), 2.59 (d, J = 14.7 Hz, 1H), 2.43 (ddd, J = 18.1, 10.8, 7.3 Hz, 1H), 2.19 (ddd, J = 11.8, 10.2, 7.2 Hz, 1H), 2.04 (ddd, J = 11.8, 10.8, 6.1 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 213.7, 138.4, 136.7, 130.1, 128.4, 126.8, 116.4, 67.5, 44.1, 43.8, 40.5, 20.7; IR (Neat Film, NaCl) 3028, 2919, 2848, 1772, 1631, 1494, 1453, 1063, 888 cm^{-1}; HRMS (MM ESI-APCI) *m/z* calc'd for $C_{14}H_{16}{}^{35}ClO$ $[M+H]^+$: 235.0884; found 235.0883; $[\alpha]_D^{26}$ +1.51 (*c* 0.56, $CHCl_3$, 94% ee).

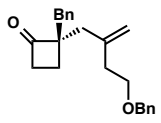
(*S*)-2-Allyl-2-benzylcyclobutanone (38)



38

Cyclobutanone **38** was isolated by flash column chromatography (SiO_2, 2% Et_2O in hexanes to 5% Et_2O in hexanes) as a colorless oil. 82% yield. R_f = 0.4 (10% EtOAc in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ7.30–7.27 (m, 2H), 7.24–7.21 (m, 1H), 7.16–7.15 (m, 2H), 5.81 (ddt, *J* = 17.2, 10.0, 7.4 Hz, 1H), 5.16–5.10 (m, 2H), 2.97 (d, *J* = 13.7 Hz, 1H), 2.78 (ddd, *J* = 18.2, 10.3, 6.5 Hz, 1H), 2.72 (d, *J* = 13.7 Hz, 1H), 2.49 (ddd, *J* = 18.2, 10.6, 6.8 Hz, 1H), 2.39 (ddt, *J* = 13.9, 7.4, 1.1 Hz, 1H), 2.67 (ddt, *J* = 13.9, 7.4, 1.1 Hz, 1H), 1.94 (ddd, *J* = 11.5, 10.6, 6.5 Hz, 1H), 1.86 (ddd, *J* = 11.5, 10.3, 6.8 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ214.9, 137.3, 133.2, 130.0, 128.3, 126.5, 118.7, 68.4, 42.9, 40.3, 39.5, 19.8; IR (Neat Film, NaCl) 3029, 2918, 1771, 1495, 1437, 1454, 1076, 920 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{14}H_{16}O$ $[M]^+$: 200.1201; found 200.1199; $[\alpha]_D^{26}$ +4.69 (*c* 0.55, $CHCl_3$, 88% ee).

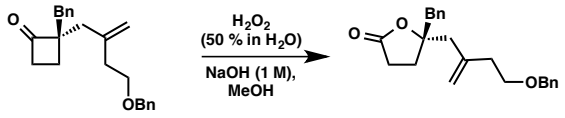
(*S*)-2-Benzyl-2-[4-(benzyloxy)-2-methylenebutyl]cyclobutanone (42d)



42d

Cyclobutanone **42d** was isolated by flash column chromatography (SiO_2, 1% EtOAc in hexanes to 3% EtOAc in hexanes) as a colorless oil (95% yield). R_f = 0.2 (10% EtOAc in

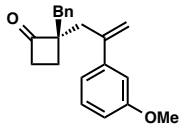
hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41–7.12 (m, 10H), 5.01 (q, J = 1.4 Hz, 1H), 4.93–4.92 (m, 1H), 4.54 (s, 2H), 3.59 (td, J = 6.8, 0.7, 2H), 2.95, 2.73 (AB system, J_{AB} = 13.7, 2H), 2.83–2.71 (m, 1H), 2.51–2.27 (m, 5H), 2.04–1.92 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 215.2, 142.6, 138.4, 137.4, 130.1, 128.4, 128.3, 127.7, 127.6, 126.5, 115.1, 72.9, 68.7, 68.3, 43.6, 41.5, 40.6, 37.0, 20.7; IR (Neat Film, NaCl) 3022, 2923, 2853, 1768, 1641, 1494, 1452, 1360, 1099, 899, 735 cm $^{-1}$; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{23}H_{27}O_2$ $[M+H]^+$: 335.2006; found 335.2020;



