CHAPTER 3

Construction of Vicinal Tertiary and All-Carbon Quaternary Stereocenters via Ir-Catalyzed Regio-, Diastereo-, and Enantioselective Allylic Alkylation and Applications in Sequential Pd-Catalysis[1]

3.1 INTRODUCTION

3.1.1 State of the art in the asymmetric construction of vicinal quaterary and tertiary carbon centers

The asymmetric construction of sterically-encumbered, vicinal stereogenic centers is of great interest to synthetic chemists due to the prevalence of such structural arrangements in natural products and bioactive compounds.[69] The limited number of methods that provide selective access to vicinal tertiary and all-carbon quaternary stereocenters highlights the challenging nature of this task. Enantioselective approaches for accessing this structural dyad have generally relied on asymmetric Michael additions[70] and Claisen rearrangements.[71] Among the methods available for forging this motif, only a relatively small number have been reported to do so by employing transition metals in a

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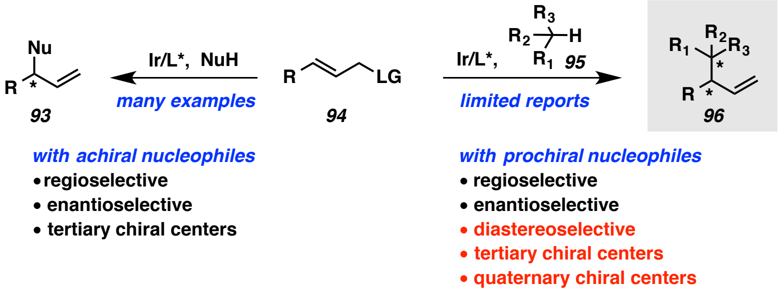
[1] This work was performed in collaboration with Wen-Bo Lui, postdoctoral researcher in the Stoltz group, and Scott Virgil, manager of the Caltech Center for Catalysis and Chemical Synthesis. This work has been published. See: Liu, W. -B.; Reeves, C. M.; Virgil, S. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2013**, *135*, 10626.

catalytic, asymmetric fashion.[72,73] Thus, further investigations into the development of metal-catalyzed methods to directly and selectively generate such stereochemical arrays should prove valuable.

Allylic alkylation chemistry represents a successful strategy for the assembly of highly congested chemical architectures by C–C bond formation[74] and, within this domain, Ir-catalyzed processes are among the most selective and highest yielding.[75,76] Initial reports from the Helmchen[77] and Hartwig[78] groups demonstrated the utility of Ir-catalyzed allylic substitutions for the synthesis of enantioenriched 3,3-disubstituted (branched) allyl compounds.[75] As this research area has developed, Ir/phosphoramidite catalysts[79] have emerged as privileged scaffolds for the regio- and enantioselective allylic alkylation of achiral nucleophiles, such as malonate derivatives and ketone enolates (Figure 3.1.1.1, **94** → **93**).[80] However, methods for Ir-catalyzed intermolecular allylic alkylation that employ prochiral nucleophiles and display high (1) regio-, (2) diastereo-, and (3) enantioselectively remain elusive (Figure 3.1.1.1, **94** → **96**).[81] Prior to our investigation, only two reports,[82] from the laboratories of Takemoto and Hartwig, detailed successful examples in attaining all three of these goals; however, in these accounts, the nucleophiles investigated were limited to amino acid derivatives and azlactones.[83]

Figure 3.1.1.1. Ir-catalyzed allylic substitution



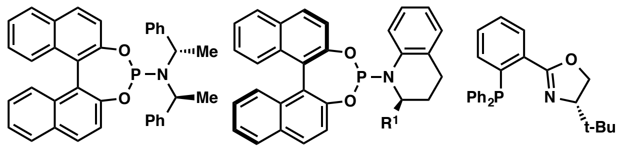
In this chapter, we detail the development of a highly regio-, diastereo-, and enantioselective Ir-catalyzed α-allylic alkylation of cyclic β-ketoesters that forges vicinal tertiary and all-carbon quaternary centers in one step and in excellent yields. Moreover, we describe the deployment of our novel 2-(trimethylsilyl)ethyl β-ketoester (TMSE β-ketoester) (see Chapter 2), which functions as an oxycarbonyl-protected enolate, enabling sequential catalyst-controlled α-allylic alkylations and, in turn, the ability to select the diastereomer produced within the nascent stereochemical dyad.

3.2 REACTION DEVELOPMENT AND OPTIMIZATION

3.2.1 Discovery and optimization of iridium catalyzed regio-, diastereo- and enantioselective allylic alkylation of cyclic ketones

Our preliminary studies focused on probing the effects of different ligands, bases, additives, and solvents on the efficiency and selectivity of the reaction. Cyclic β-ketoester **97**, cinnamyl carbonate **98**, and $[Ir(cod)Cl]_2$/phosphoramidite complexes[84] were chosen as standard reaction components at the outset of our investigations.[85] Selected results of these experiments are summarized in Table 3.2.1.1. Our investigations commenced with commonly used phosphoramidite ligand **L10**[86] and we were pleased to find that the proposed reaction proceeded smoothly under the conditions described (Table 3.2.1.1), delivering α-quaternary β-ketoester **100a** in >95% conversion and in 96% ee. Unfortunately, no diastereoselectivity was observed in this case (Table 3.2.1.1, entry 1). Use of ligand **L11**, a diastereoisomer of **L10**, again produced a high-yielding reaction, but in significantly diminished ee (32%) and modest 1:2 dr (entry 2). Inspired by the You group's use of Ir-*N*-arylphosphoramidite complexes (derived from $[Ir(cod)Cl]_2$ and **L12**)[87] to effect the diastereo- and enantioselective intramolecular allylation of indoles and pyrroles,[88] we envisioned that analogous Ir complexes may prove valuable for the generation of all-carbon quaternary stereocenters. We were delighted to discover that the use of *N*-aryl-phosphoramidite ligand **L12** furnished the desired product in 98% ee, >20:1 dr, and 95:5 branched to linear ratio (entry 3).

Figure 3.2.1.1. *Selected phosphoramidite and PHOX ligands*

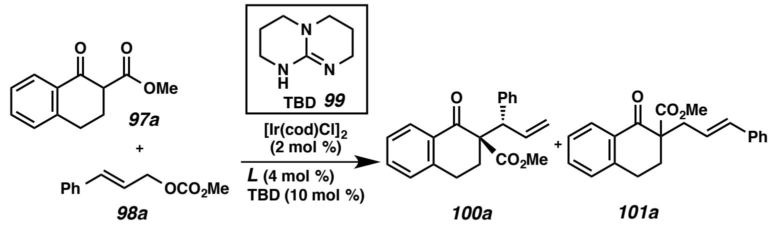


(S,S,S$_a$)-L10
(S,S,R$_a$)-L11

***(R,R$_a$)-L12*: R = Me**
***(R$_a$)-L13*: R = H**

(S)-L1

Table 3.2.1.1. *Optimization of reaction parameters.*[a]



entry	L	base or additive (equiv)	100a:101a[b]	dr of 100a[b]	ee of 100a (%)[c]
1	L10	NaH (2)	>95:5	1:1	96 (99)[d]
2	L11	NaH (2)	>95:5	1:2	32 (3)[e]
3	L12	NaH (2)	95:5	>20:1	98
4	L12	-	80:20	11:1	96
5	L12	Et_3N (2)	77:23	11:1	97
6	L12	Cs_2CO_3 (2)	63:37	6:1	93
7	L12	K_3PO_4 (2)	63:37	4:1	90
8	L12	LiO*t*-Bu (2)	95:5	>20:1	99
9	L12	LiCl (1)	88:12	14:1	98
10	L12	LiBr (1)	95:5	>20:1	>99
11	L13	LiBr (1)	80:20	12:1	96
12[f]	L1	LiBr (1)	12:88	-	-
13[g]	L12	LiBr (1)	95:5	>20:1	99

[a] Reactions performed with 0.1 mmol of **98a**, 0.2 mmol of **97a** at 0.1 M in THF at 20 °C and allowed to proceed to complete consumption of **98a**. [b] Determined by ^{1}H NMR and UHPLC-MS analysis of the crude mixture. [c] Determined by chiral HPLC analysis of the major diastereomer. [d] (ee) of the alternate diastereomer. [e] (ee) of the major diastereomer. [f] Measured after 60 h at 60% conversion. [g] 1 mol % [Ir(cod)Cl]$_2$ and 2 mol % **L12** were used.

Extensive exploration of various bases, including organic and inorganic bases, revealed that the use of LiO*t*-Bu afforded the desired product in comparable selectivities as NaH (entries 4–8). Previous reports demonstrating the marked effect of LiCl on the regioselectivity[79b,80j,81b] in Ir-catalyzed allylic alkylations prompted us to investigate this and related additives. As a result of these efforts (entries 9–10), the combination of LiBr and THF, at 25 °C, was found to provide **100a** in >20:1 dr, 95:5 branched:linear ratio, and with >99% ee (entry 10).

3.2.2 Further development of the reaction conditions

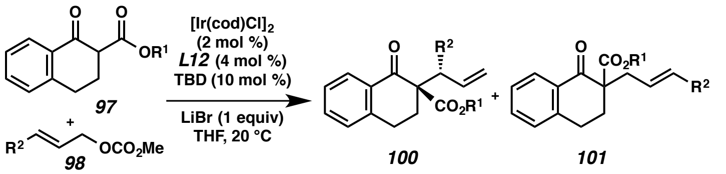
Under these superior conditions, several more ligands were examined. Use of ligand **L13**[88b] afforded **100a** in 96% ee and 12:1 dr (entry 11). Employment of *N*-aryl-phosphoramidite scaffolds proved critical to maintaining high diastereoselectivity in the reaction. Phosphinooxazoline (PHOX) type ligands (e.g. **L1**), first used in Ir-catalyzed allylation by Helmchen,[77] were also examined, but we found these to be poorly suited for our reaction (entry 12). Finally, we found that the catalyst loading could be reduced to 1 mol % (entry 13) without loss of selectivity.

