CHAPTER 4

Enantio-, Diastereo- and Regioselective Iridium-Catalyzed Asymmetric Allylic Alkylation of Acyclic β-Ketoesters[1]

4.1 INTRODUCTION

4.1.1 State of the art in the asymmetric construction of vicinal quaternary and tertiary carbon centers

As outlined in Chapter 3 (vide supra), the generation of enantioenriched all-carbon quaternary centers is complicated by the presence of vicinal tertiary stereocenters due to increased steric demands and the introduction of requisite diastereocontrol. Modern strategies for accessing these highly-congested stereochemical dyads have relied primarily on transition-metal catalysis, notably Pd-catalyzed enolate alkylation cascades,[30] Pd-catalyzed trimethylenemethane cycloadditions,[73b,e] Cu-catalyzed asymmetric Claisen rearrangements,[73f] and Mo-[73c,d] and Ir-catalyzed[83] allylic alkylations. Common to the majority of these reports is the constraint that the nascent quaternary center be formed at a cyclic nucleophile. At the outset of our studies in this area, only two groups had reported success in employing linear nucleophiles to produce vicinal

[1] This work was performed in collaboration with Wen-Bo Lui, postdoctoral researcher in the Stoltz group. This work has been published. See: Liu, W. -B.; Reeves, C. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2013**, *135*, 17298.
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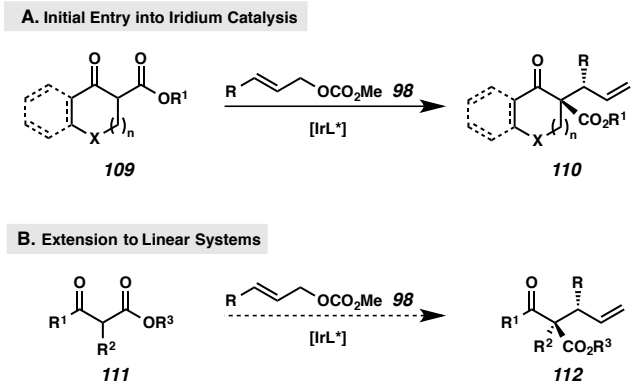
quaternary/tertiary arrays. Namely, Trost's communication on the molybdenum-catalyzed allylic alkylation of β-cyanoesters[73d] and Carreira's recent report on the allylic alkylation of aldehydes using stereodivergent dual catalysis.[83] To address these limitations, we initiated studies investigating the asymmetric allylic alkylation of linear β-ketoesters.

As described above, we have shown iridium-*N*-arylphosphoramidite catalysis[87] to be a powerful tool for accessing vicinal all-carbon quaternary and tertiary stereocenters. The success of our protocol for the regio-, diastereo- and enantioselective asymmetric allylic alkylation of cyclic β-ketoesters (Figure 4.1.1.1A)[82, 88, 97] combined with the virtual absence of reports describing the application of this transformation to acyclic β-ketoesters encouraged our further exploration of iridium catalysts in the domain of this important substrate class. In this chapter, we detail the development of the first highly regio-, diastereo- and enantioselective allylic alkylation of acyclic β-ketoesters to forge vicinal tertiary, quaternary centers (Figure 4.1.1.1B).

Figure 4.1.1.1. *Representative Ir-catalyzed asymmetric allylic alkylation*

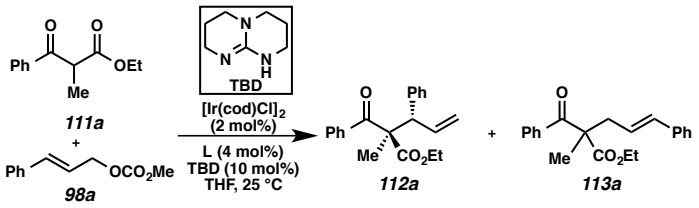


4.2 DEVELOPMENT AND OPTIMIZATION OF AN IRIDIUM-CATALYZED ALLYLIC ALKYLATION OF LINEAR β-KETOESTERS

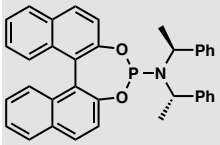
Our initial investigations in the domain of Ir-catalyzed allylic alkylation of linear β-ketoesters focused on identifying conditions that would afford both reaction efficiency and selectivity. We chose ethyl 2-methyl-3-oxo-3-phenylpropanoate (**111a**) and cinnamyl carbonate (**98a**) as standard coupling partners, and investigated several iridacycle complexes[84] at the outset of our studies. The result of these studies are shown in Table 4.2.1 (entries 1–6). We found that exposure of standard coupling components (**111a**) and (**98a**) to a combination of catalytic phosphoramidite ligand **L10•**$[Ir(cod)Cl]_2$ complex[86] and two equivalents of NaH in THF at ambient temperature afforded the desired product with good conversion, ee and regioselectivity, but low levels of diastereoselectivity (1:2) (entry 1). Use of either **L11** or **L16** under these conditions favored instead the reaction pathway yielding the undesired, linear allylic alkylation product (**113a**) in only modest conversion (entries 2 and 4). Ligands **L13** and **L17**[87,98] gave the desired branched product in good conversion but with diminished diastereoselectivity and enantioselectivity and protracted reaction times (entries 5 and 6). We were pleased to find that tetrahydroquinoline based ligand **L12**[87] rapidly furnished the desired α-quaternary β-ketoester (**112a**) in greater than 95% conversion, 95:5 regioselectivity, 13:1 dr and 99% enantiomeric excess (entry 3). Previous reports demonstrating the marked effect of metal cations over regio-[99] and diastereoselectivity[100] in iridium-catalyzed allylic alkylations prompted further investigation of both bases and additives (entries 7–15). Contrary to our previous findings (vide infra, Chapter 3), a

sluggish reaction was observed when LiBr was used in place of NaH (entry 7), presumably due to the decreased α-acidity of acyclic β-ketoesters relative to cyclic substrates. While amine and organic bases did not perform well in the chemistry, the use of alkoxide bases resulted in considerably reduced reaction times (entries 8–9). Ultimately, it was found that the use of LiO*t*-Bu as base was optimal, delivering β-ketoester **112a** with an exceptional branched to linear ratio (93:7), >20:1 diastereoselectivity, and 98% enantioselectivity in only two hours (entry 8).

