CHAPTER 2

Development of (Trimethylsilyl)Ethyl Ester-Protected Enolates and Applications in Palladium–Catalyzed Enantioselective Allylic Alkylation: Intermolecular Cross-Coupling of Functionalized Electrophiles[1]

2.1 INTRODUCTION

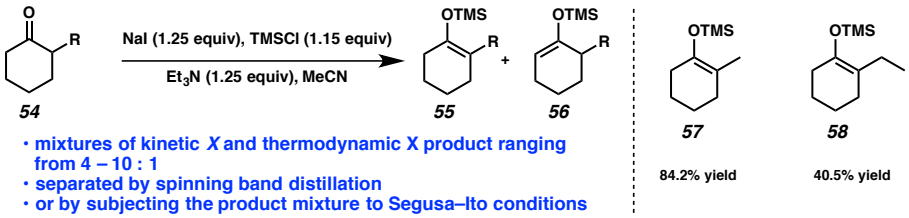
2.1.1 Latent enolates: silyl enol ethers

Latent or protected enolates such as silyl enol ethers, silyl ketene acetals, allyl enol carbonates, allyl β-keto esters and others, have found broad use in organic synthesis owing to their mild release and ease of use.[51,15] Perhaps the most well studied class of protected enolates employ oxygen-bound protecting groups (i.e. silyl enol ethers). Unfortunately, the utility of this class of compounds is often limited by poor regioselectivity when forming fully substituted enol derivatives.[52] Although much effort has been devoted to the identification of conditions that allow for selective generation of so-called "thermodynamic" enolate isomers, selectivity often drops precipitously when sterically demanding α-substitution is introduced (Figure 2.1.1.1).[53] For example, in previous studies by the Stoltz group, it was found that while formation of the

[1] This work was performed in collaboration with Douglas C. Behenna, staff scientist in the Stoltz group. This work has been published. See: Reeves, C. M.; Behenna, D. C.; Stoltz, B. M. *Org. Lett.* **2014**, *16,* 2314.

thermodynamic silyl enol ether derived from 2-methyl cyclohexanone (Figure 2.1.1.1, **57**) proceeded in 84% yield, while the corresponding ethyl substituted enol ether (Figure 2.1.1.1, **58**) was formed in only 41% yield.

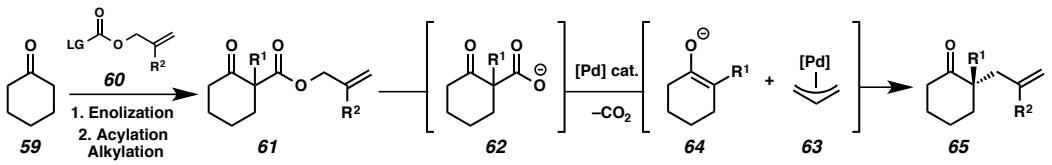
Figure 2.1.1.1. *Drawbacks of silyl enol ether synthesis*



2.1.2 Latent enolates: β-ketoesters

The problem of thermodynamic enolate masking would be solved, ideally, by the development of enolate precursors that are readily prepared and, when triggered, release the "thermodynamic" enolate under kinetic control. In the context of allylic alkylation reactions, carboxylate-protected enolates (i.e., allyl β-ketoesters, **61**, Figure 2.1.2.1) represent a significant advance toward such a solution. Allyl β-ketoesters enjoy relatively uncomplicated, selective synthesis[54] from simple ketones (i.e. **59**) and undergo deprotection upon treatment with a transition metal capable of oxidative addition. Oxidative addition affords a transition metal allyl species, in the case at hand, a palladium π-allyl species **63**, and a free carboxylate **62**. The resulting carboxylate may then spontaneously release CO_2 to give prochiral enolate **64**.[55] This enolate may then enter into a catalytic cycle and undergo α-functionalization.

Figure 2.1.2.1. *Allyl β-ketoester approach to latent enolate chemistry*



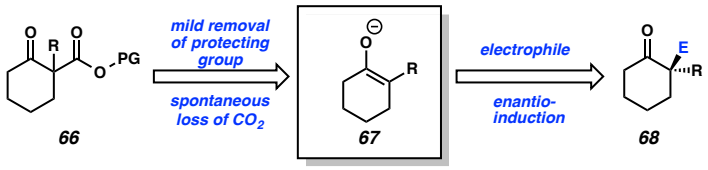
Despite these advantages, allyl β-ketoesters are not without their own limitations. Facile nucleophilic attack of the incipient enolate at the transition metal-allyl species generated during deprotection often precludes applications that do not involve allylic alkylation.[56] Moreover, with traditional carboxylate-protected enolates, any functionality borne by the allyl fragment (**60**, R^2, Figure 2.1.2.1) must be compatible with the conditions required for substrate synthesis (i.e. strong base and reactive electrophiles). Tunge and coworkers have demonstrated the utility of acyl-protected enolates, which may undergo deprotection via a retro-Claisen condensation to reveal fully-substituted enolates, that participate in catalysis.[57] However, these reactions often require the use of elevated temperatures and alkoxide base to proceed.

2.1.3 Latent enolates: TMSE β-ketoesters

Conceptually, we envisioned a new class of β-ketoester enolate precursors bearing an alkyl ester substituent labile to cleavage (Figure 2.1.3.1, **66**). Ideally, facile deprotection would liberate this alkyl fragment to reveal a free carboxylate species, which, upon spontaneous decarboxylation, would yield the desired tetrasubstituted, prochiral enolate (**67**). Electrophilic trapping of this enolate species in the presence of a

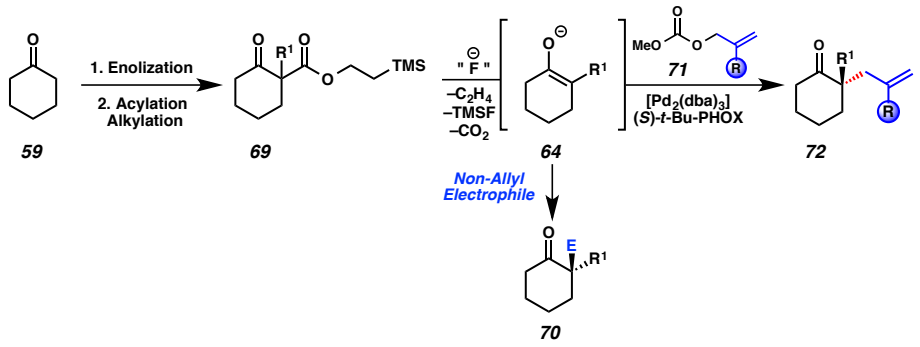
chiral catalyst would, in turn, give rise to enantioenriched α–functionalizaed carbonyl products (**68**).

Figure 2.1.3.1. *Non-allyl β-ketoester approach to latent enolate chemistry*



In considering novel carboxylate-protected enolates, our design criteria called for a substrate that could be synthesized efficiently, deprotected under mild conditions and facilitate the convergent union of complex fragments in a synthetic setting. Our approach to this problem was to develop the (trimethylsilyl)ethyl β-ketoester (TMSE β-ketoester)[58] substrate class (i.e., **69**, Figure 2.1.3.2). These compounds boast similar ease of preparation as compared with allyl β-ketoesters, but are not susceptible to transition metal-mediated deprotection. We hypothesized that use of TMSE β-ketoesters may enhance the breadth of functional group tolerance at the allyl coupling partner in asymmetric allylic alkylations, relative to allyl β-ketoesters, by virtue of the fact that the allyl fragment is not subjected to the conditions of substrate synthesis (Figure 2.1.3.2). We further reasoned that by eliminating allyl from the reaction mixture, we would obviate the problem of competing reaction pathways in non-allyl enolate trapping chemistry, and greatly expand the range of reactions in which carboxylate-protected enolates may participate.

Figure 2.1.3.2. *TMSE β-ketoester approach to latent enolate chemistry*



In this chapter, we describe the preparation and development of this substrate class and the evaluation thereof in the enantioselective palladium-catalyzed allylic alkylation of 6- and 7-membered ketone and lactam scaffolds. Furthermore, we go on to show how the use of these substrates can enable the union of complex fragments bearing functionality that would be incompatible with incorporation into traditional allyl β-ketoester substrates.

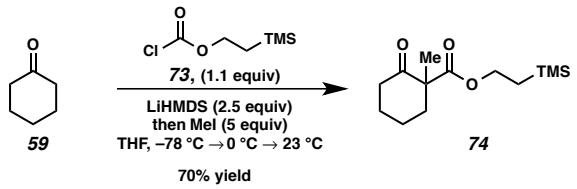
2.2 SYNTHESIS OF AND REACTION OPTIMIZATION WITH TMSE β-KETOESTERS

2.2.1 Substrate synthesis

The initial task pursuant to the goals laid out in Section 2.1.3 was to develop an efficient synthesis of TMSE β-ketoester **69**. We were pleased to find that α-methyl TMSE β-ketoester (**74**) could be prepared in a single synthetic operation from

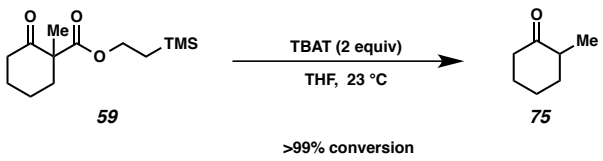
commercially available cyclohexanone (**59**), 2-(trimethylsilyl)ethyl chloroformate (**73**) and methyl iodide (MeI) in good overall yield (Scheme 2.2.1.1).

Scheme 2.2.1.1. *TMSE β-ketoester substrate synthesis*



In order to evaluate the substrate's capacity to engage in transition metal-mediated catalysis as anticipated, TMSE-β-ketoester **74** was subjected to treatment with tetrabutylammonium difluorotriphenylsilicate (TBAT) in THF at ambient temperature (Scheme 2.2.1.2). The reaction was quenched with saturated aqueous ammonium chloride, and full deprotection to 2-methyl-cyclohexanone **75** was observed after 30 min. This experiment lended proof of principal that our TMSE-β-ketoesters could indeed undergo mild deprotection and encourgaed further investigation of the substrate class.