42d **93% yield** ***49***

Enantiomeric excess determined for the corresponding Baeyer-Villiger product, which was obtained by the general procedure below. Lactone **49** was isolated by flash column chromatography (SiO_2, 4% EtOAc in hexanes) as a colorless oil (93% yield). R_f = 0.2 (20% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40–7.18 (m, 10H), 5.09 (q, J = 1.5 Hz, 1H), 4.98 (dd, J = 1.7, 0.9 Hz, 1H), 4.51 (s, 2H), 3.61 (t, J = 6.5 Hz, 2H), 3.09 (d, J = 14.1 Hz, 1H), 2.75 (d, J = 14.1 Hz, 1H), 2.61–2.38 (m, 4H), 2.23 (ddd, J = 17.6, 9.4, 5.9 Hz, 1H), 2.17–2.03 (m, 2H), 1.68 (ddd, J = 17.6, 10.0, 8.6 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.9, 141.8, 138.4, 135.5, 130.5, 128.5, 128.3, 127.7, 127.5, 127.1, 117.1, 87.8, 72.8, 68.5, 46.7, 45.6, 37.0, 29.3, 29.2; IR (Neat Film, NaCl) 3524, 3062, 3029, 2919, 2855, 1958, 1770, 1642, 1603, 1495, 1454, 1416, 1361, 1271, 1232, 1177, 1101, 1080, 1029, 932, 741 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{23}H_{27}O_3$ $[M+H]^+$: 351.1955; found 351.1951; α_D^{25} +21.17 (*c* 0.44, $CHCl_3$, 89% ee).

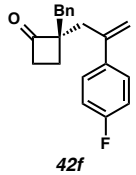
(*R*)-2-Benzyl-2-(2-[3-methoxyphenyl]allyl)cyclobutanone (42e)



42e

Cyclobutanone **42e** was isolated by flash column chromatography (SiO_2, 1% EtOAc in hexanes to 3% EtOAc in hexanes) as a colorless oil. 91% yield. R_f = 0.2 (10% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37–7.19 (m, 4H), 7.19–7.10 (m, 2H), 6.98 (ddd, *J* = 7.7, 1.7, 0.9 Hz, 1H), 6.91 (dd, *J* = 2.5, 1.6 Hz, 1H), 6.85 (ddd, *J* = 8.2, 2.6, 0.9 Hz, 1H), 5.41 (d, *J* = 1.4 Hz, 1H), 5.17 (q, *J* = 1.1 Hz, 1H), 3.83 (s, 3H), 3.03–2.86 (m, 2H), 2.86–2.68 (m, 2H), 2.63 (ddd, *J* = 18.1, 9.7, 7.1 Hz, 1H), 2.35 (ddd, *J* = 18.1, 10.1, 7.4 Hz, 1H), 1.96–1.72 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 215.0, 159.6, 144.9, 143.5, 137.3, 130.1, 129.4, 128.4, 126.6, 119.0, 117.1, 112.9, 112.4, 68.9, 55.3, 43.8, 41.2, 40.0, 20.0; IR (Neat Film, NaCl) 2913, 2829, 1766, 1595, 1572, 1488, 1451, 1286, 1221, 1170, 1039, 898, 873, 779 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{21}H_{23}O_2$ $[M+H]^+$: 307.1693; found 307.1693; α_D^{25} –4.78 (*c* 0.45, $CHCl_3$, 92% ee).