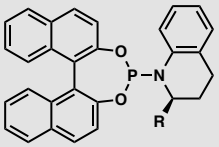
Table 4.2.1. *Optimization of the Ir-catalyzed asymmetric allylic alkylation*[a]



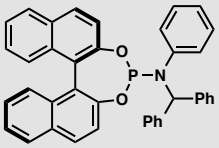
entry	*L*	base/additive (x equiv)	time (h)	conv. (%)[b]	yield (%)[c]	*112a:113a*[b]	dr of *112a*[b]	ee of *112* (%)[d]
1	*L10*	NaH (2)	22	91	–	89:11	1:1.8	81(97)
2	*L11*	NaH (2)	48	46	–	17:83	1:1	-
3	*L12*	NaH (2)	22	>95	64	95:5	13:1	99
4	*L16*	NaH (2)	48	34	–	42:58	3.5:1	-
5	*L13*	NaH (2)	72	>95	–	71:29	2:1	76
6	*L17*	NaH (2)	72	>95	–	93:7	7.3:1	72
7	*L12*	LiBr (1)	32	>95	91	95:5	>20:1	>99
8	*L12*	*LiOt-Bu (2)*	*2*	*>95*	*97*	*93:7*	*>20:1*	*98*
9	*L12*	KO*t*-Bu (2)	4	>95	–	93:7	2:1	94(87)
10	*L12*	Cs_2CO_3 (2)	4	>95	–	83:17	1:2.2	87(94)
11	*L12*	DABCO (2)	24	>95	–	81:19	1:2.7	64(82)
12	*L12*	proton sponge (2)	4	>95	–	90:10	1:1	87(93)
13	*L12*	DMAP (2)	4	>95	–	83:17	1:1.4	91(93)
14	*L12*	Bu_4NBr (1)	3	>95	–	88:12	1:2.6	87(93)
15	*L12*	$BnMe_3NBr$ (1)	4	>95	–	86:14	1:1	91(95)



(S,S,S_a)-L10
(S,S,R_a)-L11



R = Me: (R, R_a)-L12
R = Me: (R, S_a)-L16
R = H: (R_a)-L13



(R_a)-L17

[a] Reactions performed with 0.1 mmol of **98a**, 0.2 mmol of **111a** at 0.1 M in THF at 20 °C. [b] Determined by ^{1}H NMR and UHPLC-MS analysis of the crude mixture. [c] Determined by chiral SFC analysis; parenthetical value is the ee of the alternate diastereomer. [d] Not determined.

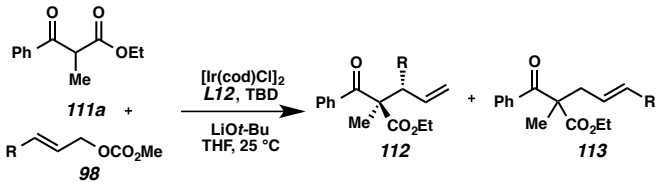
4.3 EXPLORATION OF THE REACTION SCOPE AND SUBSTITUENT EFFECTS

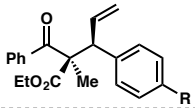
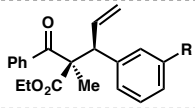
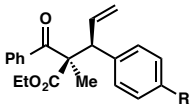
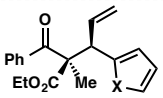
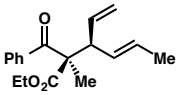
4.3.1 Exploration of the iridium-catalyzed allylic alkylation of linear β-ketoesters with respect to allyl electrophile

With optimized conditions identified, the scope of the reaction with respect to the electrophile was next explored. A highly selective reaction was observed between β-

ketoester **111a** and various cinnamyl carbonate-derived electrophiles (**98**) bearing electron-donating substitutents about the aryl group, R (Table 4.3.1.1, entries 2–4). 4-Me- (**98i**), 4-MeO- (**98b**), and 3-MeO-substitutions (**98j**) about the aryl ring gave the corresponding α-quaternary β-ketoesters (products **112b**-**112d**) in good to excellent yield, dr, ee and branched to linear ratio (Table 4.3.1.1). Electron deficient aryl substituents at the allyl group (entries 5–7) were also well tolerated, delivering the branched products **112e–112g**[101] in good to excellent yield, outstanding ee and dr, and with only slightly diminished regioselectivies. Interestingly, (4-nitro)-aryl substitution at the allyl carbonate (entry 8, substrate **98l**) led to loss of regioselectivity in the reaction, giving equal amounts of products **112h** (14:1 dr, 93% ee) and **113h** (23% ee). We were pleased to discover, however, that heteroaryl-substituted allyl carbonates (substrates **98j** and **98g**) resulted in smooth reactions and delivered the alkylated products **112i** and **112j** with excellent yield, ee and regioselectivity and with good to excellent dr (entries 9–10). Finally, we found that sorbyl carbonate **98h** was also a suitable participant in the reaction, giving the corresponding β-ketoester product (**112k**) in good yield and dr and with excellent regio- and enantioselectivities (entry 11).