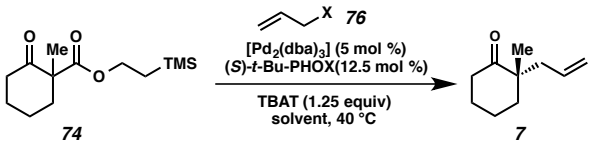
Scheme 2.2.1.2. *Fluoride-triggered deprotection of TMSE β-ketoester substrate*



2.2.2 TMSE-β-ketoester allylic alkylation optimization

With TMSE β-ketoester **74** in hand, our investigation into this substrate class commenced in the context of Pd-catalyzed allylic alkylation. We were pleased to find that exposure of β-ketoester **74** to allyl bromide, TBAT, [$Pd_2(dba)_3$] and (*S*)-*t*-Bu-PHOX[8,59] in toluene at 40 °C generated the desired α-quaternary ketone **7** in modest yield and good enantioselectivity (entry 1, Table 2.2.2.1). We next explored the scope of allyl sources that could be used in the reaction and found that a variety of diverse allyl sources were competent in the chemistry, including allyl sulfonates, allyl acetates and allyl carbonates (entries 2–5). Allyl methyl carbonate proved to be the most efficient, selective and prudent allyl source, in particular, with respect to the number of the allyl equivalents required for optimal reactivity (entry 6). Reaction parameters including relative stoichiometry (entries 7–9), solvent (entries 10–13) and temperature (entry 14) were all subsequently explored and we found that a slight excess of mixed carbonate in THF at 25 °C delivering the desired ketone in 81% yield and 86% enantioselectivity (entry 14).

Table 2.2.2.1. *TMSE β-ketoester allylic alkylation initial optimization experiments*



entry	X	equiv allyl	sovent	yield (%)[a]	ee (%)[b]
1	Br	1.0	toluene	55	83
2	OTs	1.0	1,4-dioxane	43	77
3	OMs	1.0	1,4-dioxane	45	84
4	OAc	1.0	1,4-dioxane	15	82
5	OCO_2Allyl	1.0	1,4-dioxane	78	83
6	OCO_2Me	1.0	1,4-dioxane	78	84
7	OCO_2Me	0.75	1,4-dioxane	51	82
8	OCO_2Me	1.5	1,4-dioxane	74	82
9	OCO_2Me	2.0	1,4-dioxane	73	84
10	OCO_2Me	1.1	toluene	33	82
11	OCO_2Me	1.1	MTBE	65	84
12	OCO_2Me	1.1	THF	83	83
13	OCO_2Me	1.1	tol/hex	45	93
14[c]	OCO_2Me	1.1	THF	81	86

(a) Yield determined by comparison to tridecane internal standard. (b) % ee Determined by chiral GC analysis of the crude reaction mixture. (c) Reaction performed at 25 °C.

A more rigorous investigation of the solvent effects on the reaction was subsequently conducted. Using preliminarily optimized reaction parameters, we conducted screening experiment wherein the base substrate **74** was treated with TBAT (1.25 equiv), $Pd_2(dba)_3$ (5 mol%), ligand **L1** (12.5 mol%) and methyl allyl carbonate (1.1 equiv) in a wide variety of solvent combinations. The results of these experiments are shown below in Tables 2.2.2.2 and 2.2.2.3. The results of these experiments show that reaction yield is highly variable based on the solvent employed (Table 2.2.2.2), while reaction selectivity remains relatively uniform (Table 2.2.2.3). With respect to variablility

in yield, the primary factor at play in these expeirments is hypothesized to be the relative solubility of the fluoride source used, TBAT. In toluene, TBAT is only sparingly soluble, in MTBE still only somewhat soluble, whereas TBAT is completely soluble in THF and *p*-dioxane, even at higher concentrations, thus accounting for lower observed yields in cases where low-dielectric solvents are employed. The majority of mass balance in low-yielding experiments is accounted for in recovered starting material. The fluctuation in enantioselectivity may be rationalized via the working mechanistic hypothesis for this transformation; in particular, that enantioselective allylic alkylation occurs via an inner-sphere pathway,[35] and this pathway is reinforced by less polar solvents.

Table 2.2.2.2. *TMSE β-ketoester allylic alkylation solvent effects on reaction yield*

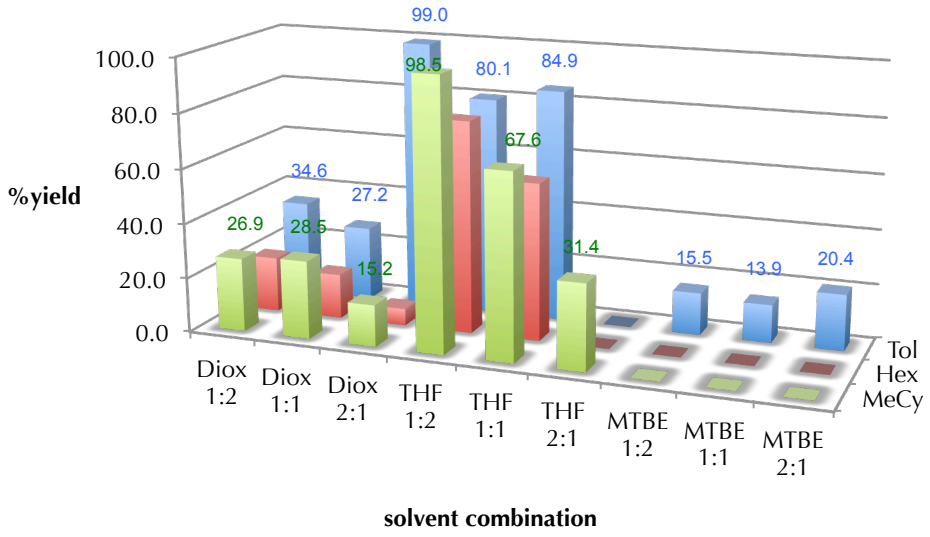
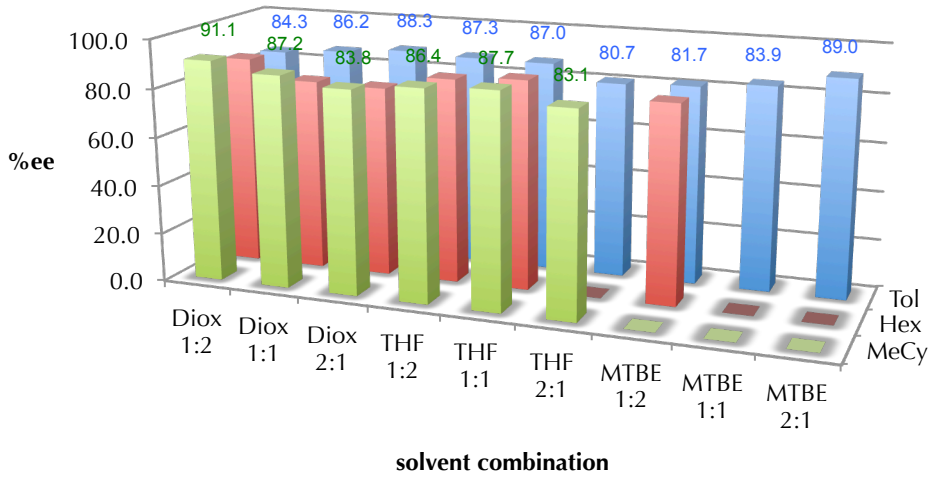


Table 2.2.2.3. *TMSE β-ketoester allylic alkylation solvent effects on reaction selectivity*



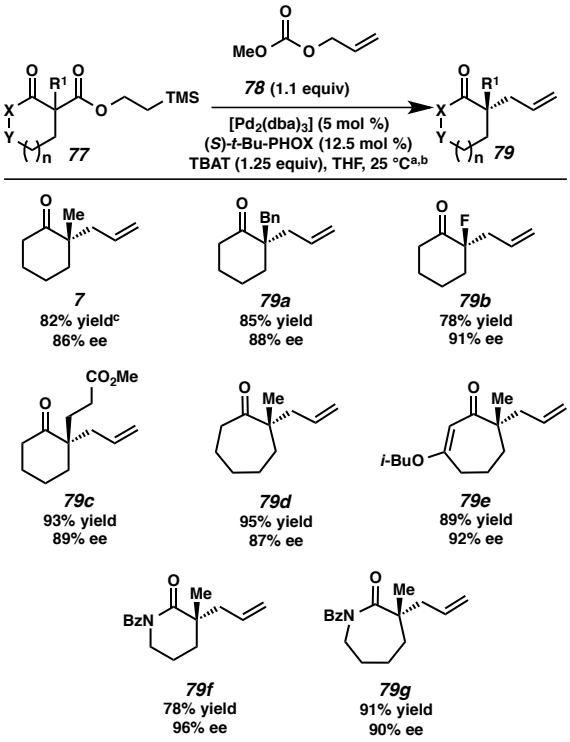
2.3 PALLADIUM-CATALYZED ALLYLIC ALYLATION WITH TMSE-β-KETOESTERS

2.3.1 Reaction scope with respect to nucleophile

Having identified optimal reaction conditions, we turned our attention to exploring reaction scope, beginning with tolerance of variability with respect to the nucleophile's α-substitution, ring size, and carbonyl functionality (Figure 2.3.1.1). Simple α-alkyl substitutions, such as α-benzyl substituted β-ketoester **77a** (R^1 = Bn, X = CH_2, Y = CH_2, n = 1, Figure 2), functioned consistently well in the chemistry; the desired benzyl substituted α-quaternary ketone **79a** was obtained in high yield and enantioselectivity. In addition to simple α-alkyl substrates (i.e. compounds **74** and **77a**), heteroatom-substituted substrate **77b** (R^1 = F, X = Y = CH_2, n = 1) proved to be a viable coupling partner and provided the corresponding α-fluoro-allylic alkylation product **79b** in good yield and excellent ee. Subjecting methyl ester-bearing substrate **77c** (R^1 = $CH_2CH_2CO_2Me$, X = Y = CH_2, n = 1) to our optimized conditions resulted in an efficient

and selective reaction, furnishing enantioenriched ketone **79c** in 93% yield and 89% ee. Substrates constituted from 7-membered rings, including ketone **77d** (R^1 = Me, X = Y = CH_2, n = 2) and vinylogous ester **77e** (R^1 = Me, X = CH, Y = CO(*i*-Bu), n = 2), were shown to be suitable coupling partners, affording α-quaternary ketone **79d** and α-quaternary vinylogous ester **79e** products in 95% and 89% yield and 87% and 92% ee, respectively. Finally, 6- and 7-membered lactams were investigated. We were pleased to find that under slightly modified reaction conditions (40 °C), the desired α-functionalized lactam products **79f** and **79g** were obtained in good to excellent yields and excellent ee's.