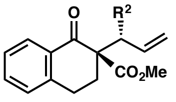
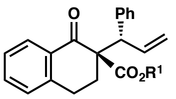
3.3 SURVEY OF REACTION SCOPE

3.3.1 Exploration of the reaction scope with respect to allyl electrophile

With optimized conditions in hand, the scope of substrates tolerated in the reaction was explored. We found that cinnamyl-derived carbonates bearing either electron-donating (–OMe) or electron-withdrawing (–Br, $–CF_3$) groups on the aromatic ring gave remarkably high dr, ee and yields (99% ee and 20:1 dr, Table 3.3.1.1, entries 1–4). The branched to linear ratio (i.e., **100**:**101**) tended to decrease as the electron deficiency of the aryl substituents increased (from 95:5 to 71:29, with 4-OMe-C_6H_4 to 4-CF_3-C_6H_4, respectively, entries 2–4). Heteroaryl substituents, such as 3-pyridyl, 2-thienyl and 2-furanyl, were also installed with uniformly excellent enantioselectivities and high diastereoselectivities (95–98% ee and 10:1–17:1 dr, entries 5–7). In addition to aromatic substituents, methyl sorbyl carbonate was also well tolerated in the chemistry providing diene **100h**, although with a slight decrease in dr and ee (8:1 dr and 90% ee, entry 8).[89] Moreover, the reaction proceeded smoothly with ethyl β-ketoester **97i**, providing the α-allyl β-ketoester **100i** with excellent yield and selectivity (entry 9).

Figure 3.3.1.1. *Substrate scope of Ir-catalyzed allylic alkylation of β-ketoesters*[a]



entry		product (*100*)	*t* (h)	*100*:*101*[b]	dr of *100*[b]	yield (%)[c]	ee of *100* (%)[d]
1		*100a*: R^2 = Ph	1	95:5	>20:1	98	>99
2		*100b:* R^2 = *p*-MeO-C_6H_4	1	95:5	20:1	99	>99
3		*100c*: R^2 = *p*-Br-C_6H_4	8	90:10	>20:1	90	99
4		*100d*: R^2 = *p*-CF_3-C_6H_4	12	71:29	>20:1	99	>99
5	*100a–100h*	*100e*: R^2 = 3-pyridyl	12	50:50	11:1	98	98
6		*100f*: R^2 = 2-thienyl	12	92:8	17:1	97	95
7		*100g*: R^2 = 2-furanyl	12	95:5	10:1	90	95
8		*100h*: R^2 = (*E*)-MeCH=CH	10	95:5	8:1	92	90
9	*100i*	*100i*: R^1 = Et	2	95:5	>20:1	98	>99

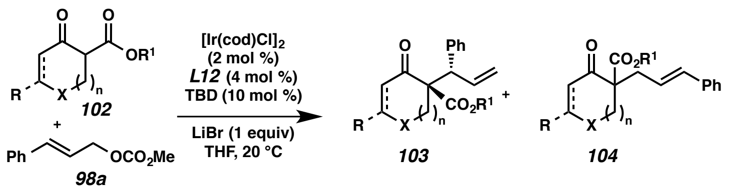
[a] Reactions performed under the conditions of Table 1, entry 10. [b] Determined by ^{1}H NMR analysis of the crude mixture. [c] Isolated yield of **100** and **101**. [d] Determined by chiral HPLC or SFC analysis of the major diastereomer.

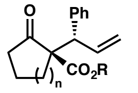
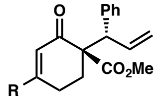
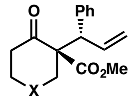
3.3.2 Exploration of the reaction scope with respect to ketoester nucleophile

Gratifyingly, aliphatic mono cyclic ketones also proved to be excellent participants in the reaction. Cyclopentanone and cyclohexanone based substrates delivered the products **103a** and **103b** in 98–99% ee and 8:1–20:1 dr, respectively (Figure

3.3.2.1, entries 1–2). Vinylogous ester, tetrahydropyran-4-one, and 4-piperidinone derivatives furnished the corresponding products (**103d–103f**) in high yields (85–99%), good diastereoselectivites (13:1–20:1), and enantioselectivities (97–99%, entries 4–6). The absolute stereochemistry of the product **103f** (>99% ee) was determined as (*R*,*R*) by single-crystal X-ray analysis.[90]

Figure 3.3.2.1. *Substrate scope of Ir-catalyzed allylic alkylation of β-ketoesters*



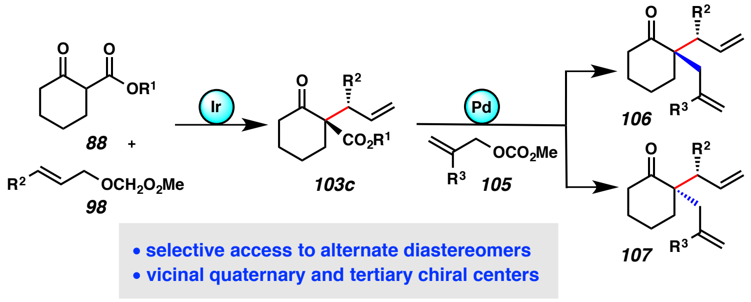
entry		product (*103*)	*t* (h)	*103*:*104*[b]	dr of *103*[b]	yield (%)[c]	ee of *103* (%)[d]
1		*103a*: n = 1, R = Et	3	93:7	8:1	85	99
2		*103b:* n = 2, R = Et	12	90:10	20:1	88	98
3		*103c*: n = 2 R = CH_2CH_2TMS	12	90:10	20:1	87	>99
4		*103d*: R = Oi-*B*	10	91:9	20:1	99	>99
5		*103e*: X = O	10	90:10	16:1	88	98
6		*103f*: X = NBn	12	85:15	13:1	85	97

[a] Reactions performed under the conditions of Table 1, entry 10. [b] Determined by ^{1}H NMR analysis of the crude mixture. [c] Isolated yield of **103** and **104**. [d] Determined by chiral HPLC or SFC analysis of the major diastereomer.

3.4 EMPLOYMENT OF TMSE-β-KETOESTERS TO ENABLE SEQUENTIAL CATALYSIS

During the course of our investigations, we became intrigued by the possibility of developing a sequential allylic alkylation reaction, in which allylation of a dicarbonyl-stabilized enolate would be followed by palladium-catalyzed decarboxylative allylic alkylation and, thus, engender the ability to select among all four possible stereochemical outcomes.[91,92] In order to realize such a consecutive allylic alkylation, we deployed our novel oxycarbonyl-protected enolate, TMSE β-ketoester **88**, which we hypothesized would successfully undergo Ir-catalyzed allylic alkylation and be poised to subsequently participate in Pd catalysis. Specifically, we envisioned that subsequent to Ir-catalyzed allylic alkyaltion TMSE β-ketoester **103c** could be triggered with fluoride, and the resulting prochiral enolate then intercepted and engaged in Pd-catalyzed allylic alkylation to deliver α-quaternary ketone **106 or 107** (Figure 3.4.1). In the case at hand, where β-ketoester **103c** contains a chiral branched R group at the a position, we anticipated that with careful choice of catalyst, we could potentially control the newly generated stereocenter independent of the absolute stereochemistry of the side chain.

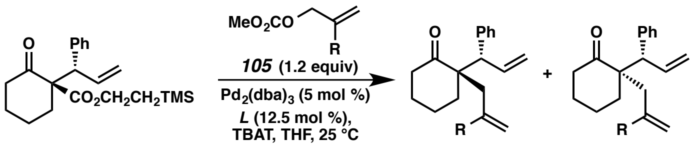
Figure 3.4.1. *Conceptualization of sequential catalysis*



- selective access to alternate diastereomers
- vicinal quaternary and tertiary chiral centers

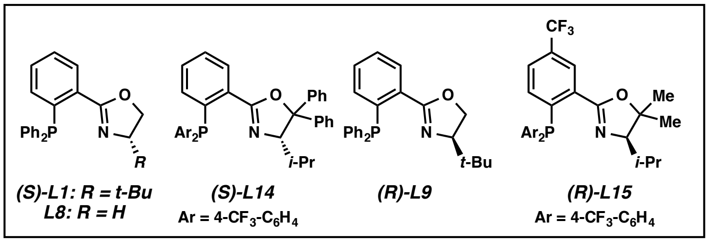
We were pleased to find that TMSE β-ketoester **88** is a highly competent substrate for Ir-catalyzed allylic alkylation and, under standard conditions, gave the desired product (**103c**) with excellent yield and selectivity (Figure 3.3.2.1, entry 3). Moreover, exposure of **103c** to catalytic $Pd_2(dba)_3$/**L8** (Figure 3.4.2) in the presence of allyl methylcarbonate and tetrabutylammonium difluorotriphenylsilicate (TBAT) generated the desired diallylated α-quaternary ketones **106** and **107** in good yield. The use of achiral PHOX ligand **L8** revealed that substrate **103c** displays inherent selectivity under Pd catalysis, furnishing **106a**[93] as the major diastereomer in a 2:1 ratio with **107a** (Figure 3.4.2, entry 1). Use of (*S*)-*t*-BuPHOX ligand (*S*)-**L1** resulted in modest reversal of the inherent diastereoselectivity to generate **107a** predominantly (entry 2). Furthermore, we were interested to find that use of ligand (*S*)-**L14**, possessing both an electronically modified phosphine and a smaller *i*-Pr substituent on the oxazoline ring in contrast to the more standard *t*-Bu, produced **107a** with improved diastereoselectivity (**106a**:**107a**, 1:8 dr) and 91% yield (entry 3). Alternatively, through judicious choice of ligand (e.g., (*R*)-**L15**), the inherent selectivity of the system could be enhanced to afford **106a**:**107a** with up to 18:1 dr favoring **106a** (entries 4–5). Cursory investigation revealed that 2-aryl and 2-alkyl substitutions at the allyl carbonate are well tolerated: allylic alkylation products **106b** and **106c** were obtained in good yields and with excellent diastereoselectivities.

Figure 3.4.2. *Development of Pd-catalyzed diastereoselective decarboxylative allylic alkylation of TMSE-β-ketoesters*[a]



103c **106** **107**

entry	product (*106/107*)	ligand	%yield[b]	dr (*106:107*)[c]
1	*106a/107a*: R = H	*L8*	91	2 : 1
2	*106a/107a*: R = H	(*S*)-*L1*	79	1 : 2.2
3	*106a/107a*: R = H	(*S*)-*L14*[d]	91	1 : 8
4	*106a/107a*: R = H	(*R*)-*L9*	73	12 : 1
5	*106a/107a*: R = H	(*R*)-*L15*	85	18 : 1
6	*106b/107b*: R = Ph	(*R*)-*L15*	87	12 : 1
7	*106c/107c*: R = Me	(*R*)-*L15*	70	13 : 1



(S)-L1: R = t-Bu
L8: R = H

(S)-L14
Ar = 4-CF_3-C_6H_4

(R)-L9

(R)-L15
Ar = 4-CF_3-C_6H_4

[a] Reactions performed with 1.2 equiv of TBAT, and 1.2 equiv of allyl methylcarbonate at 0.03 M.[b] Isolated yield of **106** and **107**. [c] Determined by ^{1}H NMR analysis of the crude mixture and confirmed by GC analysis. [d] 10 mol % ligand was used.