Table 4.3.1.1. *Exploration of the reaction scope with respect to allyl electrophile*[a]



entry	98	product (*112*)		yield (%)[b]	*112*:*113*[c]	dr of *112*[c]	ee of *112* (%)[d]
1	*98a*		*112a*: R = H	97	93:7	>20:1	98
2	*98i*		*112b*: R = Me	97	95:5	20:1	>99
3[e]	*98b*		*112c*: R = MeO	85	99:1	>20:1	>99
4	*98j*		*112d*: R = MeO	99	90:10	17:1	>99
5	*98k*		*112e*: R = Cl	98	84:16	19:1	99
6	*98c*		*112f*: R = Br	98	86:14	14:1	>99
7	*98d*		*112g*: R = CF_3	86	78:22	16:1	99
8	*98l*		*112h*: R = NO_2	78	50:50[f]	14:1	93
9	*98f*		*112i*: X = S	99	97:3	8:1	95
10	*98g*		*112j*: X = O	93	95:5	13:1	>99
11	*98h*		*112k*	76	95:5	6:1	91

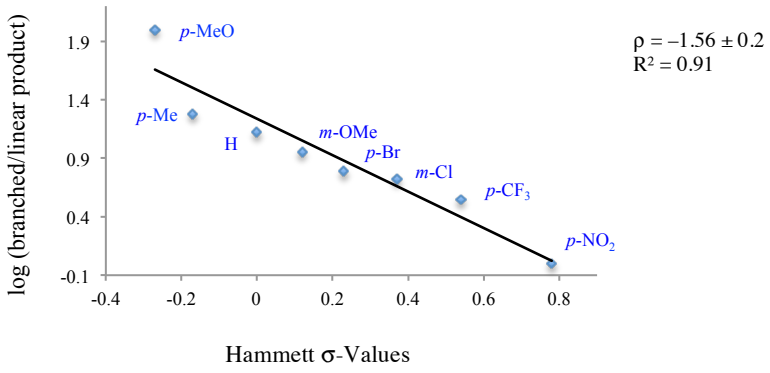
[a] Reactions performed under the conditions of Table 1, entry 8. [b] Combined isolated yield of **112** and **113**. [c] Determined by ^{1}H NMR analysis of the crude mixture. [d] Determined by chiral SFC analysis of the major diastereomer. [e] Conditions of Table 1, entry 7. [f] 23% ee for the linear product.

4.3.2 Investigation of allyl electrophile substituent effects on reaction selectivity

During the course of this investigation, a trend relating regioselectivity and electrophile electron deficiency began to emerge. Specifically, the regioselectivity of the reaction diminished as the electron deficiency of the allyl substituent increased. In order to identify the linear free energy relationship governing the reaction, we performed a

Hammett analysis relating the log of the ratio of branched to linear products, which is proportional to the relative rates of product formation, to the corresponding Hammett σ-values. The negative ρ value observed from this plot suggests that as the magnitude of electropositive charge generated at the putative allyl-Ir intermediate[8b] increases, the reaction pathway yielding the branched allylation product becomes more favorable. This analysis can be extended to account, in part, for the poor regioselectivity observed in the case of *p*-nitro substituted allyl component **98**.

Figure 4.3.2.1. *Hammett plot of the log of product ratios (**112**:**113**) from Table 2 versus Hammett σ-values*

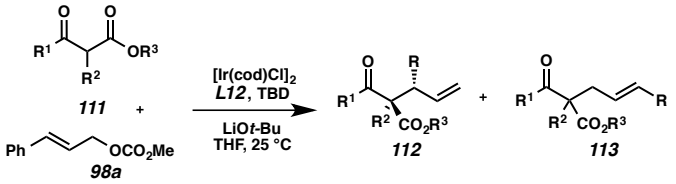


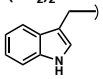
4.3.3 Exploration of the iridium-catalyzed allylic alkylation of linear β-ketoesters with respect to β-ketoester nucleophile

Having investigated reaction substrate scope with respect to the allyl electrophile, we next examined the diversity of nucleophilic coupling partners permitted in the chemistry (Table 4.3.3.1). β-Ketoesters (**111**) bearing either electron-donating or electron-withdrawing aryl substituents (R^1) at the ketone fared very well in the reaction,

delivering products **112l** and **112m** in excellent yield, dr, ee and branched to linear ratio (entries 1 and 2). Gratifyingly, a wide variety of functional groups are readily permitted at the α-position (R^2), including alkyl, benzyl, allyl, propargyl, heteroaryl and keto groups (substrates **111d–111i**, entries 3–8, respectively). The products of these reactions (products **112n–112s**, respectively) were obtained with excellent ee and regioselectivities, and in good to excellent dr and yield. To the best of our knowledge, substrate **111g** represents the first example of a terminal propargyl-substituted nucleophile to undergo Ir-catalyzed allylic substitutions.[102] Nitrile-containing substituents were tolerated in the reaction as well (substrate **111j**), and α-quaternary β-ketoester **112t** was furnished in excellent yield, ee and regioselectivity, albeit with a diminished dr of 3:1. We were pleased to learn that use of certain of α-halogenated nucleophiles (substrates **111k** and **111l**) also resulted in an efficient and selective reaction as α-fluoro and α-chloro β-ketoesters **112u** and **112v** were obtained in excellent yields, dr, ee and regioselectivity. In addition to aryl ketones, cyclohexenyl β-ketoester **111m** was found to deliver the corresponding product **112w** in excellent yield, dr, ee and branched to linear ratio with no detectable products resulting from competitive bimolecular Michael addition. Although the use of alkyl β-ketoesters **111n** and **111o** provided the desired products (**112x** and **112y**, respectively) with excellent yields, ee's and regioselectivities, we were disappointed to find that the diastereoselectivities were diminished considerably. Lastly, we found that the use of a sterically-hindered ester moiety (substrate **111p**) gave an efficient and highly enantioselective reaction but with a concurrent loss in regio- and diastereoselectivity (entry 15).