Figure 2.3.1.1. *Exploration of functional group and scaffold diversity in the fluoride-triggered palladium-catalyzed allylic alkylation reaction with respect to nucleophile*



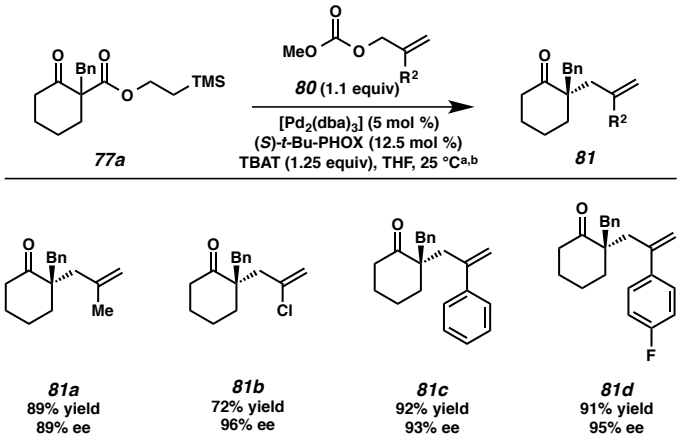
(a) Reaction conditions: 3 (1.0 equiv), 5 (1.1 equiv), [$Pd_2(dba)_3$] (5 mol%), (S)-*t*-Bu-PHOX (12.5 mol%), TBAT (1.25 equiv) in THF (0.033M) at 25 °C for 12–48 h. (b) Reaction performed on substrates **77f** and **77g** at 40 °C. (c) All reported yields are for isolated products.

2.3.2 Reaction scope with respect to electrophile

Having surveyed the scope of the reaction with respect to nucleophile α-substitution and scaffold type, we next probed the allylic alkylation with respect to substitution at the 2-allyl position. We were pleased to find that a variety of functional groups could be introduced through the use of differentially substituted allyl carbonates (**80**, $R^2 \neq H$, Figure 2.3.2.1). Simple alkyl substitution at the internal allyl position was well tolerated as 2-methylallyl ketone **81a** was obtained in 89% yield and 89% ee. 2-

Chloroallyl methyl carbonate (**80**, R^2 = Cl) also participated well in the chemistry, furnishing the corresponding α-quaternary ketone **81b** in 72% yield and 96% ee. Allyl fragments bearing electron-neutral and electron-deficient aryl groups also functioned well in the reaction, delivering the desired allylic alkylation products **81c** and **81d**, respectively, in excellent yields and ee's.

Figure 2.3.2.1. *Exploration of functional group and scaffold diversity in the fluoride-triggered palladium-catalyzed allylic alkylation reaction with respect to electrophile*



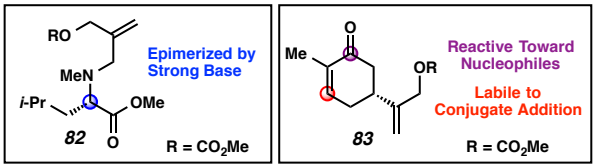
(a) Reaction conditions: 3 (1.0 equiv), 5 (1.1 equiv), $[Pd_2(dba)_3]$ (5 mol%), (S)-*t*-Bu-PHOX (12.5 mol%), TBAT (1.25 equiv) in THF (0.033M) at 25 °C for 12–48 h. (b) All reported yields are for isolated products.

2.4 COUPLING OF TMSE β-KETOESTERS WITH FUNCTIONALLY COMPLEX ELECTROPHILIC PARTNERS

While the new fluoride-triggered chemistry described thus far permits alternative access to structures previously available by allylic alkylation, a distinct advantage offered

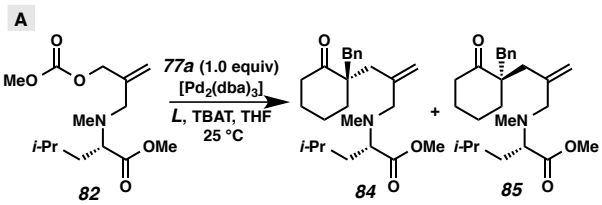
by TMSE-β-ketoesters in allylic alkylation chemistry is the ability to introduce allyl-coupling partners that would be unstable to the conditions of allyl β-ketoester substrate synthesis. To illustrate this feature of the new chemistry, we synthesized mixed carbonates **82** and **83** as coupling partners for palladium-catalyzed allylic alkylation (Figure 2.4.1). Allyl carbonate **82**, derived from leucine, bears an epimerizable stereocenter that is racemized upon treatment with strong base.[60] Since strong base (i.e. LDA, LHMDS, etc.) is typically required for enolization and acylation in the preparation of standard allyl β-ketoesters, employing electrophiles bearing base labile functionality has not previously been possible. Alternatively, allyl carbonate **83**, which was synthesized by allylic oxidation of (*S*)-carvone, also bears functionality that would be unstable to the conditions required for standard allyl β-ketoester substrate synthesis. In particular, we envisioned that attempts to acylate a ketone enolate with an allyl chloro- or allyl cyanoformate bearing enone **83** would be complicated by undesired conjugate addition and enolate chemistries (e.g. Aldol reaction, Michael addition, etc.). In both cases, our new TMSE β-ketoester chemistry allows for the independent preparation and, thus, physical separation of nucleophilic and electrophilic components until the fragment coupling stage.

Figure 2.4.1. *Complex allyl architechtures*

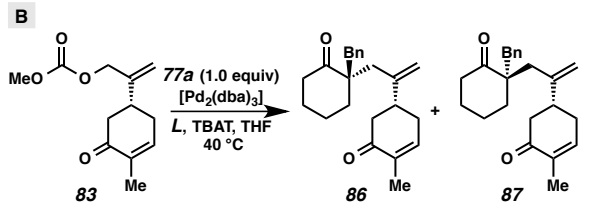


Subjecting allyl carbonate **82** and TMSE β-ketoester **77a** (R^1 = Bn, X = Y = CH_2, n = 1, Figure 2.4.2) to our fluoride-modified allylic alkylation conditions with achiral ligand **L8** revealed modest substrate-controlled diastereoselection of 1.7:1 (entry 1, Figure 2.4.2A). Use of (*S*)-*t*-Bu-PHOX (**L1**) resulted in a highly efficient and diastereoselective reaction giving the desired amino ester **84** in 95% yield and greater than 25:1 dr, with no detectable epimerization at the amino ester side chain (entry 2). The inherent diastereoselectivity could be completely reversed under catalyst control by using (*R*)-*t*-Bu-PHOX (**L9**), without significant loss in selectivity or reactivity (entry 3). Likewise, upon exposing carbonate **83** and ketoester **77a** to slightly modified allylic alkylation conditions (40 °C vs. 25 °C) with achiral ligand **L8**, we again observed an efficient reaction and slight inherent diastereoselectivity (entry 4, Figure 2.4.2B). This bias could be enhanced by using ligand **L1** to obtain α-quaternary ketone **86** in 6:1 dr and 87% yield, or overturned by use of **L9** to obtain **87** in 5:1 dr and 77% yield (entries 5 and 6).

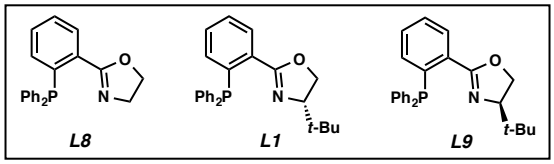
Figure 2.4.2. *Union of complex fragments by asymmetric allylic alkylation*[a]



entry	ligand	dr (*84*:*85*)[b]	yield (%)[c]
1	L1	1.7:1	91
2	L2	> 25:1	95
3	L3	1:21	93



entry	ligand	dr (*86*:*87*)[b]	yield (%)[c]
4	L1	1.4:1	85
5	L2	6:1	87
6	L3	1:5	77



(a) Reaction conditions: **77a** (1.0 equiv), **82** or **83** (1.1 equiv), $[Pd_2(dba)_3]$ (5 mol%), Ligand (12.5 mol%), TBAT (1.25 equiv) in THF (0.033M) at the indicated temperature for 24–48 h. (b) Diastereoselectivity determined by ^1H NMR analysis of the crude reaction mixture. (c) Yields are reported for combined diastereomeric mixture.

2.5 CONCLUDING REMARKS

In conclusion, we have developed a new class of substrates for enolate alkylation chemistry that benefit from ease of preparation and mild deprotection conditions that are orthogonal to those used for traditional allyl β-ketoesters. We examined the application of these compounds in palladium-catalyzed asymmetric allylic alkylation chemistry and found that a wide range of functional groups and substrate scaffolds are well tolerated,

including 6- and 7-membered ketones and lactams. We have further demonstrated the value of these compounds for uniting complex coupling partners that would be incompatible to preparation via standard allyl β-ketoester based allylic alkylation. We envision that this technology will also enable the convergent cross-coupling of synthetically challenging fragments for complex molecule synthesis. Further studies exploring the application of TMSE β-ketoesters in diverse reaction methodologies and complex natural product synthesis are ongoing in our laboratory.

2.6 EXPERIMENTAL SECTION

2.6.1 Materials and Methods

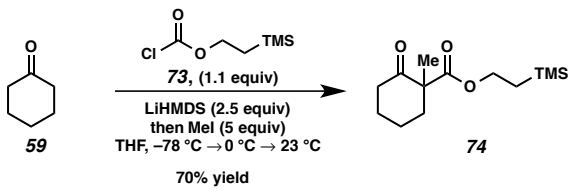
Unless otherwise stated, reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents. Solvents were dried by passage through an activated alumina column under argon.[61] Reaction progress was monitored by thin-layer chromatography (TLC). TLC 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 40–63 nm) was used for flash chromatography. ^{1}H NMR spectra were recorded on Varian Inova 300 MHz and 500 MHz spectrometers and are reported relative to residual $CHCl_3$ (δ 7.26 ppm) or C_6HD_5 (δ 7.16 ppm). ^{13}C NMR spectra were recorded on a Varian Inova 500 MHz spectrometer (125 MHz) and are reported relative to $CHCl_3$ (δ 77.16 ppm) or C_6HD_5 (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, sept = septuplet, m = multiplet, br s = broad singlet, br d = broad doublet, app = apparent. Data for ^{13}C NMR are reported in terms of chemical shifts (δ ppm). ^{19}F NMR spectra were recorded on a Varian Mercury 300 spectrometer at 282 MHz, and are reported relative to the external standard F_3CCO_2H (δ –76.53 ppm). IR spectra were obtained by use of a Perkin Elmer Spectrum BXII spectrometer or Nicolet 6700 FTIR 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). Analytical HPLC was performed with an Agilent 1100 Series HPLC utilizing a Chiralpak (AD-H or AS) or Chiralcel (OD-H, OJ-H, or OB-H) columns (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd. Analytical SFC was performed with a Mettler SFC supercritical CO_2 analytical chromatography system utilizing Chiralpak (AD-H, AS-H or IC) or Chiralcel (OD-H, OJ-H, or OB-H) columns (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd. Analytical chiral GC analysis was performed with an Agilent 6850 GC utilizing a GTA (30 m x 0.25 mm) column (1.0 mL/min carrier gas flow). High resolution mass spectra (HRMS) were obtained from Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI+), atmospheric pressure chemical ionization (APCI+), or mixed ionization mode (MM: ESI-APCI+).