3.5 CONCLUDING REMARKS

In summary, a highly regio-, diastereo-, and enantio-selective method for the synthesis of vicinal tertiary and all-carbon quaternary centers was realized through the use of an $[Ir(cod)Cl]_2$/*N*-aryl-phosphoramidite (**L12**) catalyst system. Varied substitutions were well tolerated on both the β-ketoester and allyl carbonate fragments. A sequential Ir/Pd-catalyzed dialkylation protocol was also established to deliver bis-allylated α-quaternary ketones with excellent stereoselectivity, while affording access to either product diastereomer with catalyst control. Further studies exploring the mechanisms of these reactions and exploiting their applications in the total synthesis of complex natural products are underway in our laboratory.

3.6 EXPERIMENTAL SECTION

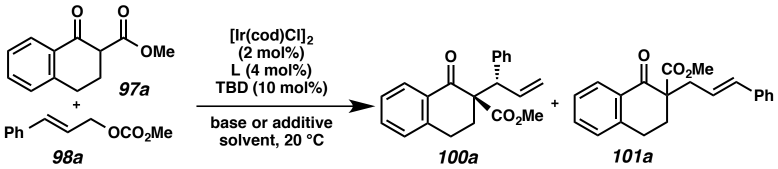
3.6.1 Materials and Methods

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) or Agilent 1290 UHPLC-LCMS. 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 500 MHz and 600 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). ^{31}P and ^{19}F NMR spectra were recorded on a Varian Mercury 300 MHz (at 121 MHz and 282 MHz, respectively). ^{19}F NMR spectra were reported relative to $CFCl_3$ (δ 0.0 ppm). ^{31}P NMR spectra were reported relative to external H_3PO_4 (δ 0.0 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). IR spectra were obtained by use of 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). 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. 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, Acros Organics, Strem, or Alfa Aesar and used as received unless otherwise stated. Ligands **L12–L13**,[87] ligands **L8–L9** and **L14–L15**,[94] allyl carbonates,[95] and β-ketoesters[96] were prepared by known methods.

3.6.2 Optimization of reaction parameters

***Table 3.6.2.1**. Optimization of reaction parameters*



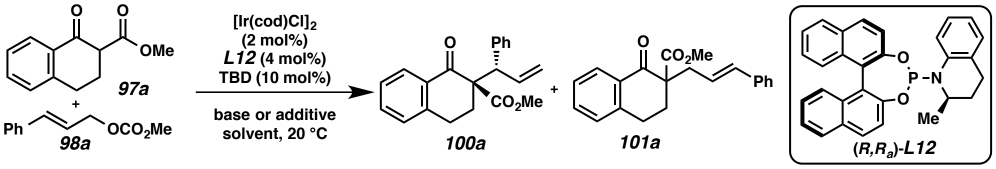
entry[a]	*L*	base/additive (equiv)	solvent	*t* (h)	conv (%)[b]	***100a*:*101a***[b]	dr of ***100a***[b]	ee of ***100a*** (%)[c]
1	***L10***	NaH (2)	THF	24	>95	>95:5	1:1.4	96 (99)[d]
2	***L11***	NaH (2)	THF	60	>95	>95:5	1:1.9	32 (3)[e]
3	***L12***	NaH (2)	THF	12	>95	95:5	>20:1	98
4	***L12***	–	THF	8	>95	80:20	11:1	96
5	***L12***	DABCO (2)	THF	8	>95	72:28	5.0:1	96
6	***L12***	TBD (2)	THF	8	>95	74:26	11:1	95
7	***L12***	Et_3N (2)	THF	8	>95	77:23	11:1	97
8	***L12***	Cs_2CO_3 (2)	THF	12	>95	63:37	6.3:1	93
9	***L12***	K_3PO_4 (2)	THF	12	>95	63:37	4.1:1	90
10	***L12***	NaHMDS (2)	THF	12	>95	75:25	8.3:1	93
11	***L12***	LiHMDS (2)	THF	12	>95	86:14	13:1	96
12	***L12***	LiO*t*-Bu (2)	THF	1	>95	95:5	>20:1	99
13	***L12***	LiCl (1)	THF	1	>95	88:12	14:1	98
14	***L12***	LiBr (1)	THF	1	>95 (98)	95:5	>20:1	>99
15	***L12***	LiI (1)	THF	1	>95	72:28	>20:1	97
16	***L10***	LiBr (1)	THF	60	<5	nd	nd	nd
17	***L11***	LiBr (1)	THF	60	<5	nd	nd	nd
18	***L13***	LiBr (1)	THF	12	>95	80:20	12:1	96
19	***L1***	LiBr (1)	THF	60	60	12:88	nd	nd
20	***L12***	LiBr (1)	*p*-dioxane	1	>95	95:5	>20:1	>99
21	***L12***	LiBr (1)	Et_2O	3	>95	76:24	11:1	96
22	***L12***	LiBr (1)	CH_2Cl_2	60	55	68:32	9.0:1	66
23	***L12***	LiBr (1)	toluene	16	>95	>95:5	>20:1	91
24[f]	***L12***	LiBr (1)	THF	12	>95	95:5	>20:1	99
25[g]	***L12***	LiBr (1)	THF	60	60	92:8	>20:1	94

[a] Reactions performed with 0.1 mmol of **98a**, 0.2 mmol of **97a** in 1 mL of solvent. [b] Determined by ^{1}H NMR or UHPLC-MS analysis of the crude reaction mixture. [d] (Ee) of the alternate diasteromer. [e] Measured on the minor isomer and the number in the parenthesis is ee of the major isomer. [f] 1 mol % of $[Ir(cod)Cl]_2$ and 2 mol % of **L12** were used. [g] 0.5 mol % of $[Ir(cod)Cl]_2$ and 1 mol % of **L12** were used.

General Procedure for Optimization Reaction (Table 3.6.2.1): All experiments were preformed in a nitrogen-filled glove box. $[Ir(cod)Cl]_2$ (1.4 mg, 0.002 mmol, 2 mol%), ligand (0.004 mmol, 4 mol%), and TBD (1.4 mg, 0.01 mmol, 10 mol%) were added to a vial equipped with a magnetic stirring bar. The vial was then charged with solvent (0.5 mL) and stirred at 20 °C for 10 min, generating an orange solution. Cinnamyl carbonate **98a** (19.2 mg, 0.1 mmol, 1.0 equiv), β-ketoester **97a** (40.4 mg, 0.2 mmol, 2.0 equiv), base or additive (as indicated below) and another 0.5 mL of solvent were added. The vial was sealed and stirred at 20 °C until allylic carbonate **98a** was fully consumed, as indicated by TLC or UHPLC-MS anaylsis. The reaction mixture was filtered through a celite pad, rinsed with CH_2Cl_2, and concentrated under reduced pressure. The ratios of constitutional isomers (branched product to linear product: **100a**:**101a**) and diastereomers (dr) were determined by ^1H NMR or UHPLC-MS.

3.6.3. General procedure for the Ir-catalyzed asymmetric allylic alkylation of β-ketoesters

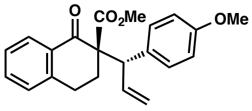
Note: the absolute configuration was determined only for compound **100f** via X-ray analysis (vide infra, Appendix 4). The absolute configuration for all other products **100** has been inferred by analogy. Isolated yields are reported in Figures 3.3.1.1 and 3.3.2.1 (vida infra). For respective HPLC or SFC conditions, please refer to Table 3.6.8.1.



(*R*)-methyl 1-oxo-2-((*S*)-1-phenylallyl)-1,2,3,4-tetrahydronaphthalene-2-carboxylate (100a). In a nitrogen-filled glove box, $[Ir(cod)Cl]_2$ (2.7 mg, 0.004 mmol, 2 mol%), ligand **L12** (3.7 mg, 0.008 mmol, 4 mol%), and TBD (2.8 mg, 0.02 mmol, 10 mol%) were added to a 2 dram scintillation vial equipped with a magnetic stirring bar. The vial was then charged with THF (1 mL) and stirred at 20 °C for 10 min, generating an orange solution. Cinnamyl carbonate (**98a**) (38.3 mg, 0.2 mmol, 1.0 equiv), LiBr (17.3 mg, 0.2 mmol, 1.0 equiv), β-ketoester **97a** (80.8 mg, 0.4 mmol, 2.0 equiv) and another 1 mL of THF were added. The vial was sealed and stirred at 20 °C until allylic carbonate **98a** was fully consumed, as indicated by TLC or UHPLC-MS analysis. THF was evaporated and the crude mixture was then dissolved in CH_2Cl_2, filtered through a celite pad, rinsed with CH_2Cl_2, and concentrated under reduced pressure. The regioselectivity (branched product to linear product: b:l = 95:5) and diastereoselectivity (dr >20:1) were determined by ^{1}H NMR or UHPLC-MS. The residue was purified by silica gel flash chromatography (gradient elution, 2→5% EtOAc in hexanes) to afford **100a** and **101a** (62.6 mg, 98% combined yield). Allylation product **100a** was isolated as a white solid by silica gel chromatography (gradient elution, 0→2% EtOAc in hexanes). >99% ee, $[\alpha]_D^{25}$ +26.3 (*c* 1.11, $CHCl_3$); R_f = 0.3 (5% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.42– 7.39 (m, 3H), 7.28–7.23 (m, 3H), 7.19–7.13 (m, 2H), 6.36 (dt, *J* = 16.8, 10.0 Hz, 1H), 5.21–5.12 (m, 2H), 4.46 (d, *J* = 10.0 Hz, 1H), 3.56 (s, 3H), 3.23 (ddd, *J* = 17.1, 12.1, 4.7 Hz, 1H), 2.88 (ddd, *J* = 17.6, 5.0, 3.0 Hz, 1H), 2.60 (ddd, *J* = 13.7, 4.7, 3.0 Hz, 1H), 2.10 (ddd, *J* = 13.6, 12.1, 5.0 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 193.2, 170.0, 143.1, 139.8, 136.6, 133.6, 132.5, 130.2, 128.8, 128.4, 128.2, 126.9, 126.7, 117.9, 62.7, 53.9, 52.6, 28.8, 26.4; IR (Neat Film, NaCl) 3066, 3028, 2948, 1731, 1685, 1636, 1599, 1491, 1453, 1433, 1358, 1298, 1283, 1238, 1214, 1169, 1108, 1080, 1032, 1001, 980, 926, 892, 808, 743 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{21}H_{21}O_3$ $[M+H]^+$: 321.1485, found 321.1489; HPLC conditions: 2% IPA, 0.6 mL/min, Chiralcel OD-H column, λ = 254 nm, t_R (min): major = 13.80, minor = 17.89.