Table 4.3.3.1. *Exploration of the reaction scope with respect to β-ketoester nucleophile*[a]



entry	111	product (*112*)	yield (%)[b]	*112*:*113*[c]	dr of *112*[c]	ee of *112* (%)[d]
1	*111b*	*112l*: R^3 = Et, R^1 = 4-MeO-C_6H_4	93	93:7	17:1	99
2	*111c*	*112m*: R^3 = Me, R^1 = 4-Br-C_6H_4	92	92:8	17:1	>99
3	*111d*	*112n*: R^2 = Et	94	90:10	>20:1	>99
4	*111e*	*112o*: R^2 = Bn	99	90:10	13:1	>99
5	*111f*	*112p*: R^2 = allyl	98	95:5	>20:1	>99
6[e]	*111g*	*112q*: R^2 = propargyl	84	81:19	13:1	>99
7[f]	*111h*	*112r*: R^2 = $(CH_2)_2COMe$	98	93:7	20:1	99
8	111i	*112s*: R^2 = 	88	95:5	7:1	>99
9	*111j*	*112t*: R^2 = CH_2CH_2CN	99	95:5	3:1	>99 (>99)[g]
10	*111k*	*112u*: R^2 = F	92	96:4	13:1	95
11	*111l*	*112v*: R^2 = Cl	96	96:4	>20:1	>99
12	*111m*	*112w*	85	90:10	12:1	99
13	*111n*	*112x*: R^1 = Cy, R^2 = Me	92	92:8	4:1	96
14	*111o*	*112y*: R^1 = Me, R^2 = Et	90	93:7	1.5:1	90 (91)[g]
15	*111p*	*112z*	95	70:30	6:1	>99

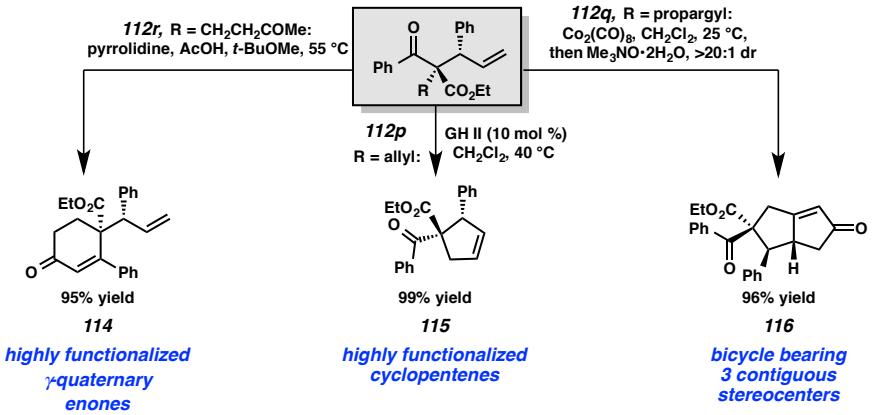
[a] Reactions performed under the conditions of Table 1, entry 8. [b] Combined isolated yield of **112** and **113**. [c] Determined by ^{1}H NMR analysis of the crude mixture. [d] Determined by chiral SFC analysis of the major diastereomer. [e] 4 mol % of $[Ir(cod)Cl]_2$ and 8 mol % of **L12** were used. [f] The reaction was run at 0.5 mmol scale. [g] ee for the minor diastereomer.

4.4 ELABORATION OF THE ALLYLIC ALKYLATION PRODUCTS

In order to exhibit the utility of our method for generating interesting and useful chiral building blocks, a number of selective transformations were carried out on

products obtained in the course of our studies (Scheme 4.4.1). Aldol condensation of β-ketoester **112r** gave γ-quaternary cyclohexenone **114** in excellent yield. Ring-closing metathesis of diallyl β-ketoester **112p** cleanly furnished cyclohexene **115** in excellent yield. Finally, Pauson–Khand cyclization of progaryl-substituted β-ketoester **112q** smoothly delivered bicycle **116** in outstanding 99% yield.

Scheme 4.4.1. *Rapid generation of molecular and stereochemical complexity employing allylic alkylation products*



4.5 CONCLUDING REMARKS

In summary, the first enantioselective catalytic allylic alkylation of linear β-ketoesters to generate vicinal quaternary and tertiary stereocenters in high yield, dr, ee and regioselectivity has been developed. The process hinges on the use of an Ir•*N*-aryl-phosphoramidite catalyst (**L12**). A variety of substitution patterns at the allyl electrophile and β-ketoester are well tolerated in the chemistry. A number of transformations were carried out on reaction products to demonstrate the value this method holds for the rapid

generation of highly functionalized chiral building blocks. Studies utilizing this method toward the synthesis of complex biologically active natural products are underway in our laboratory and will serve to showcase the utility of the method in synthetic setting. Moreover, studies to extend the scope of functionality tolerated about the electrophile in the chemistry, in particular non-aromatic substituents, should greatly expand the potential applications of this method to total synthesis.