Reagents were purchased from Sigma-Aldrich, Gelest, Strem, or Alfa Aesar and used as received unless otherwise stated. 2-(trimethylsilyl)ethyl chloroformate (**78**) was prepared according to a known procedure.[62] Allyl carbonates **82** and **83** were prepared from methyl chloroformate and the corresponding allyl alcohols by adaptation of a

known procedure.[63] β-Ketoesters **74** and **77a–77g** were prepared by adaptation of procedures by Stoltz and co-workers.[64,15] Data reported herein is for new compounds only.

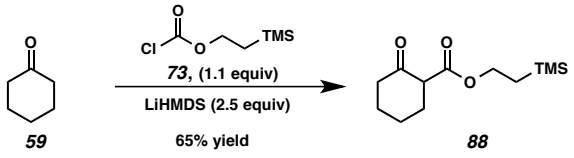
2.6.2 General procedure for TMSE β-ketoester substrate synthesis



2-(Trimethylsilyl)ethyl 1-methyl-2-oxocyclohexane-1-carboxylate (74). A flame-dried 1L round bottom flask was charged with 28.02 g (152.83 mmol, 2.5 equiv) of LiHMDS and a magnetic stirring bar in a nitrogen-filled glove box. The flask was sealed, removed from the glove-box, fitted with a N_2 line, and suspended in a dry ice/acetone bath. 300 mL of THF was added slowly to the flask and allowed to stir until the LiHMDS had completely dissolved. 6.00 g (61.13 mmol, 1.0 equiv) of cyclohexanone **59** in 130 mL of THF was added via cannula over 30 min, and the flask was removed from the cooling bath and allowed to warm to 23 °C while continuing to stir. After 30 min, the flask was suspended in a dry ice/acetone bath and 12.15 g (67.24 mmol, 1.1 equiv) of chloroformate **73** in 130 mL of THF was added over 30 min via cannula. This mixture was allowed to warm to 23 °C and stirred for 6 h. The flask was then suspended in a water/ice bath and 21.69 g (152.83 mmol, 2.5 equiv) of methyl iodide was added dropwise. This mixture was allowed to warm to 23 °C and stirred for 6 h, at which time an additional 21.69 g (152.83 mmol, 2.5 equiv) of methyl iodide was added dropwise.

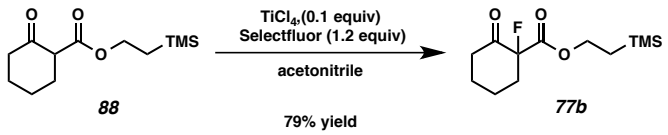
The mixture was then stirred at 23 °C until full consumption of starting material and acylated intermediate was observed by TLC analysis. 300 mL of saturated aqueous NH_4Cl was then added slowly to the mixture and stirring continued for 2 h. The mixture was then extracted with EtOAc (100 mL x 3), the collected organic fractions washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO_2, hexanes to 3% EtOAc in hexanes) to give 11.05 g (43.08 mmol) of ketoester **74** as a pale yellow oil. 70.1% yield. R_f = 0.3 (10% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.29–4.12 (m, 2H), 2.57–2.37 (m, 3H), 2.05–1.95 (m, 1H), 1.76–1.57 (m, 3H), 1.48–1.37 (m, 1H), 1.26 (s, 3H), 1.01–0.92 (m, 2H), 0.02 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 208.3, 173.2, 63.6, 57.1, 40.7, 38.2, 27.5, 22.6, 21.2, 17.3, -1.6; IR (Neat Film, NaCl) 3438, 2952, 2897, 2866, 1717, 1452, 1378, 1336, 1251, 1215, 1121, 1084, 1061, 1041, 938, 861, 834, 763 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{13}H_{25}O_3Si$ $[M + H]^+$: 257.1567; found 257.1556.

2.6.3 Procedures for the syntheses of TMSE β-ketoester intermediate 88 and ketoester 77b



2-(Trimethylsilyl)ethyl 1-H-2-oxocyclohexane-1-carboxylate (88). A flame-dried 500 mL round bottom flask was charged with 4.67 g (25.47 mmol, 1.3 equiv) of LiHMDS and a magnetic stirring bar in a nitrogen-filled glove-box. The flask was sealed, removed

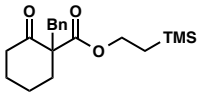
from the glove-box, fitted with a N_2 line, and suspended in a dry ice/acetone bath. 100 mL of THF was added slowly to the flask and allowed to stir until the LiHMDS had been completely dissolved. 2.00 g (20.38 mmol, 1.0 equiv) of cyclohexanone **59** in 50 mL of THF was added via cannula over 30 min, and the flask was removed from the cooling bath and allowed to warm to 23 °C while continuing to stir. After 30 min, the flask was suspended in a dry ice/acetone bath and 4.10 g (22.42 mmol, 1.1 equiv) of chloroformate **73** in 50 mL of THF was added over 30 min via cannula. This mixture was allowed to warm to 23 °C and stirred until full consumption of starting material was observed (ca. 6 h). 100 mL of saturated aqueous NH_4Cl was then added slowly and the mixture stirred for 20 min before being extracted with EtOAc (30 mL x 3). The collected organic fractions were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO_2, hexanes to 2% EtOAc in hexanes), to give 3.20 g (43.08 mmol) of ketoester **88** as a colorless oil. 64.6% yield. R_f = 0.5 (20% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.29 (s, 1H), 4.27–4.21 (m, 2H), 2.23 (dtt, J = 24.7, 6.3, 1.6 Hz, 4H), 1.76–1.51 (m, 4H), 1.17–0.86 (m, 2H), 0.04 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.9, 171.9, 97.8, 62.4, 29.1, 22.5, 22.4, 21.9, 17.3, -1.5; IR (Neat Film, NaCl) 2952, 2899, 2860, 1742, 1718, 1654, 1618, 1453, 1398, 1360, 1297, 1258, 1219, 1175, 1079, 1060, 936, 859, 837 cm^{-1}; HRMS (MM: ESI-APCI–) *m/z* calc'd for $C_{12}H_{21}O_3Si$ $[M - H]^-$: 241.1265; found 241.1270.



2-(Trimethylsilyl)ethyl 1-fluoro-2-oxocyclohexane-1-carboxylate (77b). A flame dried 100 mL round bottom flask was charged with a magnetic stirring bar, 0.35 g **88** (1.44 mmol, 1.0 equiv), 5 mL of acetonitrile and cooled to 0 °C. To this mixture was added 0.027 g $TiCl_4$ (0.144 mmol, 0.10 equiv) dropwise over 15 min. To this stirring solution was added 0.64 g Selectfluor (1.73 mmol, 1.2 equiv) in 20 mL of acetonitrile over 25 min. The mixture was then allowed to warm to 23 °C and stirred for 8 h. A 1:1 mixture of H_2O/EtOAc (20 mL) was added, and the mixture was extracted with EtOAc (20 mL x 3), dried over $MgSO_4$ and adsorbed onto 1 g SiO_2 by concentration *in vacuo*. The crude product was isolated by flash column chromatography (SiO_2, 3% Et_2O in pentane to 12% Et_2O in pentane) to give 0.29 g of **77b** as a colorless oil. 79.0% yield. R_f = 0.2 (20% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.41–4.26 (m, 2H), 2.84–2.36 (m, 3H), 2.21–2.04 (m, 1H), 2.00–1.79 (m, 4H), 1.15–0.97 (m, 2H), 0.04 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.0 (d, $^4J_{CF}$ = 19.5 Hz), 167.0 (d, $^2J_{CF}$ = 24.6 Hz), 96.4 (d, $^1J_{CF}$ = 197.0 Hz), 65.0, 39.7, 36.0 (d, $^3J_{CF}$ = 21.7 Hz), 26.6 , 21.0 (d, $^5J_{CF}$ = 6.0 Hz), 17.3 , -1.6; ^{19}F NMR (282 MHz, $CDCl_3$) δ –173.70; IR (Neat Film, NaCl) 2953, 1732, 1452, 1287, 1251, 1223, 1157, 1093, 1051, 860, 838 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{12}H_{21}FO_3SiNa$ $[M + Na]^+$: 283.1136; found 283.1145.

2.6.4 Spectroscopic data for TMSE β-ketoester substrates

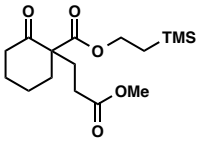
2-(Trimethylsilyl)ethyl 1-benzyl-2-oxocyclohexane-1-carboxylate (77a)



77a

Ketoester **77a** was prepared by the general procedure and was isolated by flash column chromatography (SiO_2, hexanes to 5% EtOAc in hexanes) as a colorless oil. 79.4% yield. R_f = 0.3 (20% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48–7.04 (m, 5H), 4.16 (td, J = 9.8, 7.1 Hz, 2H), 3.13 (dd, J = 125.3, 13.7 Hz, 2H), 2.60–2.35 (m, 2H), 2.05 (ddd, J = 12.4, 6.1, 3.0 Hz, 1H), 1.83–1.59 (m, 4H), 1.57–1.40 (m, 1H), 0.92 (ddd, J = 8.9, 7.2, 1.0 Hz, 2H), 0.07 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.9, 172.8, 138.3, 132.0, 129.5, 128.2, 65.2, 63.8, 42.9, 42.0, 37.5, 29.2, 24.1, 18.8, 0.0; IR (Neat Film, NaCl) 3029, 2952, 2856, 1713, 1496, 1453, 1439, 1250, 1221, 1177, 1132, 1086, 1053, 988, 932, 860, 838, 765, 744 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{19}H_{29}O_3Si$ $[M + H]^+$: 333.1880; found 333.1863.