(*R*)-2-Benzyl-2-(2-(4-fluorophenyl)allyl)cyclobutanone (42f)

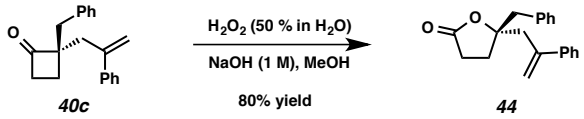


42f

Cyclobutanone **42f** was isolated by flash column chromatography (SiO_2, 3% EtOAc in hexanes to 7% EtOAc in hexanes) as a colorless oil. 94% yield. R_f = 0.3 (10% EtOAc in

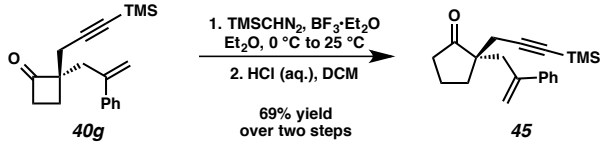
hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25–7.12 (m, 5H), 7.05–7.03 (m, 2H), 6.95–6.90 (m, 2H), 5.25 (d, *J* = 1.3 Hz, 1H), 5.05 (s, 1H), 2.88 (d, *J* = 13.7 Hz, 1H), 2.82 (dd, *J* = 14.4, 1.0 Hz, 1H), 2.66 (d, *J* = 13.7 Hz, 1H), 2.59 (d, *J* = 14.4 Hz, 1H), 2.54–2.47 (m, 1H), 2.29–2.22 (m, 1H), 1.73 (t, *J* = 8.6 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 214.6, 162.3 (d, $^1J_{CF}$ = 246.8 Hz), 144.0, 137.8 (d, $^4J_{CF}$ = 3.3 Hz), 137.1, 130.0, 128.3, 128.0 (d, $^3J_{CF}$ = 7.9 Hz), 126.6, 116.9, 115.2 (d, $^2J_{CF}$ = 21.3 Hz), 68.6, 43.7, 41.2, 40.5, 20.0; IR (Neat Film, NaCl) 2913, 1766, 1597, 1505, 1219, 1055, 837 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{20}H_{20}{}^{19}FO$ $[M+H]^+$: 295.1493; found 295.1502; $[\alpha]_D^{25}$ +3.53 (*c* 0.16, $CHCl_3$, 94% ee).

1.6.7 Procedures for derivatization of α-quaternary cyclobutanones and determination of absolute stereochemical configuration



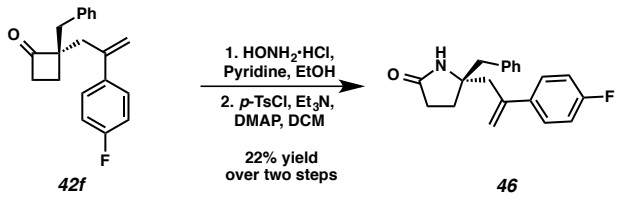
(*R*)-5-Benzyl-5-(2-phenylallyl)dihydrofuran-2(3*H*)-one (44). To a stirred solution of cyclobutanone **40c** (43 mg, 0.23 mmol) in MeOH (4.6 mL) was added NaOH (1 M in H_2O, 0.23 μL, 0.23 mmol) followed by H_2O_2 (50 wt% in H_2O, 17 mg, 0.46 mmol). The resulting mixture was stirred at room temperature for 1 h. The reaction mixture was then acidified to pH 7 with 1 N aqueous HCl and extracted with dichloromethane (2 mL x 5). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude oil was purified by flash column chromatography (SiO_2, 15% EtOAc in hexanes) to afford lactone **44** (37 mg, 0.17 mmol, 80% yield) as a colorless oil. R_f = 0.2 (20% EtOAc in hexanes); ^{1}H

NMR (300 MHz, $CDCl_3$) δ7.41–7.18 (m, 10H), 5.46 (d, J = 1.4 Hz, 1H), 5.27 (s, 1H), 3.08–2.92 (m, 3H), 2.79 (d, J = 14.1 Hz, 1H), 2.17 (ddd, J = 17.4, 9.8, 6.4 Hz, 1H), 2.04-–1.86 (m, 2H), 1.76–1.62 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ176.7, 143.4, 141.7, 135.4, 130.6, 128.6, 128.5, 127.8, 127.0, 126.3, 119.2, 87.7, 46.1, 45.3, 29.3, 28.8; IR (Neat Film, NaCl) 3029, 2918, 1771, 1495, 1437, 1454, 1076, 920 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{20}H_{21}O_2$ $[M+H]^+$: 293.1536; found 293.1536; $[\alpha]_D^{26}$ –0.60 (*c* 1.00, $CHCl_3$, 89% ee).