4.6 EXPERIMENTAL SECTION

4.6.1 Materials and Methods

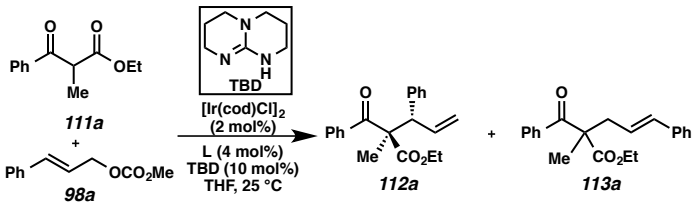
Unless otherwise stated, reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents. Solvents were dried by passage through an activated alumina column under argon.[61] Reaction progress was monitored by thin-layer chromatography (TLC) or Agilent 1290 UHPLC-MS. 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 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: $[a]_D^T$ (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**, **L16** and **L17**[87] allyl carbonates **98**,[95] and β-ketoesters **111**[103] were prepared by known methods.

4.6.2 Optimization of reaction parameters

Table 4.6.2.1 *Optimization of reaction parameters*



entry	*L*	base/additive (x equiv)	time (h)	conv. (%)[b]	yield (%)[c]	*112a:113a*[b]	dr of *112a*[b]	ee of *112* (%)[d]
1	*L10*	NaH (2)	22	91	–	89:11	1:1.8	81(97)
2	*L11*	NaH (2)	48	46	–	17:83	1:1	-
3	*L12*	NaH (2)	22	>95	64	95:5	13:1	99
4	*L16*	NaH (2)	48	34	–	42:58	3.5:1	-
5	*L13*	NaH (2)	72	>95	–	71:29	2:1	76
6	*L17*	NaH (2)	72	>95	–	93:7	7.3:1	72
7	*L12*	LiBr (1)	32	>95	91	95:5	>20:1	>99
8	*L12*	*LiO*t*-Bu (2)*	*2*	*>95*	*97*	*93:7*	*>20:1*	*98*
9	*L12*	KO*t*-Bu (2)	4	>95	–	93:7	2:1	94(87)
10	*L12*	Cs_2CO_3 (2)	4	>95	–	83:17	1:2.2	87(94)
11	*L12*	DABCO (2)	24	>95	–	81:19	1:2.7	64(82)
12	*L12*	proton sponge (2)	4	>95	–	90:10	1:1	87(93)
13	*L12*	DMAP (2)	4	>95	–	83:17	1:1.4	91(93)
14	*L12*	Bu_4NBr (1)	3	>95	–	88:12	1:2.6	87(93)
15	*L12*	$BnMe_3NBr$ (1)	4	>95	–	86:14	1:1	91(95)

[a] Reactions performed with 0.1 mmol of **98a**, 0.2 mmol of **111a** in 1 mL of THF. [b] Determined by ^{1}H NMR or UHPLC-MS analysis of the crude reaction mixture. [c] Isolated yield. [d] (ee) of the alternative diastereomer.

General Procedure for Optimization Reaction (Table 4.6.2.1): All experiments were performed in a nitrogen-filled glove box.

Procedure A (for entries 1-9): $[Ir(cod)Cl]_2$ (1.4 mg, 0.002 mmol, 2 mol%), ligand **L** (0.004 mmol, 4 mol%), and TBD (1.4 mg, 0.01 mmol, 10 mol%) were added to a 2 dram scintillation vial (vial A) equipped with a magnetic stirring bar. The vial was then charged with THF (0.5 mL) and stirred at 25 °C for 10 min, generating an orange solution. To another 2 dram scintillation vial (vial B) was added base (0.2 mmol, 2 equiv), 0.5 mL of THF and β-ketoester **111a** (41.2 mg, 0.2 mmol, 2.0 equiv). After

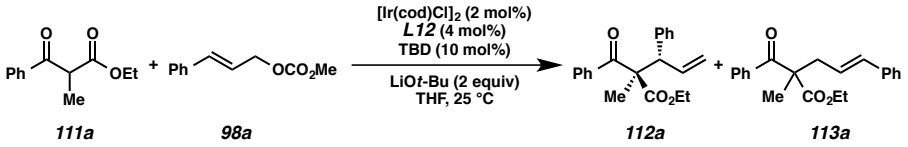
stirring for 10 min at 25 °C, the pre-formed catalyst solution (vial A) was transferred to vial B, and cinnamyl carbonate (**98a**) (19.2 mg, 0.1 mmol, 1.0 equiv) was added. The vial was sealed and stirred at 25 °C until allylic carbonate **98a** was fully consumed, as indicated by UHPLC-MS analysis. Upon completion of the reaction the vial was removed from the glove-box and uncapped. Saturated NH_4Cl aqueous solution was added and the mixture was extracted with CH_2Cl_2 (10 mL x 3), the combined organic phase was washed with brine, dried over Mg_2SO_4, filtered and concentrated *in vacuo*. The regioselectivity (branched product to linear product, b:l) and diastereoselectivity (dr) were determined by ^1H NMR. The residue was purified by silica gel flash chromatography (gradient elution, 0→1→2% EtOAc in hexanes) to afford the desired product.