2-(Trimethylsilyl)ethyl 1-(3-methoxy-3-oxopropyl)-2-oxocyclohexane-1-carboxylate (77c)

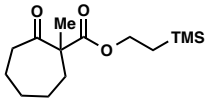


77c

Ketoester **77c** was prepared according to the general procedure, using methyl acrylate in place of methyl iodide, and isolated by flash column chromatography (SiO_2, 5% EtOAc in hexanes to 10% EtOAc in hexanes) as a colorless oil. 81.2% yield. R_f = 0.3 (25%

EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.28–4.08 (m, 2H), 3.62 (s, 3H), 2.41 (dddd, *J* = 14.6, 12.9, 6.5, 2.7 Hz, 4H), 2.27–2.06 (m, 2H), 2.02–1.92 (m, 1H), 1.92–1.84 (m, 1H), 1.76–1.51 (m, 3H), 1.40 (ddd, *J* = 13.5, 12.1, 4.2 Hz, 1H), 1.03–0.91 (m, 2H), 0.00 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.6, 173.5, 171.8, 63.9, 60.0, 51.6, 41.0, 36.3, 29.7, 29.4, 27.5, 22.5, 17.4, -1.6; IR (Neat Film, NaCl) 3432, 2952, 2899, 2866, 1740, 1713, 1437, 1377, 1340, 1308, 1250, 1175, 1137, 1093, 1075, 1062, 1040, 943, 861, 838, 763, 695 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{16}H_{28}O_5SiNa$ [M + Na]$^{+}$: 351.1598; found 351.1602.

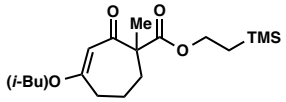
2-(Trimethylsilyl)ethyl 1-methyl-2-oxocycloheptane-1-carboxylate (77d)



77d

Ketoester **77d** was prepared by the general procedure and purified by flash column chromatography (SiO_2, hexanes to 5% EtOAc in hexanes) as a colorless oil. 78% yield. R_f = 0.4 (20% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.25–4.14 (m, 2H), 2.78–2.68 (m, 1H), 2.49 (ddd, *J* = 12.2, 8.6, 2.5 Hz, 1H), 2.19–2.10 (m, 1H), 1.88–1.71 (m, 3H), 1.71–1.48 (m, 3H), 1.43–1.34 (m, 1H), 1.33 (s, 3H), 1.06–0.94 (m, 2H), 0.03 (s, 9H);^{13}C NMR (126 MHz, $CDCl_3$) δ 210.5, 173.7, 63.6, 58.8, 42.0, 35.4, 30.1, 25.8, 24.7, 21.5, 17.3, -1.6; IR (Neat Film, NaCl) 2949, 2861, 1736, 1710, 1458, 1378, 1250, 1232, 1152, 1105, 1062, 942, 860, 838 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{14}H_{26}O_3Si$ [M + Na]$^{+}$: 293.1543; found 293.1543.

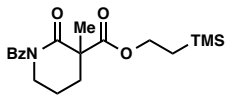
2-(Trimethylsilyl)ethyl 4-isobutyl-1-methyl-2-oxocyclohept-3-ene-1-carboxylate (77e)



77e

Vinylogous ester **77e** was prepared by the general procedure, starting from 3-isobutoxycyclohept-2-en-1-one, and purified by flash column chromatography (SiO_2, hexanes to 10% EtOAc in hexanes) as a colorless oil. 85% yield. R_f = 0.3 (20% EtOAc in hexanes); ^{1}H NMR (500 MHz, C_6D_6) δ 5.66–5.53 (m, 1H), 4.32–4.07 (m, 2H), 3.16–3.00 (m, 2H), 2.57 (dddd, *J* = 17.7, 10.1, 3.9, 1.2 Hz, 1H), 2.50–2.37 (m, 1H), 2.20 (ddd, *J* = 17.7, 7.0, 3.6 Hz, 1H), 1.77–1.67 (m, 2H), 1.66 (s, 3H), 1.59–1.41 (m, 2H), 0.88 (ddd, *J* = 10.0, 7.0, 2.1 Hz, 2H), 0.71 (dd, *J* = 6.7, 4.2 Hz, 6H), -0.13 (s, 9H); ^{13}C NMR (126 MHz, C_6D_6) δ 197.1, 173.9, 171.7, 105.6, 74.0, 62.9, 58.9, 33.9, 33.7, 27.6, 24.1, 18.7, 18.7, 17.0, -2.1; IR (Neat Film, NaCl) 2951, 1684, 1452, 1386, 1327, 1281, 1251, 1139, 1053, 859, 839, 718, 693, 658 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{28}H_{33}O_3Si$ $[M + H]^+$: 341.2143; found 341.2139.

2-(Trimethylsilyl)ethyl 1-benzoyl-3-methyl-2-oxopiperidine-3-carboxylate (77f)

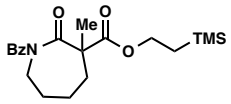


77f

Amide ester **77f** was prepared by the general procedure, starting from *N*-benzoyl-2-piperidone, and purified by flash column chromatography (SiO_2, 5% EtOAc in hexanes

to 25% EtOAc in hexanes) as a colorless oil. 89% yield. R_f = 0.3 (35% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76–7.72 (m, 2H), 7.47 (ddt, *J* = 8.0, 6.9, 1.3 Hz, 1H), 7.41–7.36 (m, 2H), 4.38–4.24 (m, 2H), 3.91–3.82 (m, 1H), 3.78 (dtd, *J* = 12.9, 5.2, 1.4 Hz, 1H), 2.47 (dddd, *J* = 13.8, 5.7, 4.3, 1.4 Hz, 1H), 2.06–1.91 (m, 2H), 1.85–1.74 (m, 1H), 1.46 (s, 3H), 1.14–1.05 (m, 2H), 0.07 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.0, 173.1, 173.0, 135.9, 131.6, 129.0 128.0, 64.4, 52.9, 46.8, 33.7, 22.4, 20.2, 17.5, -1.5; IR (Neat Film, NaCl) 3062, 2953, 2896, 1726, 1703, 1683, 1449, 1389, 1277, 1251, 1192, 1140, 1062, 932, 859, 838, 723, 694 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{19}H_{27}NO_4SiNa$ $[M + Na]^+$: 384.1602; found 384.1611.

2-(Trimethylsilyl)ethyl 1-benzoyl-3-methyl-2-oxoazepane-3-carboxylate (77g)

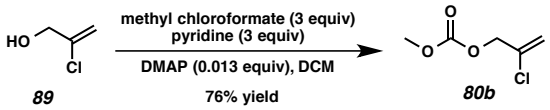


77g

Amide ester **77g** was prepared by the general procedure, starting from 1-benzoylazepan-2-one, and purified by flash column chromatography (SiO_2, 5% EtOAc in hexanes to 25% EtOAc in hexanes) as a colorless oil. 77% yield. R_f = 0.3 (35% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72–7.68 (m, 2H), 7.50–7.45 (m, 1H), 7.39 (ddt, *J* = 8.2, 6.6, 1.1 Hz, 2H), 4.47–4.39 (m, 1H), 4.38–4.31 (m, 2H), 3.15 (ddd, *J* = 15.7, 11.2, 1.2 Hz, 1H), 2.22 (dtd, *J* = 14.8, 3.6, 1.8 Hz, 1H), 2.01–1.90 (m, 2H), 1.89–1.77 (m, 1H), 1.61 (dddt, *J* = 20.7, 12.0, 5.0, 3.2 Hz, 3H), 1.44 (s, 3H), 1.14–1.06 (m, 2H), 0.08 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.6, 174.9, 173.1, 136.4, 131.5, 128.1, 127.9, 64.3,

55.0, 44.0, 34.4, 27.9, 26.9, 25.0, 17.5, -1.5; IR (Neat Film, NaCl) 2956, 1729, 1661, 1614, 1455, 1383, 1249, 1169, 1115, 860, 838 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{20}H_{29}NO_4SiNa$ $[M + Na]^+$: 398.1758; found 398.1775.

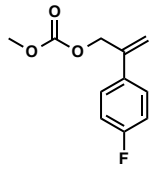
2.6.5 General procedure for allyl carbonate substrate syntheses



2-Chloroallyl methyl carbonate (80b). To a flame-dried 50 mL round bottom flask charged with a magnetic stirring bar, 1.00 g 2-chloroallyl alcohol (**89**) (10.8 mmol, 1.0 equiv), 2.56 g of pyridine (32.4 mmol, 3.0 equiv), 0.016 g of dimethylaminopyridine (0.14 mmol, 0.013 equiv) and 22 mL of DCM at 0 °C, was added 3.06 g of methyl chloroformate (32.43 mmol, 3 equiv), dropwise over 10 min. The solution was allowed to warm to 23 °C and stirred for 12 h. The mixture was then diluted with 40 mL of DCM, washed consecutively with 50 mL H_2O and 50 mL brine before being dried over $MgSO_4$ and directly subjected to flash column chromatography (SiO_2, pentane to 5% Et_2O in pentane). 1.23 g of 2-Chloroallyl methyl carbonate was isolated as a colorless oil. 75.6% yield. R_f = 0.6 (20% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.49 (dt, *J* = 2.0, 1.2 Hz, 1H), 5.41 (dt, *J* = 1.8, 0.9 Hz, 1H), 4.68–4.67 (m, 2H), 3.80 (d, *J* = 1.2 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.1, 135.2, 115.2, 69.0, 55.1; IR (Neat Film, NaCl) 3008, 2959, 2255, 1752, 1639, 1444, 1383, 1358, 1265, 1182, 1116, 974,

908, 790, 745 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_5H_8ClO_3$ $[M + H]^+$: 151.0156; found 151.0150.