(*S*)-2-(2-Phenylallyl)-2-(3-(trimethylsilyl)prop-2-yn-1-yl)cyclopentanone (45). To a solution of **40g** (0.1023 g, 0.345 mmol) in Et_2O (3.5 mL), cooled to 0 °C with a water/ice bath, under an atmosphere of N_2, was added BF_3 etherate (0.112 mL, 0.379 mmol) dropwise followed by trimethylsilyldiazomethane (0.345 mL, 2 M solution in hexane) dropwise. The mixture was allowed to warm to 25 °C and stirred for 18 hours, at which point the reaction was determined to be complete by TLC analysis. To the mixture was added 3 mL of saturated aqueous $NaHCO_3$. After stirring for 30 min, this mixture was extracted with Et_2O (5 mL x 3), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, 1% EtOAc in hexanes to 5% EtOAc in hexanes) to afford α-trimethylsilylcyclopentanone as a colorless oil. The identity of the α-trimethylsilylcyclopentanone was confirmed by ^{1}H NMR analysis; the product was taken on without further characterization. R_f = 0.3 (10% EtOAc in hexanes);

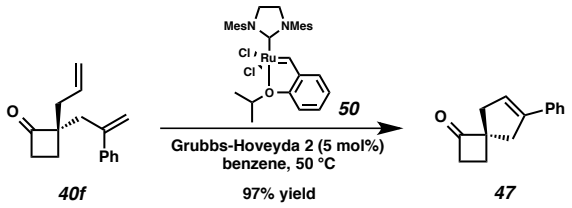
To a solution of α-trimethylsilylcyclopentanone (61 mg, 0.159 mmol) in 2 ml dichloromethane was added 2 mL of 1 N aqueous HCl in H_2O at 25 °C. The mixture was stirred for 24 hours at which point the reaction was determined to be complete by TLC analysis. The mixture was diluted with dichloromethane (2 ml) and then extracted with dichloromethane (5 mL x 3). The collected organic layers were then washed with brine (5 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude oil was purified by flash column chromatography (SiO_2, hexanes to 1% EtOAc in hexanes) to afford cyclopentanone **45** (47 mg, 0.153 mmol, 69% yield over two steps) as a colorless oil. R_f = 0.3 (10% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58–7.12 (m, 5H), 5.32 (d, *J* = 1.6 Hz, 1H), 5.14–4.97 (m, 1H), 2.83–2.73 (m, 2H), 2.22 (dd, *J* = 16.9, 38.9 Hz, 2H), 2.16–2.08 (m, 1H), 2.03–1.91 (m, 2H), 1.89–1.71 (m, 3H), 0.14 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 221.0, 145.1, 141.6, 128.3, 127.6, 126.5, 117.4, 103.7, 87.1, 52.2, 39.8, 38.4, 31.4, 27.4, 18.7, 0.0; IR (Neat Film, NaCl) 3080, 2958, 1738, 1623, 1494, 1447, 1404, 1308, 1249, 1154, 1046, 1029, 973, 904, 841, 778, 759 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{20}H_{26}OSi$ $[M]^+$: 310.1753; found 310.1765; $[\alpha]_D^{25}$ +4.13 (*c* 0.50, $CHCl_3$, 93% ee).



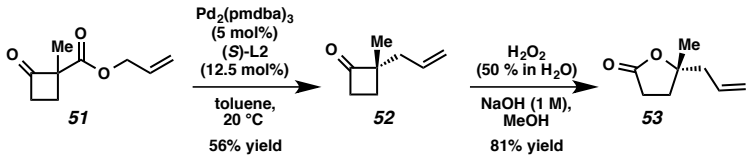
42f *46*

(*R*)-5-Allyl-5-(2-phenylallyl)pyrrolidin-2-one (46). To a solution of cyclobutanone **42f** (65 mg, 0.221 mmol) in 7 mL absolute ethanol was added hydroxylamine hydrochloride (76 mg, 1.104 mmol), followed by pyridine (0.27 ml, 3.31 mmol) and the mixture was stirred at 25 °C for 24 hours. The crude mixture was concentrated *in vacuo* and loaded