Procedure B (for entries 10-15): $[Ir(cod)Cl]_2$ (1.4 mg, 0.002 mmol, 2 mol%), ligand **L** (0.004 mmol, 4 mol%), and TBD (1.4 mg, 0.01 mmol, 10 mol%) were added to a 2 dram scintillation vial equipped with a magnetic stirring bar. The vial was then charged with THF (0.5 mL) and stirred at 25 °C for 10 min, generating an orange solution. Cinnamyl carbonate (**98a**) (19.2 mg, 0.1 mmol, 1.0 equiv), β-ketoester **111a** (41.2 mg, 0.2 mmol, 2.0 equiv), base (0.2 mmol, 2 equiv) or additive (0.1 mmol, 1.0 equiv) and an additional 0.5 mL of THF were added. The vial was sealed and stirred at 25 °C until allylic carbonate **98a** was fully consumed, as indicated by UHPLC-MS analysis. Upon completion of the reaction the vial was removed from the glove-box and uncapped and THF evaporated under reduced pressure. Et_2O was added to the crude mixture and the resulting precipitate was filtered through a celite pad, rinsed with Et_2O and the filtrate was concentrated under reduced pressure. The regioselectivity (branched

product to linear product: b:l) and diastereoselectivity (dr) were determined by ^{1}H NMR. The residue was purified by silica gel flash chromatography (gradient elution, 0→1→2% EtOAc in hexanes) to afford the desired product.

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

Note that the absolute configuration was determined only for compound **112f** *via X-ray analysis of its derivative (vide infra). The absolute configuration for all other products* ***3*** *has been inferred by analogy. Isolated yields are reported in Tables 2 and 3 (see manuscript). For respective SFC conditions, please refer to Table 4.6.8.1. The relative configuration of product derivative* ***116*** *was determined by 2D NMR studies, see appendix A6 for details. The relative configurations of all other products determined by anaolgy.*



111a ***98a*** ***112a*** ***113a***

In a nitrogen-filled glove box, $[Ir(cod)Cl]_2$ (1.4 mg, 0.002 mmol, 2 mol%), ligand **L12** (1.8 mg, 0.004 mmol, 4 mol%), and TBD (1.4 mg, 0.01 mmol, 10 mol%) were added to a 2 dram scintillation vial equipped with a magnetic stirring bar. The vial was then charged with THF (0.5 mL) and stirred at 25 °C for 10 min, generating an orange solution. To another 2 dram scintillation vial was added LiO*t*-Bu (16.0 mg, 0.2 mmol, 2

equiv) and 0.5 mL of THF, then β-ketoester **111a** (41.2 mg, 0.2 mmol, 2.0 equiv) was added. After stirring for 10 min, the above pre-formed catalyst solution was transferred to this vial, followed by cinnamyl carbonate (**98a**) (19.2 mg, 0.1 mmol, 1.0 equiv). The vial was sealed and stirred at 25 °C until allylic carbonate **98a** was fully consumed, as indicated by UHPLC-MS analysis. Upon completion of the reaction the vial was removed from the glove-box and uncapped and saturated NH_4Cl aqueous solution was added. The mixture was extracted with CH_2Cl_2 (10 mL x 3), the combined organic layers washed with brine, dried over Mg_2SO_4, filtered and concentrated under reduced pressure. The regioselectivity (branched product to linear product: b:l = 93:7) and diastereoselectivity (dr >20:1) were determined by ^{1}H NMR of the crude reaction mixture. The residue was purified by silica gel flash chromatography (gradient elution, 0→1→2% EtOAc in hexanes) to afford product (31.2 mg, 97% yield) as a colorless oil.

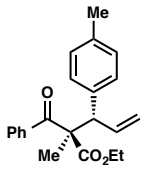
Ethyl-(2*R*,3*S*)-2-benzoyl-2-methyl-3-phenylpent-4-enoate (112a).

Ketoester **112a** was isolated by silica gel chromatography (gradient elution, 0→1→2% EtOAc in hexanes) as a colorless oil. >99% ee, $[\alpha]_D^{25}$ +76.6 (*c* 0.77, $CHCl_3$); R_f = 0.4 (5% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69–7.60 (m, 2H), 7.52–7.43 (m, 1H), 7.38–7.33 (m, 2H), 7.26–7.15 (m, 5H), 6.35 (ddd, *J* = 17.0, 10.3, 8.3 Hz, 1H), 5.13 (ddd, *J* = 10.2, 1.7, 0.9 Hz, 1H), 5.07 (ddd, *J* = 17.0, 1.8, 1.2 Hz, 1H), 4.39 (dd, *J* = 8.3, 1.1 Hz, 1H), 4.09 (qd, *J* = 7.2, 0.6 Hz, 2H), 1.53 (s, 3H), 1.04 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 198.0, 173.0, 139.5, 137.8, 137.2, 132.3, 130.1, 128.4, 128.20, 128.17, 127.1, 117.5, 61.8, 61.6, 54.8, 21.0, 13.8; IR (Neat Film, NaCl) 3062, 3028, 2981, 2939, 2902, 1731, 1686, 1682, 1597, 1582, 1493, 1452, 1446, 1377, 1311,

1243, 1218, 1186, 1096, 1018, 1001, 962, 920, 860, 758 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{21}H_{23}O_3$ $[M+H]^+$: 323.1642, found 323.1647; SFC conditions: 5% IPA, 2.5 mL/min, Chiralpak IC column, λ = 254 nm, t_R (min): major = 4.12, minor = 6.14.

4.6.4. Spectroscopic data for Ir-catalyzed allylic alkylation products

Ethyl (2*R*,3*S*)-2-benzoyl-2-methyl-3-(*p*-tolyl)pent-4-enoate (112b).