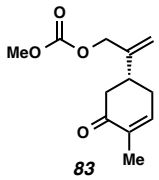
2.6.6. Spectroscopic data for allyl carbonate substrates



80d

2-(4-Fluorophenyl)allyl methyl carbonate (80d) was prepared by the general procedure from 2-(4-fluorophenyl)allyl alcohol and isolated as a colorless oil by flash column chromatography (SiO_2, pentane to 5% Et_2O in pentane). 87% yield. R_f = 0.4 (20% EtOAc in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 7.44–7.36 (m, 2H), 7.09–6.99 (m, 2H), 5.51 (s, 1H), 5.39 (tt, *J* = 1.2, 0.5 Hz, 1H), 5.00 (dd, *J* = 1.3, 0.6 Hz, 2H), 3.79 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.65 (d, $^1J_{CF}$ = 247.0 Hz), 155.54, 141.1, 133.85, 127.74 (d, $^3J_{CF}$ = 7.8 Hz), 115.85 (d, $^4J_{CF}$ = 1.4 Hz), 115.41 (d, $^2J_{CF}$ = 21.9 Hz), 69.09 , 54.89; ^{19}F NMR (282 MHz, $CDCl_3$) δ –126.95; IR (Neat Film, NaCl) 3007, 2959, 1893, 1750, 1634, 1603, 1511, 1447, 1372, 1260, 1164, 1102, 969, 918, 839, 791, 742 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{11}H_{12}FO_3$ $[M + H]^+$: 211.0765; found 211.0772.

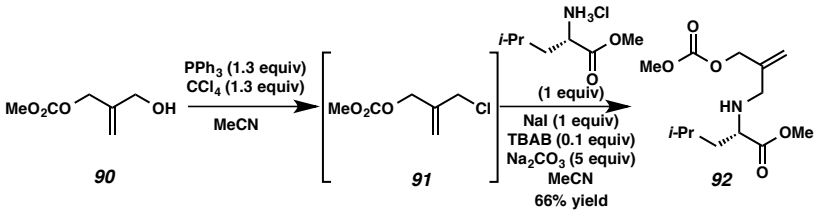
(*R*)-Methyl (2-(4-methyl-5-oxocyclohex-3-en-1-yl)allyl) carbonate (83)



83

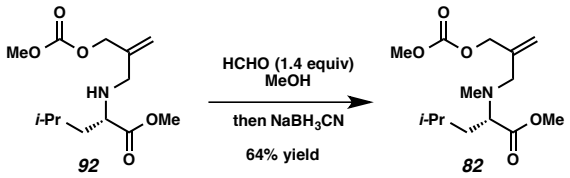
Enone carbonate **83** was prepared by the general method from known allylic alcohol (*R*)-5-(3-hydroxyprop-1-en-2-yl)-2-methylcyclohex-2-en-1-one (i.e. (*R*)-10-hydroxy carvone)[65] and isolated as a colorless oil by flash column chromatography (SiO_2, 5% EtOAc in henxanes to 20% EtOAc in hexanes). 91% yield. R_f = 0.2 (20% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.74 (ddd, *J* = 5.9, 2.7, 1.4 Hz, 1H), 5.22 (dt, *J* = 1.3, 0.7 Hz, 1H), 5.07 (dd, *J* = 1.4, 0.7 Hz, 1H), 4.64 (ddt, *J* = 3.8, 1.2, 0.5 Hz, 2H), 3.79 (s, 3H), 2.97–2.74 (m, 1H), 2.63 (ddd, *J* = 16.1, 3.8, 1.6 Hz, 1H), 2.52 (dddt, *J* = 18.2, 6.0, 4.5, 1.5 Hz, 1H), 2.39 (dd, *J* = 16.1, 13.2 Hz, 1H), 2.31 (ddt, *J* = 18.2, 10.8, 2.5 Hz, 1H), 1.78 (dt, *J* = 2.6, 1.3 Hz, 3H);^{13}C NMR (126 MHz, $CDCl_3$) δ 198.9, 155.5, 144.7, 144.0, 135.6, 114.3, 69.1, 54.9, 42.9, 38.2, 31.3, 15.7; IR (Neat Film, NaCl) 2958, 2928, 2893, 1750, 1671, 1444, 1364, 1266, 1107, 984, 954, 913, 791 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{12}H_{17}O_4$ $[M + H]^+$: 225.1121; found 225.1118.

2.6.7 Procedure for the synthesis allyl carbonate 82



Methyl *N*-(2-(((methoxycarbonyl)oxy)methyl)allyl)-*L*-leucinate (92). Known hydroxy carbonate **90**[66] was prepared by the general method. Following the procedure of Altmann and co-workers,[67] 0.77 g of **90** (5.27 mmol, 1.0 equiv) was added to flame-dried round bottom flask charged with a magnetic stirring bar and 0.66 mL of acetonitrile. The solution was cooled to 0 °C and 1.80 g of triphenylphosphine (6.83 mmol, 1.3 equiv) and 0.66 mL of carbontetrachloride (6.85 mmol, 1.3 equiv) were added sequentially. The resulting slurry was allowed to warm to 23 °C and stirred for 2 h before being subjected directly to flash column chromatography. The resulting crude oil, **91** was determined to be ca. 95% pure by ^{1}H NMR analysis and used without further purification (yield not determined). Following a known procedure,[68] 0.47 g of crude allylic chloride intermediate **91** (2.855 mmol, 1.5 equiv) was combined with 0.28 g of NaI (1.90 mmol, 1.0 equiv), 0.346 g of (*L*)-leucine methyl ester hydrochloride (1.90 mmol, 1.0 equiv), 0.061 g of tetrabutylammonium bromide (0.19 mmol, 0.1 equiv), 1.01 g Na_2CO_3 (9.52 mmol, 5 equiv) and 20 mL acetonitrile in a 50 mL round bottom flask equipped with a magnetic stirring bar. The flask was fitted with a reflux condenser and the mixture stirred at 82 °C for 14 h. The vessel was then cooled to 23 °C and the mixture diluted with 50 mL Et_2O, washed with H_2O (20 mL x 2), dried over $MgSO_4$ and concentrated *in vacuo*.

The crude oil was purified by flash column chromatography (SiO_2, 5% EtOAc in hexanes to 15% EtOAc in hexanes) to give 0.52 g of amino ester **92** as a colorless oil. 66.1% yield from crude **91**. R_f = 0.2 (40% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.23–5.08 (m, 2H), 4.66 (t, *J* = 1.0 Hz, 2H), 3.79 (s, 3H), 3.71 (s, 3H), 3.25 (t, *J* = 7.3 Hz, 1H), 3.19 (dd, *J* = 80.0, 13.8 Hz, 1H), 1.74 (dq, *J* = 13.5, 6.7 Hz, 1H), 1.51 (br s, 2H), 1.43 (t, *J* = 7.2 Hz, 2H), 0.89 (dd, *J* = 9.2, 6.6 Hz, 6H);^{13}C NMR (126 MHz, $CDCl_3$) δ 176.5, 155.7, 141.7, 115.0, 68.9, 59.1, 54.9, 51.7, 50.4, 42.9, 24.9, 22.9, 22.2; IR (Neat Film, NaCl) 2956, 2868, 1750, 1737, 1443, 1368, 1267, 1196, 1151, 980, 943, 792 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{13}H_{24}NO_5$ [M + H]$^+$: 274.1649; found 274.1659.

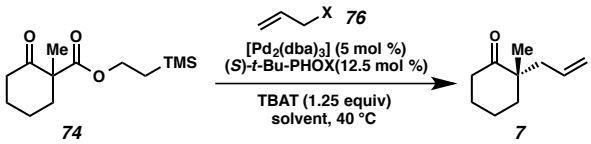


Methyl *N*-(2-(((methoxycarbonyl)oxy)methyl)allyl)-*N*-methyl-*L*-leucinate (82). To a 10 mL round bottom flask containing a magnetic stirring bar and a solution of 0.37 g **92** (1.35 mmol, 1.0 equiv) in 4 mL of methanol was added 0.056 g of formaldehyde (1.88 mmol, 1.4 equiv) as a 37% solution in H_2O. The mixture was stirred at 23 °C for 12 h at which point 0.11 g sodium cyanoborohydride was carefully added. After an additional 12 h of stirring, the mixture was diluted with H_2O (5 mL), extracted with EtOAc (5 mL x 3), dried over $MgSO_4$, concentrated *in vacuo* and subjected directly to purification by flash column chromatography (SiO_2, 10% EtOAc in hexanes to 25% EtOAc in hexanes) to yield 0.25 g of carbonate **82** as a colorless oil. 63.8% yield. R_f = 0.5 (33% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.30–5.07 (m, 2H), 4.63 (t, *J* = 1.0 Hz, 2H), 3.79

(s, 3H), 3.69 (s, 3H), 3.34 (dd, J = 8.3, 7.0 Hz, 1H), 3.18 (dd, J = 75.0, 13.8 Hz, 2H), 2.22 (s, 3H), 1.73–1.61 (m, 1H), 1.61–1.46 (m, 2H), 0.90 (dd, J = 17.5, 6.6 Hz, 6H);^{13}C NMR (126 MHz, $CDCl_3$) δ 173.3, 155.6, 141.2, 115.4, 68.5, 63.8, 57.3, 54.7, 50.9, 38.4, 37.0, 24.7, 22.9, 21.9; IR (Neat Film, NaCl) 2955, 2870, 2803, 1751, 1658, 1444, 1385, 1368, 1269, 1193, 1157, 1126, 1072, 978, 945, 792 cm^{-1}; HRMS (MM: ESI-APCI+) m/z calc'd for $C_{14}H_{26}NO_5$ $[M + H]^+$: 288.1805; found 288.1795.