directly onto a flash column. Flash column chromatography (SiO_2, 8% EtOAc in hexanes to 11% EtOAc in hexanes) afforded the corresponding oxime, whose identity was confirmed by ^{1}H NMR and which was taken on without further characterization; R_f = 0.2 (25% EtOAc in hexanes); To a mixture of 4-toluenesulfonyl chloride (83 mg, 0.43 mmol), triethylamine (0.06 mL, 0.43 mmol) and catalytic 4-dimethylaminopyridine in 2.5 mL of dichloromethane under an atmosphere of N_2 was added dropwise a solution of oxime (54 mg, 0.175 mmol) in 1 mL of dichloromethane. The mixture was stirred at 25 °C for 4 hours. The crude mixture was washed with H_2O (5 mL), washed with brine (5 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude oil was purified by flash column chromatography (SiO_2, 3% EtOAc in hexanes to EtOAc) to afford lactam **46** (16 mg, 0.05 mmol, 22% yield over two steps) as a pale yellow oil. R_f = 0.4 (EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34–7.07 (m, 7H), 7.07–6.96 (m, 2H), 5.35 (d, J = 1.3 Hz, 1H), 5.26 (s, 1H), 5.15 (q, J = 1.0 Hz, 1H), 2.87–2.63 (m, 4H), 2.06–1.85 (m, 3H), 1.69–1.55 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 176.9, 162.4 (d, $^1J_{CF}$ = 247.4 Hz), 143.7, 138.0 (d, $^4J_{CF}$ = 3.4 Hz), 136.1, 130.3, 128.5, 127.8 (d, $^3J_{CF}$ = 8.0 Hz), 127.0, 118.6, 115.7 (d, $^2J_{CF}$ = 21.4 Hz), 62.0, 47.0, 46.5, 30.9, 30.1; IR (Neat Film, NaCl) 3196, 3081, 2927, 1690, 1601, 1507, 1452, 1260, 1224, 1159, 1087, 906, 842, 750 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{20}H_{20}ONF$ $[M]^+$: 309.1529; found 309.1517; $[\alpha]_D^{25}$ +53.19 (*c* 0.08, $CHCl_3$, 94% ee).



(*R*)-6-phenylspiro[3.4]oct-6-en-1-one (47). To a flask charged with Grubbs-Hoveyda an atmosphere of argon was added a solution of cyclobutanone **40f** (50 mg, 0.221 mmol) in 5 mL benzene. The reaction mixture was heated to 50 °C and stirred for one hour, at which point the reaction was determined to be complete by TLC analysis. The reaction vessel was cooled to 25 °C and 1 mL of ethyl vinyl ether was added. After 30 min of stirring, the crude mixture was purified directly by flash column chromatography (SiO_2, hexanes to 3% EtOAc in hexanes) to afford spirocycle **9** (43 mg, 0.215 mmol, 97% yield) as a colorless oil. R_f = 0.3 (10% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37–7.31 (m, 2H), 7.32–7.21 (m, 2H), 7.24–7.15 (m, 1H), 5.97 (p, *J* = 2.4 Hz, 1H), 3.19 (dq, *J* = 16.0, 2.2 Hz, 1H), 3.04 (t, *J* = 8.61 Hz, 2H), 3.04–2.97 (m, 1H), 2.81 (dq, *J* = 16.0, 1.7 Hz, 1H), 2.63 (dtd, *J* = 17.5, 2.5, 1.4 Hz, 1H), 2.09 (td, *J* = 8.9, 2.5 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 214.1, 140.0, 135.6, 128.4, 127.3, 125.6, 122.9, 67.9, 43.6, 43.1, 42.8, 28.3; IR (Neat Film, NaCl) 2890, 2924, 1765, 1595, 1491, 1385, 1298, 1241, 1056, 747 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{14}H_{15}O$ $[M+H]^+$: 199.1117; found 199.1120; $[\alpha]_D^{25}$ –41.23 (*c* 0.30, $CHCl_3$, 92% ee).