3.6.4. Spectroscopic data for Ir-catalyzed allylic alkylation products

(*R*)-methyl 2-((*S*)-1-(4-methoxyphenyl)allyl)-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (100b)

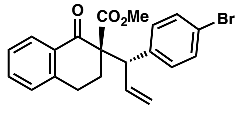


100b

Ketoester **100b** was isolated by silica gel chromatography (gradient elution, 0→5% EtOAc in hexanes) as a white solid. >99% ee, $[\alpha]_D^{25}$ +38.5 (*c* 0.93, $CHCl_3$); R_f = 0.3 (5% EtOAc in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 8.03 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.41 (td, *J* = 7.5, 1.5 Hz, 1H), 7.37–7.31 (m, 2H), 7.31–7.21 (m, 1H), 7.21–7.12 (m, 1H), 6.86–6.75 (m, 2H), 6.32 (dt, *J* = 16.8, 10.0 Hz, 1H), 5.20–5.09 (m, 2H), 4.41 (d, *J* = 9.9 Hz, 1H), 3.75 (s, 3H), 3.56 (s, 3H), 3.23 (ddd, *J* = 17.1, 12.2, 4.6 Hz, 1H), 2.88 (ddd, *J* = 17.6, 4.9, 2.9 Hz, 1H), 2.58 (ddd, *J* = 13.6, 4.7, 3.0 Hz, 1H), 2.11 (ddd, *J* = 13.6, 12.2, 5.0 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 193.3, 170.1, 158.4, 143.2, 136.8, 133.6, 132.5, 131.8, 131.2, 128.8, 128.4, 126.7, 117.6, 113.5, 62.8, 55.3, 53.2, 52.6, 28.7, 26.4; IR (Neat Film, NaCl) 3073, 3003, 2950, 2836, 1732, 1687, 1636, 1608, 1601, 1581, 1511, 1454, 1442, 1435, 1357, 1337, 1303, 1242, 1215, 1181, 1114, 1078, 1033, 1000, 981, 923, 893, 834, 808, 749 cm^{-1}; HRMS (ESI+) *m/z* calc'd for fragment $C_{10}H_{11}O$ [M-

$C_{11}H_{12}O_3$+H]$^+$: 147.0804, found 147.0807; HPLC conditions: 2% IPA, 0.6 mL/min, Chiralpak AD-H column, λ = 254 nm, t_R (min): minor = 27.44, major = 37.29.

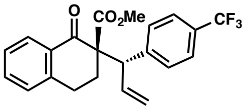
(*R*)-methyl 2-((*S*)-1-(4-bromophenyl)allyl)-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (100c)



100c

Ketoester **100c** was isolated by silica gel chromatography (gradient elution, 0→3% EtOAc in hexanes) as a colorless oil. 99% ee, $[\alpha]_D^{25}$ +49.1 (*c* 1.18, $CHCl_3$); R_f = 0.4 (5% EtOAc in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 8.02 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.43 (td, *J* = 7.5, 1.5 Hz, 1H), 7.39–7.35 (m, 2H), 7.32–7.27 (m, 2H), 7.27–7.25 (m, 1H), 7.15 (dt, *J* = 7.7, 0.9 Hz, 1H), 6.29 (dt, *J* = 16.7, 10.0 Hz, 1H), 5.32–5.03 (m, 2H), 4.37 (d, *J* = 9.9 Hz, 1H), 3.54 (s, 3H), 3.29–3.15 (m, 1H), 2.88 (ddd, *J* = 17.5, 4.9, 2.8 Hz, 1H), 2.57 (ddd, *J* = 13.6, 4.7, 2.9 Hz, 1H), 2.09 (ddd, *J* = 13.5, 12.3, 4.9 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 193.2, 169.9, 143.0, 139.0, 136.1, 133.8, 132.4, 132.0, 131.2, 128.8, 128.4, 126.8, 121.0, 118.5, 62.5, 53.7, 52.7, 29.1, 26.4; IR (Neat Film, NaCl) 3074, 3025, 2949, 1732, 1687, 1683, 1633, 1601, 1488, 1454, 1435, 1403, 1357, 1297, 1240, 1215, 1170, 1141, 1112, 1075, 1032, 1010, 981, 925, 892, 831, 808, 750, 741 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{21}H_{20}{}^{79}BrO_3$ [M+H]$^+$: 399.0590, found 399.0585; HPLC conditions: 2% IPA, 0.6 mL/min, Chiralpak AD-H column, λ = 254 nm, t_R (min): minor = 19.71, major = 23.59.

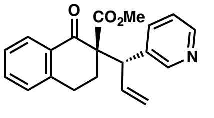
(*R*)-methyl 1-oxo-2-((*S*)-1-(4-(trifluoromethyl)phenyl)allyl)-1,2,3,4-tetrahydronaphthalene-2-carboxylate (100d)



100d

Ketoester **100d** was isolated by silica gel chromatography (gradient elution, 0→5% EtOAc in hexanes) as a colorless oil. >99% ee, $[\alpha]_D^{25}$ +32.4 (*c* 1.51, $CHCl_3$); R_f = 0.3 (5% EtOAc in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 8.03 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.57 (d, *J* = 8.4 Hz, 2H), 7.52 (d, *J* = 8.3 Hz, 2H), 7.44 (td, *J* = 7.5, 1.4 Hz, 1H), 7.28 (t, *J* = 7.5, 1H), 7.16 (d, *J* = 7.7 Hz, 1H), 6.34 (dt, *J* = 16.7, 10.1 Hz, 1H), 5.33–5.08 (m, 2H), 4.45 (d, *J* = 10.0 Hz, 1H), 3.54 (s, 3H), 3.29–3.16 (m, 1H), 2.90 (ddd, *J* = 17.6, 4.9, 2.7 Hz, 1H), 2.60 (ddd, *J* = 13.6, 4.7, 2.8 Hz, 1H), 2.11 (ddd, *J* = 13.5, 12.3, 5.0 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 193.1, 169.9, 144.1, 143.0, 135.8, 133.8, 132.4, 130.6, 129.1 (q, $^2J_{CF}$ = 32.4 Hz), 128.8, 128.4, 126.8, 125.0 (q, $^3J_{CF}$ = 3.8 Hz), 124.3 (q, $^1J_{CF}$ = 272.0 Hz), 118.8, 62.5, 54.1, 52.7, 29.3, 26.4; IR (Neat Film, NaCl) 3074, 2952, 1736, 1733, 1689, 1683, 1616, 1601, 1454, 1435, 1413, 1327, 1241, 1217, 1166, 1123, 1070, 1019, 927, 846, 809, 751, 742 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{22}H_{20}{}^{19}F_3O_3$ $[M+H]^+$: 389.1359, found 389.1346; SFC conditions: 5% IPA, 4.0 mL/min, Chiralpak AD-H column, λ = 254 nm, t_R (min): minor = 3.38, major = 3.91.

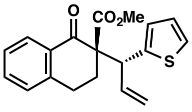
(*R*)-methyl 1-oxo-2-((*S*)-1-(pyridin-3-yl)allyl)-1,2,3,4-tetrahydronaphthalene-2-carboxylate (100e)



100e

Ketoester **100e** was isolated by silica gel chromatography (gradient elution 20→50% EtOAc in hexanes) as a white solid. 98% ee, $[\alpha]_D^{25}$ +64.6 (*c* 0.46, $CHCl_3$); R_f = 0.4 (50% EtOAc in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 8.60 (s, 1H), 8.43 (dd, *J* = 5.0, 1.7 Hz, 1H), 8.02 (dd, *J* = 8.3, 1.3 Hz, 1H), 7.93 (dt, *J* = 8.0, 2.0 Hz, 1H), 7.44 (td, *J* = 7.5, 1.5 Hz, 1H), 7.28 (t, *J* = 7.6 Hz, 1H), 7.23 (dd, *J* = 8.0, 4.8 Hz, 1H), 7.17 (d, *J* = 7.7 Hz, 1H), 6.36–6.29 (m, 1H), 5.22–5.18 (m, 2H), 4.31 (d, *J* = 9.8 Hz, 1H), 3.53 (s, 3H), 3.21 (ddd, *J* = 17.2, 12.3, 4.7 Hz, 1H), 2.91 (ddd, *J* = 17.5, 4.9, 2.7 Hz, 1H), 2.60 (ddd, *J* = 13.5, 4.7, 2.8 Hz, 1H), 2.17 (ddd, *J* = 13.4, 12.3, 4.9 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 193.3, 170.0, 150.9, 147.9, 142.9, 138.4, 136.0, 135.5, 133.9, 132.5, 128.8, 128.4, 126.9, 123.3, 119.2, 62.4, 52.7, 52.5, 29.7, 26.5; IR (Neat Film, NaCl) 3029, 2950, 2848, 1732, 1687, 1599, 1573, 1479, 1454, 1429, 1356, 1295, 1274, 1241, 1216, 1171, 1122, 1077, 1025, 999, 979, 926, 807, 749, 716 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{20}H_{20}NO_3$ $[M+H]^+$: 322.1438, found 322.1442; HPLC conditions: 10% IPA, 1.0 mL/min, Chiralpak AD-H column, λ = 254 nm, t_R (min): minor = 13.45, major = 15.72.