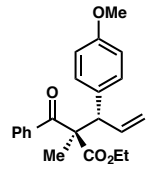


112b

Ketoester **112b** was isolated by silica gel chromatography (gradient elution, 0→1→2% EtOAc in hexanes) as a colorless oil. 99% ee, $[\alpha]_D^{25}$ +80.4 (*c* 1.82, $CHCl_3$); R_f = 0.4 (5% EtOAc in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 7.69–7.65 (m, 2H), 7.47 (ddt, *J* = 8.6, 7.0, 1.3 Hz, 1H), 7.39–7.33 (m, 2H), 7.11–7.02 (m, 4H), 6.33 (ddd, *J* = 16.9, 10.2, 8.3 Hz, 1H), 5.11 (ddd, *J* = 10.3, 1.8, 1.0 Hz, 1H), 5.07 (ddd, *J* = 17.0, 1.9, 1.2 Hz, 1H), 4.38 (dd, *J* = 8.3, 1.2 Hz, 1H), 4.09 (qd, *J* = 7.1, 2.6 Hz, 2H), 2.29 (s, 3H), 1.54 (s, 3H), 1.05 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 198.1, 173.0, 137.9, 137.2, 136.6, 136.4, 132.3, 129.9, 128.9, 128.4, 128.2, 117.3, 61.8, 61.5, 54.3, 21.1, 20.9, 13.8; IR (Neat Film, NaCl) 3058, 3023, 2981, 2938, 1736, 1732, 1682, 1687, 1636, 1597, 1580, 1513, 1446, 1376, 1310, 1243, 1219, 1186, 1115, 1104, 1021, 1001, 963, 919, 820, 793 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{22}H_{25}O_3$ $[M+H]^+$: 337.1798, found 337.1805; SFC

conditions: 5% IPA, 2.5 mL/min, Chiralpak IC column, λ = 254 nm, t_R (min): major = 6.71, minor = 9.45.

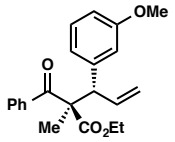
Ethyl (2*R*,3*S*)-2-benzoyl-3-(4-methoxyphenyl)-2-methylpent-4-enoate (112c).



112c

Ketoester **112c** was isolated by silica gel chromatography (gradient elution, 2→5% EtOAc in hexanes) as a colorless oil. >99% ee, $[\alpha]_D^{25}$ +81.5 (*c* 2.02, $CHCl_3$); R_f = 0.2 (5% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70–7.63 (m, 2H), 7.52–7.43 (m, 1H), 7.38–7.32 (m, 2H), 7.15–7.08 (m, 2H), 6.85–6.74 (m, 2H), 6.32 (ddd, *J* = 17.0, 10.3, 8.2 Hz, 1H), 5.11 (ddd, *J* = 10.3, 1.8, 1.0 Hz, 1H), 5.05 (ddd, *J* = 17.0, 1.8, 1.2 Hz, 1H), 4.37 (d, *J* = 8.2 Hz, 1H), 4.09 (qd, *J* = 7.1, 0.9 Hz, 2H), 3.76 (s, 3H), 1.51 (s, 3H), 1.05 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 198.1, 173.0, 158.5, 138.0, 137.3, 132.3, 131.4, 131.1, 128.4, 128.2, 117.2, 113.5, 61.9, 61.5, 55.3, 53.9, 20.8, 13.9; IR (Neat Film, NaCl) 3067, 2981, 2937, 2904, 2835, 1731, 1686, 1682, 1610, 1597, 1581, 1511, 1446, 1376, 1302, 1245, 1218, 1181, 1114, 1101, 1034, 963, 922, 830 cm^{-1}; HRMS (ESI+) *m/z* calc'd for fragment $C_{10}H_{11}O$ $[M\text{-}C_{11}H_{12}O_3+H]^+$: 147.0804, found 147.0808; SFC conditions: 5% IPA, 2.5 mL/min, Chiralpak AD-H column, λ = 254 nm, t_R (min): minor = 11.17, major = 12.67.

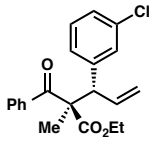
Ethyl (2*R*,3*S*)-2-benzoyl-3-(-methoxyphenyl)-2-methylpent-4-enoate (112d).



112d

Ketoester **112d** was isolated by silica gel chromatography (gradient elution, 0→1→2% EtOAc in hexanes) as a colorless oil. >99% ee, $[\alpha]_D^{25}$ +85.1 (*c* 1.21, $CHCl_3$); R_f = 0.3 (5% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70–7.63 (m, 2H), 7.52–7.43 (m, 1H), 7.42–7.32 (m, 2H), 7.23–7.11 (m, 1H), 6.82–6.71 (m, 3H), 6.32 (ddd, *J* = 16.9, 10.3, 8.3 Hz, 1H), 5.13 (ddd, *J* = 10.3, 1.8, 0.9 Hz, 1H), 5.09 (ddd, *J* = 17.0, 1.8, 1.2 Hz, 1H), 4.37 (dt, *J* = 8.3, 1.1 Hz, 1H), 4.09 (qd, *J* = 7.2, 1.3 Hz, 2H), 3.74 (s, 3H), 1.53 (s, 3H), 1.05 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 198.0, 172.9, 159.3, 141.0, 137.6, 137.3, 132.3, 129.1, 128.4, 128.2, 122.4, 117.6, 116.0, 112.4, 61.8, 61.6, 55.2, 54.8, 21.0, 13.8; IR (Neat Film, NaCl) 3078, 2982, 2940, 2835, 1731, 1683, 1598, 1583, 1488, 1454, 1377, 1315, 1245, 1217, 1186, 1162, 1096, 1049, 1019, 1001, 963, 922, 861, 781 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{22}H_{25}O_4$ $[M+H]^+$: 353.1747, found 353.1761; SFC conditions: 2% MeOH, 2.5 mL/min, Chiralpak IC column, λ = 254 nm, t_R (min): major = 12.24, minor = 13.50.