(*S*)-5-allyl-5-methyldihydrofuran-2(3*H*)-one (53). Dihydrofuranone **53** was generated from 2-carboxyallylcyclobutanone **51**, via cyclobutanone **52**, following the general procedures described above (see SI 3, SI 10 and SI 16). When compared with known compound (5*S*)-(+)-5-allyl-5-methyldihydrofuran-2(3*H*)-one, the optical rotation value for **53** was found to be of the same sign and of nearly identical magnitude ($[\alpha]_D^{25}$ +2.96 (c 1.5, CH_3OH), literature value: $[\alpha]_D^{17}$ +3.33 (c 1.27, CH_3OH)).[50] The absolute configurations of all other compounds described herein were established by analogy to **52**. Cyclobutanone **51** was isolated by flash column chromatography (SiO_2, 3% Et_2O in pentane to 7% Et_2O in pentane) as a colorless oil. 84% yield. R_f = 0.4 (15% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.90 (ddt, *J* = 17.2, 10.5, 5.6 Hz, 1H), 5.38–5.14 (m, 2H), 4.63 (dt, *J* = 5.6, 1.4 Hz, 2H), 3.42–3.06 (m, 2H), 2.65 (td, *J* = 11.3, 6.3 Hz, 1H), 1.88 (ddd, *J* = 11.6, 9.9, 7.5 Hz, 1H), 1.49 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 204.6, 169.8, 131.6, 118.4, 65.9, 45.2, 23.1, 18.6; IR (Neat Film, NaCl) 2933, 1792, 1730, 1457, 1376, 1274, 1193, 1147, 1050, 983 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_9H_{12}O_2$ $[M+H]^+$: 153.0910; found 153.0905. Cyclobutanone **52** was isolated by flash column chromatography (SiO_2, 1% Et_2O in pentane to 5% Et_2O in pentane) as a colorless oil. 56% yield. R_f = 0.3 (10% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.76 (ddt, *J* = 16.6, 10.5, 7.3 Hz, 1H), 5.14–5.05 (m, 2H), 3.08–2.89 (m, 2H), 2.31 (ddt, *J* = 13.8, 7.2, 1.2 Hz, 1H), 2.21 (ddt, *J* = 13.8, 7.5, 1.1 Hz, 1H), 1.98 (ddd, *J* = 11.3, 10.3, 6.7 Hz, 1H), 1.73 (ddd, *J* = 11.3, 10.1, 6.9 Hz, 1H), 1.19 (s, 3H); ^{13}C NMR (126 MHz,

$CDCl_3$) δ 214.1, 140.0, 135.6, 128.4, 127.3, 125.6, 122.9, 67.9, 43.6, 43.1, 42.8, 28.3; IR (Neat Film, NaCl) 2929, 2854, 1728, 1323, 1261, 1170, 1129, 1060, 1019, 799 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_8H_{12}O$ $[M+H]^+$: 125.0961; found 125.0955. Enantiomeric excess was determined for the corresponding Baeyer-Villiger product **53**, which was isolated as by flash column chromatography (SiO_2, 10% Et_2O in pentane) as a colorless oil (81% yield). Spectroscopic and physical data for **53** were identical to those reported in the literature.[7] ($[\alpha]_D^{25}$ +2.96 (c 1.5, CH_3OH), 83% ee).