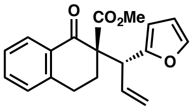
(*R*)-methyl 1-oxo-2-((*R*)-1-(thiophen-2-yl)allyl)-1,2,3,4-tetrahydronaphthalene-2-carboxylate (100f)



100f

Ketoester **100f** was isolated by silica gel chromatography (gradient elution, 0→3% EtOAc in hexanes) as a white solid. 95% ee, $[\alpha]_D^{25}$ –14.2 (*c* 0.86, $CHCl_3$); R_f = 0.4 (5% EtOAc in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 8.08 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.44 (td, *J* = 7.5, 1.4 Hz, 1H), 7.29 (t, *J* = 7.6 Hz, 1H), 7.17 (d, *J* = 7.7 Hz, 1H), 7.14 (dd, *J* = 5.1, 1.2 Hz, 1H), 6.93 (ddd, *J* = 3.6, 1.2, 0.7 Hz, 1H), 6.88 (dd, *J* = 5.1, 3.5 Hz, 1H), 6.23 (dt, *J* = 16.8, 10.0 Hz, 1H), 5.26–5.12 (m, 2H), 4.76 (d, *J* = 10.0 Hz, 1H), 3.59 (s, 3H), 3.25 (ddd, *J* = 17.2, 12.0, 4.8 Hz, 1H), 2.89 (ddd, *J* = 17.5, 5.0, 3.1 Hz, 1H), 2.55 (ddd, *J* = 13.7, 4.8, 3.1 Hz, 1H), 2.12 (ddd, *J* = 13.6, 12.0, 5.0 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 193.2, 169.7, 143.2, 142.3, 135.9, 133.8, 132.3, 128.9, 128.4, 126.9, 126.8, 126.4, 124.9, 118.3, 62.9, 52.7, 49.5, 28.0, 26.2; IR (Neat Film, NaCl) 3071, 2949, 2925, 2853, 1731, 1686, 1639, 1599, 1484, 1453, 1433, 1354, 1293, 1272, 1240, 1214, 1170, 1119, 1078, 1032, 979, 924, 891, 853, 807, 749 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{19}H_{19}SO_3$ $[M+H]^+$: 327.1049, found 327.1048; SFC conditions: 10% IPA, 4.0 mL/min, Chiralcel OJ-H column, λ = 254 nm, t_R (min): major = 2.96, minor = 3.63.

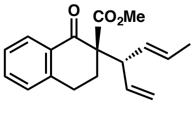
(*R*)-methyl 2-((*R*)-1-(furan-2-yl)allyl)-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (100g)



100g

Ketoester **100g** was isolated by silica gel chromatography (gradient elution, 0→3% EtOAc in hexanes) as a colorless oil. 95% ee, $[\alpha]_D^{25}$ +22.5 (*c* 1.17, $CHCl_3$); R_f = 0.4 (5% EtOAc in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 8.06 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.45 (td, *J* = 7.5, 1.5 Hz, 1H), 7.28 (t, *J* = 7.6 Hz, 1H), 7.25 (dd, *J* = 1.9, 0.9 Hz, 1H), 7.17 (d, *J* = 7.7 Hz, 1H), 6.25 (dd, *J* = 3.2, 1.8 Hz, 1H), 6.19–6.09 (m, 2H), 5.26–5.18 (m, 2H), 4.63 (d, *J* = 9.8 Hz, 1H), 3.63 (s, 3H), 3.24 (ddd, *J* = 17.3, 12.2, 4.8 Hz, 1H), 2.88 (ddd, *J* = 17.5, 4.9, 3.1 Hz, 1H), 2.57 (ddd, *J* = 13.8, 4.8, 3.1 Hz, 1H), 1.99 (ddd, *J* = 13.8, 12.1, 5.0 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 192.7, 169.7, 153.4, 143.3, 141.6, 133.7, 133.6, 132.1, 128.9, 128.4, 126.7, 119.2, 110.3, 108.4, 62.2, 52.7, 47.9, 28.1, 26.1; IR (Neat Film, NaCl) 3116, 3075, 3024, 2950, 2848, 1734, 1731, 1689, 1639, 1600, 1500, 1485, 1453, 1433, 1356, 1293, 1271, 1243, 1216, 1172, 1155, 1120, 1110, 1078, 1012, 981, 965, 928, 905, 892, 806, 745, 736 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{19}H_{19}O_4$ $[M+H]^+$: 311.1278, found 311.1275; SFC conditions: 10% IPA, 2.5 mL/min, Chiralpak AD-H column, λ = 254 nm, t_R (min): major = 5.21, minor = 6.03.

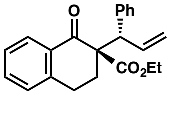
(*R*)-methyl 2-((*S*,*E*)-hexa-1,4-dien-3-yl)-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (100h)



100h

Ketoester **100h** was isolated by silica gel chromatography (gradient elution, 0→2% EtOAc in hexanes) as a colorless oil. 90% ee, $[\alpha]_D^{25}$ +46.4 (*c* 1.02, $CHCl_3$); $R_f = 0.5$ (5% EtOAc in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 8.05 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.45 (td, *J* = 7.5, 1.5 Hz, 1H), 7.30 (t, *J* = 7.6 Hz, 1H), 7.19 (d, *J* = 7.7 Hz, 1H), 5.98–5.87 (m, 1H), 5.74 (ddd, *J* = 15.3, 8.0, 1.6 Hz, 1H), 5.57–5.48 (m, 1H), 5.08–5.03 (m, 2H), 3.61 (s, 3H), 3.47 (t, *J* = 8.4 Hz, 1H), 3.12 (ddd, *J* = 17.0, 12.0, 4.7 Hz, 1H), 2.91 (dt, *J* = 17.4, 4.1 Hz, 1H), 2.45 (ddd, *J* = 13.7, 4.7, 3.3 Hz, 1H), 2.25 (ddd, *J* = 13.7, 11.9, 4.9 Hz, 1H), 1.65 (ddd, *J* = 6.4, 1.7, 0.7 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 194.2, 171.0, 143.1, 136.7, 133.6, 132.8, 129.8, 128.8, 128.2, 128.2, 126.8, 117.6, 62.0, 53.2, 52.4, 29.5, 26.5, 18.2; IR (Neat Film, NaCl) 3075, 3028, 2951, 2854, 1732, 1688, 1600, 1454, 1438, 1356, 1300, 1272, 1235, 1214, 1169, 1122, 1090, 999, 974, 917, 890, 803, 747 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{18}H_{21}O_3$ $[M+H]^+$: 288.1485, found 288.1489; SFC conditions: 2% MeOH, 2.5 mL/min, Chiralpak IC column, λ = 254 nm, t_R (min): minor = 8.23, major = 8.87.

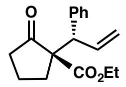
(***R***)-ethyl 1-oxo-2-((***S***)-1-phenylallyl)-1,2,3,4-tetrahydronaphthalene-2-carboxylate (100i)



100i

Ketoester **100i** was isolated by silica gel chromatography (gradient elution, 0→5% EtOAc in hexanes) as a white solid, >99% ee, $[\alpha]_D^{25}$ +42.7 (*c* 1.09, $CHCl_3$); R_f = 0.3 (5% EtOAc in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 8.03 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.46–7.39 (m, 3H), 7.29–7.23 (m, 3H), 7.20–7.12 (m, 2H), 6.37 (dt, *J* = 16.8, 10.0 Hz, 1H), 5.20–5.07 (m, 2H), 4.40 (d, *J* = 9.9 Hz, 1H), 4.07–3.94 (m, 2H), 3.22 (ddd, *J* = 17.3, 12.2, 4.8 Hz, 1H), 2.88 (ddd, *J* = 17.5, 5.0, 2.9 Hz, 1H), 2.58 (ddd, *J* = 13.6, 4.7, 3.0 Hz, 1H), 2.12 (ddd, *J* = 13.6, 12.1, 5.0 Hz, 1H), 1.06 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 193.4, 169.7, 143.0, 140.0, 136.7, 133.5, 132.7, 130.3, 128.7, 128.3, 128.1, 126.9, 126.7, 117.9, 62.3, 61.6, 54.1, 29.2, 26.4, 14.0; IR (Neat Film, NaCl) 3063, 3027, 2978, 2934, 1727, 1699, 1689, 1685, 1599, 1490, 1452, 1363, 1298, 1282, 1235, 1212, 1157, 1107, 1080, 1018, 926, 899, 787, 773, 743 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{22}H_{23}O_3$ $[M+H]^+$: 335.1642, found 335.1651; SFC conditions: 5% IPA, 2.5 mL/min, Chiralpak AD-H column, λ = 254 nm, t_R (min): minor = 13.82, major = 16.53.

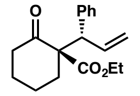
(*R*)-ethyl 2-oxo-1-((*S*)-1-phenylallyl)cyclopentanecarboxylate (103a)



103a

Ketoester **103a** was isolated by silica gel chromatography (gradient elution, 0→5% EtOAc in hexanes) as a colorless oil. 99% ee, $[\alpha]_D^{25}$ –52.5 (*c* 1.04, $CHCl_3$); R_f = 0.3 (5% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31–7.15 (m, 5H), 6.14–6.03 (m, 1H), 5.20–5.10 (m, 2H), 4.37 (d, *J* = 8.9 Hz, 1H), 4.22–4.09 (m, 2H), 2.67 (dddd, *J* = 13.4, 7.1, 3.5, 1.7 Hz, 1H), 2.24–2.14 (m, 1H), 2.13–2.02 (m, 1H), 1.84–1.71 (m, 1H), 1.69–1.59 (m, 1H), 1.59–1.49 (m, 1H), 1.24 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 213.4, 169.2, 139.3, 136.3, 129.9, 128.4, 127.1, 117.8, 65.9, 61.9, 52.8, 38.9, 28.5, 19.7, 14.2; IR (Neat Film, NaCl) 3083, 3062, 3030, 2979, 2891, 1752, 1719, 1639, 1601, 1493, 1465, 1452, 1405, 1365, 1315, 1223, 1138, 1105, 1026, 1003, 923, 864, 826, 757, 707 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{17}H_{21}O_3$ $[M+H]^+$: 273.1485, found 273.1483; HPLC conditions: 2% IPA, 0.6 mL/min, Chiralcel OD-H column, λ = 210 nm, t_R (min): major = 11.23, minor = 12.73.