2.6.8 Optimization of reaction parameters

Table 2.6.8.1. *Optimization of reaction parameters*



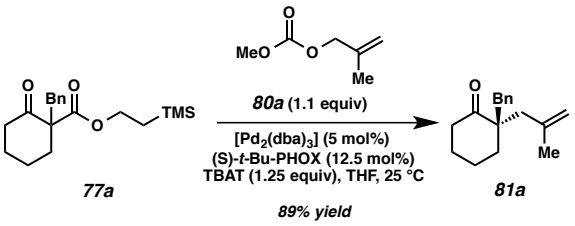
entry	X	equiv allyl	sovent	yield (%)[a]	ee (%)[b]
1	Br	1.0	toluene	55	83
2	OTs	1.0	1,4-dioxane	43	77
3	OMs	1.0	1,4-dioxane	45	84
4	OAc	1.0	1,4-dioxane	15	82
5	OCO_2Allyl	1.0	1,4-dioxane	78	83
6	OCO_2Me	1.0	1,4-dioxane	78	84
7	OCO_2Me	0.75	1,4-dioxane	51	82
8	OCO_2Me	1.5	1,4-dioxane	74	82
9	OCO_2Me	2.0	1,4-dioxane	73	84
10	OCO_2Me	1.1	toluene	33	82
11	OCO_2Me	1.1	MTBE	65	84
12	OCO_2Me	1.1	THF	83	83
13	OCO_2Me	1.1	tol/hex	45	93
14[c]	OCO_2Me	1.1	THF	81	86

General Procedure for Optimization Experiments: Inside a nitrogen-filled glove-box, an oven-dried 0.5 dram vial was charged with a magnetic stirring bar, 0.0046 g

$[Pd_2(dba)_3]$ (0.005 mmol, 0.05 equiv), 0.0047 g (*S*)-*t*-Bu-PHOX (0.0125 mmol, 0.125 equiv), 0.067 g TBAT (0.125 mmol, 1.25 equiv), 0.018 g tridecane (0.10 mmol, 1.0 equiv) and 3.0 mL THF. This mixture was stirred at 25 °C for 30 min at which time 0.026 g of β-ketoester **74** (0.10 mmol, 1.0 equiv) and 0.013 g of allyl methyl carbonate (0.11 mmol, 1.1 equiv) were added, neat. The vial was capped and stirring continued for 12 h at which time the vial was removed from the glove-box, uncapped and the magnetic stirring bar removed. The reaction mixture was diluted with hexanes (2 mL) and passed through a pipette plug (SiO_2) with 4 mL of hexanes followed by 4 mL of Et_2O. From the combined organic fractions, a sample was prepared and the mixture analyzed by GC.

2.6.9 General procedure for Pd-catalyzed allylic alkylation

Please note that the absolute configuration for all products **79** and **81** has been inferred by analogy to previous studies. For isolated yields, see the main text of vide supra. For respective GC, HPLC or SFC conditions, as well as optical rotation data, please refer to Table 2.6.11.

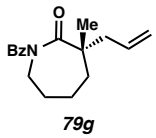


(*S*)-2-benzyl-2-(2-methylallyl)cyclohexan-1-one (**81a**). Inside a nitrogen filled glove-box, an oven-dried 20 mL scintillation vial was charged with a magnetic stirring bar, 0.011 g $[Pd_2(dba)_3]$ (0.012 mmol, 0.05 equiv), 0.011 g (*S*)-*t*-Bu-PHOX (0.029 mmol, 0.125 equiv), 0.15 g TBAT (0.28 mmol, 1.25 equiv) and 7 mL THF. This mixture was

stirred at 25 °C for 30 min at which time 0.075 g of β-ketoester **77a** (0.23 mmol, 1.0 equiv) and 0.033 g of allyl methyl carbonate (0.25 mmol, 1.1 equiv) were added, neat. The vial was capped and stirring continued for 16 h at which time the vial was removed from the glove-box, uncapped and magnetic stirring bar removed. The reaction mixture was concentrated *in vacuo*. The resulting crude semisolid was purified by flash column chromatography (SiO_2, hexanes to 2% EtOAc in hexanes) to give ketone **81a** as a colorless oil. 89% yield. 89% ee, $[\alpha]_D^{25}$ –20.1 (*c* 1.2, $CHCl_3$); R_f = 0.3 (10% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27–7.23 (m, 2H), 7.22–7.17 (m, 1H), 7.15–7.11 (m, 2H), 4.86 (dd, *J* = 2.0, 1.4 Hz, 1H), 4.69 (dd, *J* = 2.0, 1.0 Hz, 1H), 2.93 (dd, *J* = 114.0, 13.7 Hz, 2H), 2.60–2.49 (m, 1H), 2.44–2.38 (m, 1H), 2.37 (s, 3H), 1.92–1.84 (m, 1H), 1.81–1.69 (m, 2H), 1.67 (dd, *J* = 1.5, 0.8 Hz, 3H), 1.64–1.56 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 214.8, 142.2, 137.8, 130.9, 127.9, 126.2, 114.7, 52.5, 43.2, 41.7, 39.7, 35.7, 26.7, 24.6, 20.8; IR (Neat Film, NaCl) 3026, 2935, 2863, 1700, 1448, 1123, 893, 746 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{17}H_{23}O$ $[M + H]^+$: 243.1743, found 243.1745; SFC conditions: 1% MeOH, 2.5 mL/min, Chiralpak OD–H column, λ = 210 nm, t_R (min): major = 5.79, minor = 6.48.

2.6.10 Spectroscopic data for Pd-catalyzed allylic alkylation products

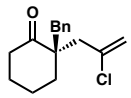
(*S*)-3-Allyl-1-benzoyl-3-methylazepan-2-one (79g)



79g

Lactam **79g** was prepared by the general procedure and isolated by flash column chromatography (SiO_2, 5% EtOAc in hexanes to 25% EtOAc in hexanes) as a colorless oil. 91% yield. 90% ee, $[\alpha]_D^{25}$ –35.2 (*c* 1.7, $CHCl_3$); R_f = 0.2 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52–7.48 (m, 2H), 7.47–7.42 (m, 1H), 7.39–7.35 (m, 2H), 5.72 (dddd, *J* = 17.1, 10.3, 7.6, 7.1 Hz, 1H), 5.13–5.06 (m, 2H), 4.13–4.05 (m, 1H), 3.91 (ddd, *J* = 14.8, 8.8, 2.0 Hz, 1H), 2.40 (dddt, *J* = 71.6, 13.7, 7.6, 1.2 Hz, 2H), 1.91–1.78 (m, 4H), 1.78–1.67 (m, 2H), 1.29 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 182.5, 174.7, 137.0, 133.7, 131.0, 128.1, 127.4, 118.7, 47.7, 44.7, 42.6, 35.1, 28.0, 24.9, 23.3; IR (Neat Film, NaCl) 3072, 2830, 1676, 1448, 1279, 1244, 1224, 1148, 1117, 1096, 971, 951, 919, 790, 726, 695 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{17}H_{21}NO_2$ $[M + H]^+$: 272.1645, found 272.1660; HPLC conditions: 5% IPA, 1.0 mL/min, Chiralpak OJ–H column, λ = 220 nm, t_R (min): major = 5.60, minor = 5.00.

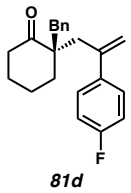
(*R*)-2-Benzyl-2-(2-chloroallyl)cyclohexan-1-one (81b)



81b

Ketone **81b** was prepared according to the general procedure and isolated by flash column chromatography (SiO_2, 5% EtOAc in hexanes to 10% EtOAc in hexanes) as a colorless oil. 72% yield. 96% ee, $[\alpha]_D^{25}$ –7.0 (*c* 1.4, $CHCl_3$); R_f = 0.4 (10% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39–7.16 (m, 2H), 7.20–7.08 (m, 3H), 5.30 (d, *J* = 1.3 Hz, 1H), 5.17 (t, *J* = 1.2 Hz, 1H), 2.99 (dd, *J* = 40.6, 14.1 Hz, 2H), 2.69 (dd, *J* = 56.9, 15.6 Hz, 2H), 2.66–2.34 (m, 2H), 1.97–1.63 (m, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 213.5, 137.0, 130.7, 128.1, 127.7, 126.5, 116.6, 52.5, 43.9, 41.3, 39.7, 35.1, 26.5, 20.9; IR (Neat Film, NaCl) 2939, 2858, 1705, 1631, 1494, 1452, 1429, 1118, 1088, 889, 701 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{16}H_{20}ClO$ $[M + H]^+$: 263.1197, found 263.1199; SFC conditions: 3% MeOH, 2.5 mL/min, Chiralpak OD-H column, λ = 210 nm, t_R (min): major = 6.09, minor = 7.04.

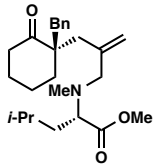
(*R*)-2-Benzyl-2-(2-(4-fluorophenyl)allyl)cyclohexan-1-one (81d)



81d

Ketone **81d** was prepared according to the general procedure, and isolated by flash column chromatography (SiO_2, 1% EtOAc in hexanes to 3% EtOAc in hexanes) as a colorless oil. 91% yield. 95% ee, $[\alpha]_D^{25}$ –9.9 (*c* 2.0, $CHCl_3$); R_f = 0.3 (10% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37–7.12 (m, 5H), 7.11–6.85 (m, 4H), 5.26 (d, *J* = 1.3 Hz, 1H), 5.09 (d, *J* = 1.5 Hz, 1H), 2.86 (dd, *J* = 102.0, 13.7 Hz, 2H), 2.87–2.73 (m, 2H), 2.31 (tt, *J* = 6.2, 2.5 Hz, 2H), 1.83–1.50 (m 6H) ; ^{13}C NMR (126 MHz, $CDCl_3$) δ 214.3 , 162.2 (d, $^1J_{CF}$ = 246.2 Hz), 144.5, 139.2 (d, $^4J_{CF}$ = 3.3 Hz), 137.8, 130.7, 128.2 (d, $^3J_{CF}$ = 7.9 Hz), 127.9, 126.3, 117.6, 115.0 (d, $^2J_{CF}$ = 21.3 Hz), 53.3, 41.7, 40.9, 39.7, 35.1, 26.1, 20.8; ^{19}F NMR (282 MHz, $CDCl_3$) δ –128.24; IR (Neat Film, NaCl) 3027, 2939, 2864, 1703, 1602, 1508, 1453, 1223, 1159, 1126, 905, 841, 750 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{22}H_{24}FO$ $[M + H]^+$: 323.1806, found 323.1809; SFC conditions: 10% MeOH, 2.5 mL/min, Chiralpak OJ-H column, λ = 210 nm, t_R (min): major = 8.59, minor = 10.15.