1.6.8 Determination of enantiomeric excess

Table 1.6.8 Determination of enantiomeric excess

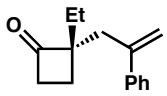
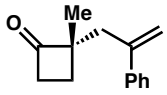
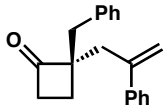
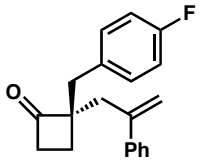
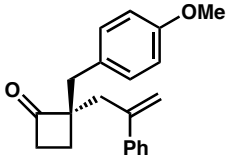
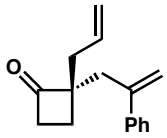
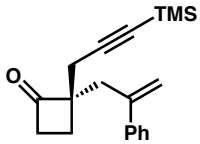
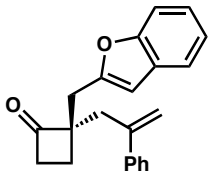
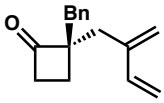
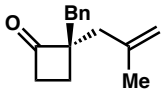
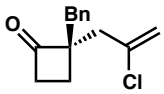
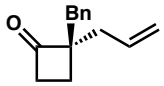
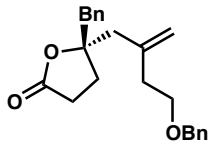
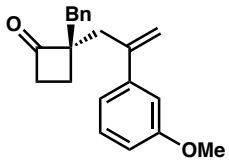
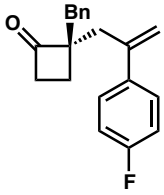
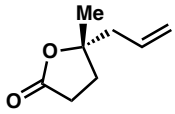
entry	compound	assay method and conditions	retention time of major isomer (min)	retention time of minor isomer (min)	%ee
1		SFC, 10% MeOH in CO_2, 2.5 mL/min, AS-H col.	5.31	6.02	*99*
2		SFC, 3% MeOH in CO_2, 2.5 mL/min, AS-H col.	2.68	3.08	*90*
3		SFC, 3% MeOH in CO_2, 3 mL/min, OJ-H col.	8.91	7.93	*95*
4		SFC, 2% MeOH in CO_2, 3 mL/min, OJ-H col.	10.43	11.45	*93*
5		SFC, 2% MeOH in CO_2, 2.5 mL/min, AS-H col.	8.82	8.38	*97*
6		SFC, 1% MeOH in CO_2 2.5 mL/min, AS-H col.	3.37	3.15	*92*
7		SFC, 2% MeOH in CO_2 3.0 mL/min, OJ-H col.	2.68	4.32	*93*
8		HPLC, 2% *i*PrOH in hexanes, 0.6 mL/min, AD col.	9.74	8.94	*92*

Table 1.6.8 Determination of enantiomeric excess (continued)

entry	compound	assay method and conditions	retention time of major isomer (min)	retention time of minor isomer (min)	%ee
9		SFC, 1% MeOH in CO_2 2.5 mL/min, OB-H col.	3.40	2.83	*91*
10		SFC, 1% MeOH in CO_2, 3 mL/min, OB-H col.	2.76	2.53	*90*
11		GC, 110 °C, isotherm 1 mL/min, GTA col.	10.41	11.34	*93*
12		SFC, 1% MeOH in CO_2, 2.5 mL/min, OB-H col.	3.38	2.93	*86*
13		SFC, 10% MeOH in CO_2, 3.0 mL/min, AD-H col.	6.09	7.29	*89*
14		SFC, 1% MeOH in CO_2, 2.5 mL/min, AS-H col.	16.17	14.84	*92*
15		SFC, 1% MeOH in CO_2, 3 mL/min, AS-H col.	7.29	6.78	*94*
16		GC, 130 °C, isotherm 1 mL/min, GTA col.	10.15	13.32	*83*

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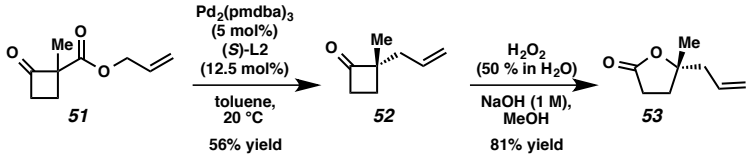
(34) Derivatization of allylic alkylation product 2-allyl-2-methylcyclobutanone **52** to known compound (5*S*)-5-allyl-5-methyldihydrofuran-2(3*H*)-one **53** (below) allowed for comparison of optical rotation data and, by chemical correlation, confirmed (5*S*) absolute configuration (see supporting information). The absolute stereo-configuration of all other products generated in this study were assigned by analogy. These data are consistent with the absolute configurations observed in previous studies on 5-, 6- and 7-membered rings (see ref. 14).



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