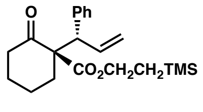
(*R*)-ethyl 2-oxo-1-((*S*)-1-phenylallyl)cyclohexanecarboxylate (103b)



103b

Ketoester **103b** was isolated by silica gel chromatography (gradient elution, 0→5% EtOAc in hexanes) as a white solid. 98% ee, $[\alpha]_D^{25}$ +140.6 (*c* 1.25, $CHCl_3$); R_f = 0.4 (5% EtOAc in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 7.36–7.30 (m, 2H), 7.29–7.22 (m, 2H), 7.21–7.15 (m, 1H), 6.33 (ddd, *J* = 16.9, 10.2, 9.2 Hz, 1H), 5.13–4.99 (m, 2H), 4.11–3.96 (m, 2H), 3.93 (d, *J* = 9.2 Hz, 1H), 2.47–2.39 (m, 2H), 2.36–2.29 (m, 1H), 1.92 (dddd, *J* = 9.5, 4.8, 2.7, 1.5 Hz, 1H), 1.79–1.47 (m, 3H), 1.12 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 206.7, 170.8, 140.0, 137.5, 130.3, 128.0, 126.8, 117.4, 65.5, 61.4, 54.6, 42.1, 35.0, 27.2, 22.8, 14.0; IR (Neat Film, NaCl) 3077, 3028, 2977, 2939, 2865, 1714, 1635, 1600, 1491, 1452, 1388, 1365, 1340, 1309, 1262, 1231, 1204, 1133, 1085, 1020, 1002, 919, 854, 756, 704 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{18}H_{23}O_3$ $[M+H]^+$: 287.1642, found 287.1639; SFC conditions: 10% IPA, 4.0 mL/min, Chiralpak IC column, λ = 210 nm, t_R (min): minor = 1.69, major = 1.94.

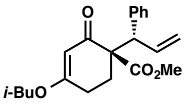
(*R*)-2-(trimethylsilyl)ethyl 2-oxo-1-((*S*)-1-phenylallyl)cyclohexanecarboxylate (103c)



103c

Ketoester **103c** was isolated by silica gel chromatography (gradient elution, 0→2% i-BuOAc in hexanes) as a colorless oil. >99% ee, $[\alpha]_D^{25}$ +91.6 (*c* 0.45, $CHCl_3$); R_f = 0.4 (10% EtOAc in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 7.37–7.32 (m, 2H), 7.24 (ddd, *J* = 8.2, 6.9, 1.4 Hz, 2H), 7.21–7.15 (m, 1H), 6.34 (ddd, *J* = 16.9, 10.2, 9.2 Hz, 1H), 5.21–4.86 (m, 2H), 4.05 (dddd, *J* = 58.0, 11.8, 10.8, 5.9 Hz, 2H), 3.92 (d, *J* = 9.2 Hz, 1H), 2.46–2.40 (m, 2H), 2.38–2.28 (m, 1H), 1.98–1.87 (m, 1H), 1.80–1.71 (m, 1H), 1.72–1.47 (m, 3H), 0.82 (qdd, *J* = 13.6, 11.7, 5.7 Hz, 2H), 0.01 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 206.6, 170.9, 139.9, 137.4, 130.2, 127.9, 126.7, 117.3, 65.4, 63.7, 54.5, 42.0, 34.9, 27.0, 22.7, 17.2, –1.6; IR (Neat Film, NaCl) 2950, 1712, 1452, 1250, 1231, 1133, 921, 859, 837 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{21}H_{30}NaO_3Si$ $[M+Na]^+$: 381.1856, found 381.1865; SFC conditions: 3% IPA, 2.5 mL/min, Chiralcel OJ–H column, λ = 210 nm, t_R (min): minor = 1.93, major = 2.24.

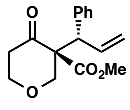
(*R*)-methyl 4-isobutoxy-2-oxo-1-((*S*)-1-phenylallyl)cyclohex-3-enecarboxylate (103d)



103d

Ketoester **103d** was isolated by silica gel chromatography (gradient elution, 0→10% EtOAc in hexanes) as a colorless oil. >99% ee, $[\alpha]_D^{25}$ +31.5 (*c* 1.88, $CHCl_3$); R_f = 0.4 (10% EtOAc in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 7.34–7.29 (m, 2H), 7.27–7.20 (m, 2H), 7.20–7.13 (m, 1H), 6.24 (dt, *J* = 16.7, 10.2 Hz, 1H), 5.28 (s, 1H), 5.18 (ddd, *J* = 16.8, 1.9, 0.8 Hz, 1H), 5.12 (dd, *J* = 10.0, 1.8 Hz, 1H), 4.62 (d, *J* = 10.4 Hz, 1H), 3.64 (s, 3H), 3.53–3.45 (m, 2H), 2.79 (dddd, *J* = 18.3, 11.8, 5.1, 1.6 Hz, 1H), 2.43 (ddd, *J* = 13.4, 5.1, 2.4 Hz, 1H), 2.26 (ddd, *J* = 18.2, 5.5, 2.4 Hz, 1H), 1.94 (dt, *J* = 13.3, 6.7 Hz, 1H), 1.83 (ddd, *J* = 13.4, 11.8, 5.5 Hz, 1H), 0.91 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 192.8, 177.2, 170.0, 139.7, 136.1, 130.2, 128.1, 126.8, 118.0, 102.9, 74.9, 61.1, 52.6, 52.1, 27.7, 26.7, 25.2, 19.11, 19.08; IR (Neat Film, NaCl) 3073, 3029, 2958, 2874, 1727, 1664, 1607, 1582, 1491, 1470, 1452, 1443, 1431, 1406, 1384, 1369, 1316, 1298, 1231, 1193, 1177, 1140, 1116, 1079, 1012, 987, 921, 903, 844, 817, 788, 764, 724 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{21}H_{27}O_4$ $[M+H]^+$: 343.1904, found 343.1905; SFC conditions: 10% IPA, 2.5 mL/min, Chiralcel OD-H column, λ = 254 nm, t_R (min): major = 3.71, minor = 6.24.

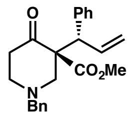
(*S*)-methyl 4-oxo-3-((*S*)-1-phenylallyl)tetrahydro-2*H*-pyran-3-carboxylate (103e)



103e

Ketoester **103e** was isolated by silica gel chromatography (gradient elution, 5→10% EtOAc in hexanes) as a colorless oil. 98% ee, $[\alpha]_D^{25}$ +71.1 (*c* 0.88, $CHCl_3$); R_f = 0.2 (10% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35–7.30 (m, 2H), 7.31–7.25 (m, 2H), 7.24–7.19 (m, 1H), 6.43 (ddd, *J* = 16.9, 10.2, 9.4 Hz, 1H), 5.19–5.03 (m, 2H), 4.28 (dd, *J* = 11.9, 1.2 Hz, 1H), 4.03 (dddd, *J* = 11.1, 6.2, 4.9, 1.3 Hz, 1H), 3.98 (d, *J* = 9.4 Hz, 1H), 3.82 (dddd, *J* = 11.3, 9.0, 4.5, 0.6 Hz, 1H), 3.67 (d, *J* = 11.8 Hz, 1H), 3.61 (s, 3H), 2.70 (ddd, *J* = 14.5, 8.9, 6.2 Hz, 1H), 2.57 (dt, *J* = 14.5, 4.7 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 202.8, 169.7, 138.6, 136.7, 129.8, 128.4, 127.4, 118.0, 73.2, 68.6, 67.1, 52.4, 51.6, 41.9; IR (Neat Film, NaCl) 3063, 3029, 2973, 2951, 2863, 1746, 1716, 1635, 1600, 1492, 1472, 1454, 1433, 1378, 1360, 1310, 1290, 1229, 1212, 1176, 1140, 1112, 1085, 1033, 1001, 978, 925, 826, 763, 741 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{16}H_{19}O_4$ $[M+H]^+$: 275.1278, found 275.1282; SFC conditions: 5% IPA, 2.5 mL/min, Chiralpak AD-H column, λ = 210 nm, t_R (min): minor = 4.65, major = 4.95.

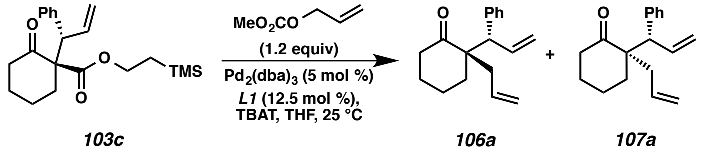
(*S*)-methyl 1-benzyl-4-oxo-3-((*S*)-1-phenylallyl)piperidine-3-carboxylate (103f)



103f

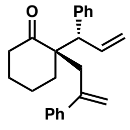
Ketoester **103f** was isolated by silica gel chromatography (gradient elution, 5→10% EtOAc in hexanes) as a colorless oil. 97% ee, $[\alpha]_D^{25}$ +34.3 (*c* 0.87, $CHCl_3$); R_f = 0.3 (10% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39–7.29 (m, 5H), 7.28–7.24 (m, 2H), 7.24–7.14 (m, 3H), 6.44 (ddd, *J* = 16.9, 10.2, 9.3 Hz, 1H), 5.12–5.04 (m, 2H), 4.03 (d, *J* = 9.4 Hz, 1H), 3.59 (s, 3H), 3.64–3.54 (m, 2H), 3.15 (dd, *J* = 11.9, 2.0 Hz, 1H), 2.82–2.75 (m, 1H), 2.71 (ddd, *J* = 14.1, 8.5, 5.7 Hz, 1H), 2.65–2.56 (m, 2H), 2.53 (ddd, *J* = 13.9, 5.4, 4.3 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 205.3, 170.6, 139.4, 138.0, 137.4, 129.9, 129.2, 128.5, 128.2, 127.5, 127.1, 117.6, 66.1, 62.0, 60.2, 53.4, 53.0, 52.0, 40.9; IR (Neat Film, NaCl) 3060, 3027, 2949, 2811, 2765, 1718, 1631, 1600, 1584, 1493, 1468, 1452, 1432, 1364, 1345, 1310, 1286, 1228, 1194, 1138, 1073, 1047, 1028, 1001, 973, 922, 821, 740 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{23}H_{26}NO_3$ $[M+H]^+$: 364.1907, found 364.1908; SFC conditions: 10% IPA, 4.0 mL/min, Chiralpak AD-H column, λ = 210 nm, t_R (min): major = 2.49, minor = 2.94.