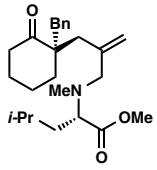
Methyl *N*-(2-(((*R*)-1-benzyl-2-oxocyclohexyl)methyl)allyl)-*N*-methyl-*L*-leucinate (84)



84

Ketone **84** was prepared by the general procedure and isolated by flash column chromatography (SiO_2, 2% EtOAc in hexanes to 5% EtOAc in hexanes) as a colorless oil. 95% yield. >25:1 dr, $[\alpha]_D^{25}$ –20.57 (*c* 1.75, $CHCl_3$); R_f = 0.5 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25–7.21 (m, 2H), 7.21–7.16 (m, 1H), 7.15–7.11 (m, 2H), 5.12 (q, *J* = 1.3 Hz, 1H), 4.94–4.88 (m, 1H), 3.67 (s, 3H), 3.33 (t, *J* = 7.6 Hz, 1H), 3.05–2.90 (m, 2H), 2.93 (dd, *J* = 176.8, 13.7 Hz, 2H), 2.67–2.54 (m, 2H), 2.40–2.31 (m, 1H), 2.25 (dd, *J* = 15.1, 1.1 Hz, 1H), 2.20 (s, 3H), 1.90 (ddq, *J* = 8.0, 4.3, 1.9 Hz, 1H), 1.81–1.47 (m, 8H), 0.90 (dd, *J* = 11.9, 6.6 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 214.9, 173.3, 143.0, 138.1, 130.9, 127.8, 126.1, 116.5, 62.9, 61.8, 52.6, 50.8, 41.2, 39.5, 38.9, 38.4, 36.8, 36.5, 26.9, 24.8, 23.0, 22.2, 20.8; IR (Neat Film, NaCl) 2949, 2868, 1732, 1703, 1641, 1452, 1189, 1152, 1122, 1019, 910, 702 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{25}H_{37}NO_3$ $[M + H]^+$: 400.2836, found 400.2860.

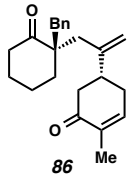
Methyl *N*-(2-(((*S*)-1-benzyl-2-oxocyclohexyl)methyl)allyl)-*N*-methyl-*L*-leucinate (85)



85

Ketone **85** was prepared by the general procedure, using ligand **L9** instead of **L1**, and isolated by flash column chromatography (SiO_2, 2% EtOAc in hexanes to 5% EtOAc in hexanes) as a colorless oil. 95% yield. 1:21 dr, $[\alpha]_D^{25}$ +12.94 (*c* 1.25, $CHCl_3$); R_f = 0.5 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25–7.21 (m, 2H), 7.21–7.16 (m, 1H), 7.16–7.12 (m, 2H), 5.11 (d, *J* = 1.5 Hz, 1H), 4.89 (d, *J* = 1.7 Hz, 1H), 3.68 (s, 3H), 3.29 (dd, *J* = 7.7, 7.0 Hz, 1H), 3.03–2.93 (m, 2H), 2.92 (dd, *J* = 197.9, 13.7 Hz, 2H), 2.68–2.58 (m, 2H), 2.34 (dt, *J* = 13.8, 4.9 Hz, 1H), 2.27–2.21 (m, 1H), 2.19 (s, 3H), 1.91 (d, *J* = 12.8 Hz, 1H), 1.85–1.56 (m, 8H), 0.89 (dd, *J* = 12.4, 6.3 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 214.8, 173.2, 143.2, 138.2, 131.0, 127.8, 126.1, 116.5, 63.3, 61.6, 52.5, 50.8, 41.1, 39.5, 39.3, 38.2, 36.7, 36.7, 26.9, 24.9, 22.8, 22.5, 20.8; IR (Neat Film, NaCl) 3027, 2950, 2867, 1734, 1702, 1641, 1602, 1495, 1452, 1192, 1154, 1125, 1030, 909, 749, 702 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{25}H_{37}NO_3$ $[M + H]^+$: 400.2846, found 400.2855.

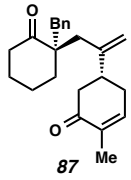
(*R*)-5-(3-((*S*)-1-Benzyl-2-oxocyclohexyl)prop-1-en-2-yl)-2-methylcyclohex-2-en-1-one (86)



86

Ketone **86** was prepared by the general procedure, at 40 °C, and isolated by flash column chromatography (SiO_2, 3% EtOAc in hexanes to 15% EtOAc in hexanes) as a colorless oil. 87% combined yield (**86** and **87**). Characterization data reported for major diastereomer. 6:1 dr, $[\alpha]_D^{25}$ +49.25 (*c* 0.25, $CHCl_3$); R_f = 0.1 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25–7.18 (m, 3H), 7.12–7.02 (m, 2H), 6.72 (dq, *J* = 4.2, 1.3 Hz, 1H), 4.97–4.91 (m, 1H), 4.82 (d, *J* = 1.2 Hz, 1H), 3.03–2.83 (m, 2H), 2.64–2.49 (m, 2H), 2.49–2.37 (m, 4H), 2.38–2.09 (m, 3H), 1.85–1.78 (m, 2H), 1.77 (dt, *J* = 2.6, 1.3 Hz, 3H), 1.76–1.61 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 214.7, 199.8, 147.4, 144.7, 137.3, 135.3, 130.6, 128.0, 126.5, 113.1, 52.5, 43.6, 42.2, 41.8, 39.5, 39.4, 35.6, 31.9, 26.7, 20.8, 15.7; IR (Neat Film, NaCl) 2923, 2863, 1702, 1672, 1494, 1450, 1365, 1248, 1109, 901, 750, 703 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{23}H_{28}O_2Na$ $[M + Na]^+$: 359.1982, found 359.1988.

(*R*)-5-(3-((*S*)-1-Benzyl-2-oxocyclohexyl)prop-1-en-2-yl)-2-methylcyclohex-2-en-1-one (87)

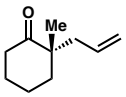
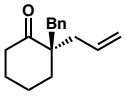
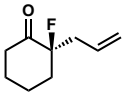
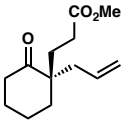
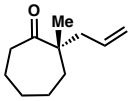
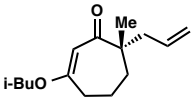
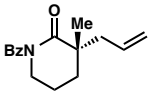
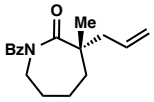
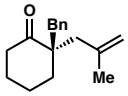
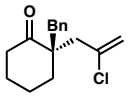
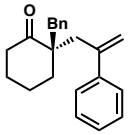
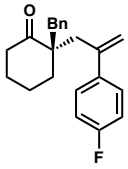


87

Ketone **87** was prepared by the general procedure, at 40 °C, and isolated by flash column chromatography (SiO_2, 3% EtOAc in hexanes to 15% EtOAc in hexanes) as a colorless oil. 77% combined yield (**86** and **87**). Characterization data reported for major diastereomer. 6:1 dr, $[\alpha]_D^{25}$ –10.60 (*c* 0.50, $CHCl_3$); R_f = 0.1 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25–7.18 (m, 3H), 7.12–7.02 (m, 2H), 6.73 (dq, *J* = 4.2, 1.3 Hz, 1H), 4.98 (s, 1H), 4.84 (s, 1H), 3.01–2.86 (m, 2H), 2.59–2.38 (m, 4H), 2.36–2.11 (m, 3H), 1.88–1.81 (m, 2H), 1.76 (dt, *J* = 2.6, 1.3 Hz, 3H), 1.76–1.61 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 214.6, 199.8, 147.1, 144.5, 137.5, 135.4, 130.6, 128.0, 126.4, 112.7, 52.5, 43.7, 42.6, 41.7, 39.6, 39.2, 35.9, 31.9, 26.8, 20.8, 15.7; IR (Neat Film, NaCl) 2923, 2863, 1702, 1672, 1494, 1450, 1365, 1248, 1109, 901, 750, 703 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{23}H_{28}O_2Na$ $[M + Na]^+$: 359.1982, found 359.1985.

2.6.11 Determination of enantiomeric excess and optical rotations

Table 2.6.11.1. *Determination of enantiomeric excess and optical rotations*

entry	compound	analytic conditions	ee (%)	polarimetry
1		GC G-TA, 105 °C, isotherm t_R (min): major 7.80, minor 8.24	86	$[\alpha]_D^{25}$ −11.7 (*c* 0.6, $CHCl_3$)
2		SFC Chiralpak OJ-H, λ = 210 nm 3% IPA/CO_2, 2.5 mL/min, t_R (min): major 5.74, minor 4.71	88	$[\alpha]_D^{25}$ −13.6 (*c* 1.3, $CHCl_3$)
3		GC G-TA, 110 °C, isotherm t_R (min): major 5.039, minor 5.41	91	$[\alpha]_D^{25}$ −68.74 (*c* 1.5, $CHCl_3$)
4		GC G-TA, 120 °C, isotherm t_R (min): major 15.3, minor 22.18	89	$[\alpha]_D^{25}$ 10.51 (*c* 1.6, $CHCl_3$)
5		GC G-TA, 110 °C, isotherm t_R (min): major 6.45, minor 7.23	87	$[\alpha]_D^{25}$ −22.13 (*c* 1.4, $CHCl_3$)
6		HPLC Chiralcel OD-H, λ = 220 nm 1% IPA/hexanes, 1.0 mL/min t_R(min): major 6.12, minor 7.16	92	$[\alpha]_D^{25}$ −65.6 (*c* 1.0, $CHCl_3$)
7		SFC Chiralpak AD-H, λ = 254 nm 5% MeOH/CO_2, 2.5 mL/min, t_R (min): major 5.54, minor 6.23	96	$[\alpha]_D^{25}$ −76.5 (*c* 2.1, $CHCl_3$)
8		HPLC Chiralcel OJ-H, λ = 220 nm 5% IPA/hexanes, 1.0 mL/min t_R(min): major 5.60, minor 5.00	90	$[\alpha]_D^{25}$ −35.2 (*c* 1.7, $CHCl_3$)
9		SFC Chiralpak OD-H, λ = 210 nm 1% MeOH/CO_2, 2.5 mL/min, t_R (min): major 5.79, minor 6.48	89	$[\alpha]_D^{25}$ −20.1 (*c* 1.2, $CHCl_3$)
10		SFC Chiralpak OD-H, λ = 210 nm 3% MeOH/CO_2, 2.5 mL/min t_R (min): major 6.09, minor 7.04	96	$[\alpha]_D^{25}$ −7.0 (*c* 1.4, $CHCl_3$)
11		SFC Chiralpak OJ-H, λ= 210 nm 4% IPA/CO_2, 4.0 mL/min t_R (min): major 7.86, minor 8.66	93	$[\alpha]_D^{25}$ −10.5 (*c* 0.8, $CHCl_3$)
12		SFC Chiralcel OJ-H, λ = 210 nm 10% MeOH/CO_2, 2.5 mL/min t_R (min): major 8.59, minor 10.15	95	$[\alpha]_D^{25}$ −9.9 (*c* 2.0, $CHCl_3$)

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