3.6.5. General procedure for Pd-catalyzed allylic alkylation



(*R*)-2-allyl-2-((*S*)-1-phenylallyl)cyclohexanone (106a). To a 0.5 dram scintillation vial equipped with a magnetic stir bar were added $Pd_2(dba)_3$ (1.3 mg, 0.0014 mmol), **L8** (1.2 mg, 0.0035 mmol), TBAT (16.6 mg, 0.031 mmol) and THF (0.9 mL) in a nitrogen-filled glove box. The dark purple mixture was stirred at ambient glove box temperature (ca. 30 °C) for 35 minutes at which point the mixture had become red-orange. Ketoester **103c** (10.0 mg, 0.028 mmol) and allyl methylcarbonate (4.1 mg, 0.035 mmol) were then added neat to the reaction mixture. The resulting yellow-green reaction mixture was stirred at 20 °C until full conversion of the starting material was indicated by TLC analysis (reaction times typically ranged from 24 to 36 hours). The vial was removed from the glove box, uncapped and diluted with 2 ml of hexanes. Filtration through a celite pad afforded the crude residue, which was concentrated *in vacuo* and analyzed by ^{1}H NMR to determine the diastereomeric ratio of **106a** and **107a** (2:1). The residue was purified by silica gel flash chromatography (gradient elution, 0→2% EtOAc in hexanes) to afford **106a** and **107a** (6.5 mg, 91% combined yield) as a colorless oil. 99% ee (The enantiomeric excesses of the products **106a** and **107a** are inferred from the corresponding Ir-catalyzed allylic alkylation products (**103c**)). Spectroscopic data for compound **106a** is as follows: $[\alpha]_D^{25}$ –1.9 (*c* 0.48, $CHCl_3$); $R_f = 0.3$ (0.4% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33–7.28 (m, 2H), 7.25–7.20 (m, 3H), 6.20 (dt, *J* = 16.8, 10.1 Hz, 1H), 5.68 (dddd, *J* = 17.1, 10.1, 8.8, 5.4 Hz, 1H), 5.09 (ddd, *J* = 10.1, 1.6, 0.4 Hz, 1H), 5.08 (ddd, *J* = 16.7, 1.7, 0.8 Hz, 1H), 4.98 (dddd, *J* = 10.2, 2.3, 1.3, 0.7 Hz, 1H), 4.92–4.86 (m, 1H), 3.92 (d, *J* = 9.9 Hz, 1H), 2.75 (dd, *J* = 13.7, 5.4 Hz, 1H), 2.56–2.10 (m, 2H), 2.11–1.59 (m, 7H); ^{13}C NMR (126 MHz, CDCl$_3$) δ 212.9, 140.1, 136.3, 134.9, 130.0, 128.1, 126.8, 117.9, 117.4, 55.7, 52.8, 40.5, 37.6, 31.9, 26.2, 21.1; IR (Neat Film, NaCl) 3073, 3028, 2937, 2864, 1833, 1701, 1636, 1600, 1452, 1432, 1313, 1219, 1125, 1056, 1002, 916, 849, 787, 765 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{18}H_{23}O$ $[M+H]^+$: 255.1754; found 255.1743. Spectroscopic data for compound **107a** is as follows: $[\alpha]_D^{25}$ +6.1 (*c* 0.75, CHCl$_3$); R_f = 0.3 (0.4% EtOAc in hexanes); ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.33–7.28 (m, 2H), 7.25–7.20 (m, 3H), 6.19 (dt, *J* = 16.8, 10.1 Hz, 1H), 5.65 (dddd, *J* = 17.1, 10.1, 8.8, 5.4 Hz, 1H), 5.17 (dd, *J* = 1.7, 1.0, 1H), 5.15 (dd, *J* = 1.7, 1.0, 1H) 5.07–5.02 (m, 2H) 3.95 (d, *J* = 8.5, 1H), 2.75 (dd, *J* = 13.7, 5.4 Hz, 1H), 2.56–2.10 (m, 2H), 2.11–1.59 (m, 7H); ^{13}C NMR (126 MHz, CDCl$_3$) δ 213.2, 140.3, 138.0, 134.1, 129.8, 128.3, 126.8, 118.0, 117.8, 55.6, 53.4, 40.6, 38.6, 32.2, 25.6, 20.8; IR (Neat Film, NaCl) 3073, 3028, 2937, 2864, 1833, 1701, 1636, 1600, 1452, 1432, 1313, 1219, 1125, 1056, 1002, 916, 849, 787, 765 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{18}H_{23}O$ $[M+H]^+$: 255.1754; found 255.1750.

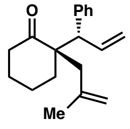
(*R*)-2-((*S*)-1-phenylallyl)-2-(2-phenylallyl)cyclohexanone (106b)



106b

Ketone **106b** was isolated by silica gel chromatography (gradient elution, 0→1% Et_2O in hexanes) as a colorless oil. $[\alpha]_D^{25}$ –50.9 (*c* 0.22, $CHCl_3$); R_f = 0.5 (10% EtOAc in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 7.32–7.13 (m, 10H), 6.24 (dt, *J* = 16.8, 10.1 Hz, 1H), 5.29 (d, *J* = 1.8 Hz, 1H), 5.22–5.02 (m, 3H), 3.92 (d, *J* = 10.0 Hz, 1H), 2.95 (ddd, *J* = 377.8, 13.8, 0.9 Hz, 2H), 2.15–2.00 (m, 2H), 1.76–1.57 (m, 4H), 1.54–1.43 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 212.8, 145.6, 142.8, 140.3, 136.2, 129.9, 128.1, 128.0, 127.0, 126.7, 126.5, 118.2, 117.7, 56.6, 54.4, 40.6, 37.6, 30.6, 24.8, 21.4; IR (Neat Film, NaCl) 2937, 2859, 1701, 1624, 1597, 1451, 1310, 1256, 1207, 1125 910, 779 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{24}H_{26}O$ $[M+H]^+$: 331.2056, found 331.2065.

(*R*)-2-(2-methylallyl)-2-((*S*)-1-phenylallyl)cyclohexanone (106c)

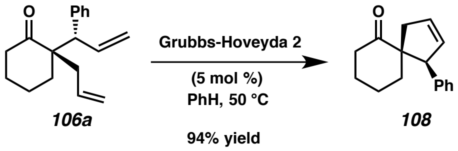


106c

Ketone **106c** was isolated by silica gel chromatography (gradient elution, 0→2% EtOAc in hexanes) as a colorless oil. $[\alpha]_D^{25}$ –41.7 (*c* 0.46, $CHCl_3$); R_f = 0.4 (5% EtOAc in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 7.33–7.28 (m, 2H), 7.25–7.19 (m, 3H), 6.19 (dt, *J* = 16.8, 10.1 Hz, 1H), 5.08 (dd, *J* = 10.2, 1.6 Hz, 1H), 5.03 (ddd, *J* = 16.8, 1.6, 0.8 Hz, 1H), 4.74 (ddt, *J* = 2.7, 1.8, 0.9 Hz, 1H), 4.52 (ddt, *J* = 2.4, 1.6, 0.9 Hz, 1H), 3.86 (d, *J* = 10.0 Hz, 1H), 2.90 (d, *J* = 13.1 Hz, 1H), 2.37 (dtd, *J* = 16.2, 4.9, 1.6 Hz, 1H), 2.25 (ddd, *J* = 15.9, 11.3, 6.0 Hz, 1H), 2.00 (d, *J* = 13.7 Hz, 1H), 1.93–1.78 (m, 2H), 1.74–1.63 (m, 4H), 1.59 (dt, *J* = 1.4, 0.7 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 212.8, 143.0, 140.3, 136.5, 130.1, 128.2, 126.9, 117.4, 115.3, 55.5, 54.2, 40.7, 40.2, 30.8, 25.5, 25.1, 21.4; IR (Neat Film, NaCl) 3071, 3030, 2940, 2865, 1704, 1637, 1599, 1452, 1375, 1314, 1209, 1124, 994, 916, 893, 756 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{19}H_{25}O$ $[M+H]^+$: 269.1920; found 269.1920.

3.6.6. Determination of the relative configuration of compound 106a

The relative configuration of compound **106a** was determined via NOE analysis of the corresponding spirocycle, **108**, obtained via ring-closing metathesis. The experimental procedure by which **108** was generated is as follows:

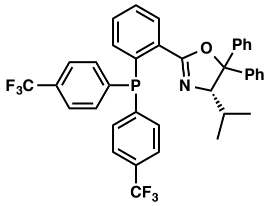


(1*S*,5*R*)-1-phenylspiro[4.5]dec-2-en-6-one (108). To a flask charged with Grubbs-Hoveyda second generation catalyst (1.85 mg, 0.0030 mmol) under an atmosphere of argon was added a solution of cyclohexanone **106a** (15.0 mg, 0.059 mmol) in 6 mL benzene. The reaction mixture was heated to 50 °C and stirred for 4 hours, at which point the reaction was determined to be complete by TLC analysis. The reaction vessel was cooled to 25 °C and 0.5 mL of ethyl vinyl ether was added. After 30 minutes of stirring, the crude mixture was purified directly by silica gel chromatography (gradient elution, 0→3% EtOAc in hexanes) to afford spirocycle **108** (12.7 mg, 0.056 mmol, 94% yield) as a colorless oil. $[\alpha]_D^{25}$ –133.6 (*c* 0.25, $CHCl_3$); R_f = 0.5 (10% EtOAc in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 7.32–7.24 (m, 2H), 7.24–7.18 (m, 1H), 7.18–7.12 (m, 2H), 6.01–5.52 (m, 1H), 4.75 (p, *J* = 2.1 Hz, 1H), 2.66–2.56 (m, 2H), 2.56–2.44 (m, 2H), 1.95–1.85 (m, 1H), 1.64–1.49 (m, 3H), 1.42 (dtd, *J* = 14.66, 3.6, 2.3 Hz, 1H), 1.35–0.72 (m, 1H), 1.01 (ddd, *J* = 13.9, 11.3, 4.5 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 212.9, 140.6, 133.8, 129.3, 128.0, 127.4, 126.4, 59.8, 53.7, 42.8, 39.6, 35.5, 26.8, 22.2; IR (Neat Film, NaCl) 3944, 3693, 3053, 2986, 2941, 2866, 2685, 2305, 1698, 1422, 1264, 1129, 896, 756 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{16}H_{19}O$ $[M+H]^+$: 227.1430; found 227.1431.

3.6.7. Spectroscopic data for new phosphinooxazoline ligands

Phosphinooxazoline ligands **L14** and **L15** employed in these studies were generously donated by Dr. Robert A. Craig. They were generated following the method reported by McDougal and Stoltz. Comprehensive preparatory detail can be found in the Thesis of Dr. Craig.

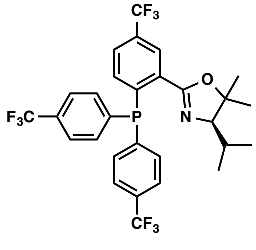
(*S*)-2-(2-(bis(4-(trifluoromethyl)phenyl)phosphino)phenyl)-4-isopropyl-5,5-diphenyl-4,5-dihydrooxazole (*L14*)



L14

$[\alpha]_D^{25}$ –163.33 (*c* 0.75, $CHCl_3$,); R_f = 0.3 (4:1 hexanes in dichloromethane); ^1H NMR (500 MHz, C_6D_6) δ 8.22 (ddd, *J* = 7.8, 3.9, 1.4 Hz, 1H), 7.29 (ddd, *J* = 49.4, 8.4, 1.4 Hz, 4H), 7.21–7.14 (m, 5H), 7.10–7.02 (m, 7H), 7.02–6.94 (m, 3H), 6.89 (td, *J* = 7.6, 1.4 Hz, 1H), 6.81 (ddd, *J* = 7.9, 3.4, 1.3 Hz, 1H), 4.66 (d, *J* = 4.5 Hz, 1H), 1.74 (td, *J* = 6.6, 4.6 Hz, 1H), 0.83 (d, *J* = 6.7 Hz, 3H), 0.59 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (126 MHz, C_6D_6) δ 160.1 (d, J_{CP} = 3.2 Hz), 145.8 , 144.4–143.9 (m) 141.2 , 137.9 (d, J_{CP} = 27.4 Hz), 134.9, 134.5 (dd, J_{CP} = 70.9, 20.8 Hz), 132.6 (d, J_{CP} = 21.4 HZ), 131.3 , 130.6 (dd, J_{CP} = 32.3, 18.4 Hz), 130.3 (d, J_{CP} = 3.2 Hz), 129.1, 127.5 (d, J_{CF} = 11.2 Hz), 126.8, 125.3 (ddt, J_{CF} = 14.7, 7.6, 3.8 Hz), 124.8 (d, J_{CF} = 273.5 Hz), 93.1, 81.1 (d J_{CP} = 2.0 Hz), 30.60, 22.0; ^{19}F NMR (282 MHz, C_6D_6) δ –62.44, –62.53; ^{31}P NMR (121MHz, C_6D_6) δ –7.59; IR (Neat Film, NaCl) 3060, 2961, 1654, 1605, 1493, 1470, 1448, 1396, 1323, 1166, 1127, 1060, 1016, 954, 832, 756 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{28}H_{30}{}^{19}F_6NOP$ $[M+H]^+$: 662.2042, found 662.2080.

(*R*)-2-(2-(bis(4-(trifluoromethyl)phenyl)phosphino)-5-(trifluoromethyl)phenyl)-4-isopropyl-5,5-dimethyl-4,5-dihydrooxazole (*L15*)



L15

$[\alpha]_D^{25}$ +9.45 (*c* 3.20, $CHCl_3$,); R_f = 0.3 (4:1 hexanes in dichloromethane); ^{1}H NMR (500 MHz, C_6D_6) δ 8.57 (dd, *J* = 3.3, 2.0 Hz, 1H), 7.41–7.36 (m, 4H), 7.21–7.15 (m, 4H), 7.10 (dd, *J* = 8.2, 2.0 Hz, 1H), 6.78 (dd, *J* = 8.0, 3.0 Hz, 1H), 3.22 (d, *J* = 8.4 Hz, 1H), 1.55 (ddt, *J* = 13.0, 8.3, 6.5 Hz, 1H), 1.21 (s, 3H), 1.08 (s, 3H), 0.99 (d, J = 6.5 Hz, 3H), 0.75 (d, J = 6.5 Hz, 3H); ^{13}C NMR (126 MHz, C_6D_6) δ 159.1 (d, J_{CP} = 4.0 Hz), 143.5 (t, J_{CP} = 14.8 Hz), 142.7 (d, J_{CP} = 30.6 Hz), 134.5 (dd, J_{CP} = 21.3, 15.7 Hz), 133.7 (d, J_{CP} = 19.5 Hz), 131.1 (q, J_{CF} = 3.6 Hz), 126.4–126.1 (m), 125.9 (d, J_{CF} = 3.2 Hz), 126.5–125.0 (m), 123.8 (d, J_{CF} = 3.3 Hz), 123.3, 87.2, 81.7 (d, J_{CP} = 1.5 Hz), 29.1, 28.8, 21.1, 20.8, 20.8 (d, J_{CP} = 1.8 Hz); ^{19}F NMR (282 MHz, C_6D_6) δ –62.63, –62.85; ^{31}P NMR (121MHz, C_6D_6) δ –7.10; IR (Neat Film, NaCl) 2974, 1652, 1397, 1323, 1165, 1128, 1060, 1017, 832, 756 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{29}H_{26}O^{19}F_9NP$ [M+H]$^+$: 606.1608, found 606.1585.

3.6.8 Determination of enantiomeric excess

Table 3.6.8.1. *Determination of enantiomeric excess*

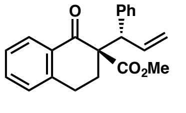
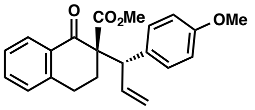
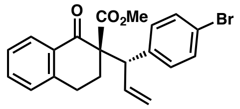
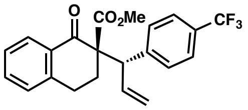
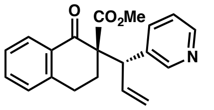
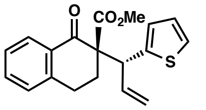
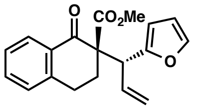
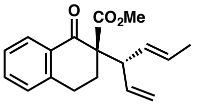
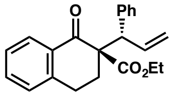
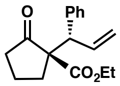
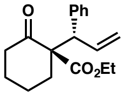
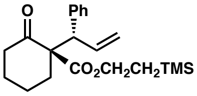
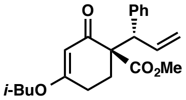
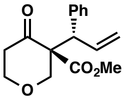
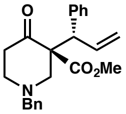
entry	compound	analytic conditions	ee (%)
1		**HPLC** **Chiralcel OD-H, ∈≈ = 254 nm** **2% IPA/hexanes, 0.6 mL/min** **t_R (min): major 13.80, minor 17.89**	>99
2		**HPLC** **Chiralpak AD-H, ∈≈ = 254 nm** **2% IPA/hexanes, 0.6 mL/min** **t_R (min): minor 27.44, major 37.29**	>99
3		**HPLC** **Chiralpak AD-H, ∈≈ = 254 nm** **2% IPA/hexanes, 0.6 mL/min** **t_R (min): minor 19.71, major 23.59**	99
4		**SFC** **Chiralpak AD-H, ∈≈ = 254 nm** **5% IPA/CO_2, 4.0 mL/min** **t_R (min): minor 3.38, major 3.91**	>99
5		**HPLC** **Chiralpak AD-H, ∈≈ = 254 nm** **90% IPA/hexanes, 1.0 mL/min** **t_R (min): minor 13.45, major 15.72**	98
6		**SFC** **Chiralcel OJ-H, ∈≈ = 254 nm** **10% IPA/CO_2, 4.0 mL/min,** **t_R (min): major 2.96, minor 3.63**	95
7		**SFC** **Chiralpak AD-H, ∈≈ = 254 nm** **10% IPA/CO_2, 2.5 mL/min,** **t_R (min): major 5.21, minor 6.03**	95
8		**SFC** **Chiralpak IC, ∈≈ = 254 nm** **2% MeOH/CO_2, 2.5 mL/min,** **t_R (min): minor 8.23, major 8.87**	90

Table 3.6.8.2 *Determination of enantiomeric excess continued*

entry	compound	analytic conditions	ee (%)
9		SFC Chiralpak AD-H, ∈≈ = 254 nm 5% IPA/CO_2, 2.5 mL/min, t_R (min): minor 13.82, major 16.53	>99
10		HPLC Chiralcel OD-H, ∈≈ = 220 nm 2% IPA/hexanes, 0.6 mL/min t_R(min): major 11.23, minor 12.73	99
11		SFC Chiralpak IC, ∈≈ = 210 nm 10% IPA/CO_2, 4.0 mL/min t_R (min): minor 1.69, major 1.94	98
12		SFC Chiralcel OJ-H, ∈≈ = 210 nm 3% IPA/CO_2, 2.5 mL/min t_R (min): minor 1.93, major 2.24	>99
13		SFC Chiralcel OD-H, ∈≈ = 254 nm 10% IPA/CO_2, 2.5 mL/min t_R (min): major 3.71, minor 6.24	>99
14		SFC Chiralpak AD-H, ∈≈ = 210 nm 5% IPA/CO_2, 2.5 mL/min t_R (min): minor 4.65, major 4.95	98
15		SFC Chiralpak AD-H, ∈≈ = 210 nm 10% IPA/CO_2, 4.0 mL/min t_R (min): major 2.49, minor 2.94	97

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(89) Poor regioselectivity was observed when aliphatic allyl carbonates, such as crotyl carbonate, were employed.

(90) See Appendix A4 for details.

(91) We and others have extensively investigated the enantioselective decarboxylative allylic alkylation of cyclic systems, see references 3, 9, 10, 15, 16a, 16d, 25 and: Burger, E. C.; Barron, B. R.; Tunge, J. A. *Synlett* **2006**, 2824.

(92) Attempts to establish a single-vessel diallylation protocol have, thus far, proved unsuccessful. Subjecting allyl 2-oxocyclohexanecarboxylate to the optimized reaction conditions resulted in nonstereoselective decarboxylative allylic alkylation. Sequential addition of all reaction components also failed.

(93) See experimental section for the determination of the relative configuration. **Error! Bookmark not defined.**

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