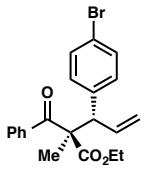
Ethyl (2*R*,3*S*)-2-benzoyl-3-(3-chlorophenyl)-2-methylpent-4-enoate (112e).



112e

Ketoester **112e** was isolated by silica gel chromatography (gradient elution, 0→1→2% EtOAc in hexanes) as a colorless oil. 99% ee, $[\alpha]_D^{25}$ +99.1 (*c* 1.13, $CHCl_3$); R_f = 0.3 (5% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70–7.63 (m, 2H), 7.48 (ddt, *J* = 7.8, 6.9, 1.2 Hz, 1H), 7.41–7.33 (m, 2H), 7.22–7.19 (m, 1H), 7.19–7.14 (m, 2H), 7.14–7.08 (m, 1H), 6.30 (ddd, *J* = 17.0, 10.2, 8.4 Hz, 1H), 5.15 (ddd, *J* = 10.3, 1.6, 0.9 Hz, 1H), 5.07 (dt, *J* = 17.0, 1.4 Hz, 1H), 4.34 (d, *J* = 8.4 Hz, 1H), 4.10 (q, *J* = 7.2 Hz, 2H), 1.52 (s, 3H), 1.06 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.6, 172.6, 141.7, 137.0, 136.9, 133.9, 132.5, 130.3, 129.3, 128.5, 128.4, 128.3, 127.2, 118.1, 61.7, 61.7, 54.5, 20.9, 13.8; IR (Neat Film, NaCl) 3068, 2982, 2943, 1732, 1682, 1595, 1574, 1475, 1446, 1378, 1301, 1245, 1218, 1194, 1095, 1018, 1001, 963, 924, 784 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{21}H_{22}ClO_3$ $[M+H]^+$: 357.1252, found 357.1260; SFC conditions: 10% IPA, 4.0 mL/min, Chiralpak IC column, λ = 254 nm, t_R (min): major = 1.59, minor = 1.77.

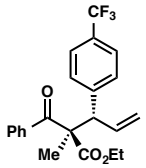
Ethyl (2*R*,3*S*)-2-benzoyl-3-(4-bromophenyl)-2-methylpent-4-enoate (112f).



112f

Ketoester **112f** was isolated by silica gel chromatography (gradient elution, 0→1→2% EtOAc in hexanes) as a colorless oil. >99% ee, $[\alpha]_D^{25}$ +89.0 (*c* 1.42, $CHCl_3$); R_f = 0.3 (5% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70–7.63 (m, 2H), 7.50–7.45 (m, 1H), 7.40–7.33 (m, 4H), 7.13–7.08 (m, 2H), 6.29 (ddd, *J* = 16.9, 10.2, 8.2 Hz, 1H), 5.16–5.11 (m, 1H), 5.05 (dt, *J* = 17.0, 1.4 Hz, 1H), 4.36 (d, *J* = 8.2 Hz, 1H), 4.08 (q, *J* = 7.1 Hz, 2H), 1.51 (s, 3H), 1.05 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.6, 172.7, 138.6, 137.2, 136.9, 132.5, 131.9, 131.2, 128.5, 128.3, 121.1, 117.9, 61.7, 61.6, 54.1, 20.8, 13.8; IR (Neat Film, NaCl) 3077, 2981, 2938, 1728, 1683, 1597, 1488, 1446, 1377, 1305, 1243, 1217, 1186, 1099, 1076, 1010, 963, 922, 822, 802, 716 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{21}H_{22}BrO_3$ $[M+H]^+$: 401.0747, found 401.0754; SFC conditions: 10% IPA, 4.0 mL/min, Chiralpak AD-H column, λ = 210 nm, t_R (min): minor = 2.95, major = 3.47.

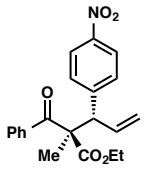
Ethyl (2*R*,3*S*)-2-benzoyl-2-methyl-3-(4-(trifluoromethyl)phenyl)pent-4-enoate (112g).



112g

Ketoester **112g** was isolated by silica gel chromatography (gradient elution, 0→1→2% EtOAc in hexanes) as a colorless oil. >99% ee, $[\alpha]_D^{25}$ +77.4 (*c* 0.94, $CHCl_3$); R_f = 0.3 (5% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69–7.63 (m, 2H), 7.53–7.45 (m, 3H), 7.39–7.35 (m, 4H), 6.33 (ddd, *J* = 16.9, 10.2, 8.4 Hz, 1H), 5.16 (ddd, *J* = 10.2, 1.6, 0.9 Hz, 1H), 5.07 (dt, *J* = 17.0, 1.4 Hz, 1H), 4.44 (d, *J* = 8.4 Hz, 1H), 4.09 (q, *J* = 7.1 Hz, 2H), 1.53 (s, 3H), 1.04 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.5, 172.6, 143.9, 136.9, 136.8, 132.6, 130.6, 129.2 (q, *J* = 32.4 Hz), 128.5, 128.3, 125.0 (q, *J* = 3.7 Hz), 124.3 (d, *J* = 271.8 Hz), 118.3, 61.8, 61.6, 54.6, 20.8, 13.8; IR (Neat Film, NaCl) 3070, 2984, 2941, 1732, 1687, 1682, 1617, 1597, 1581, 1446, 1413, 1379, 1327, 1245, 1220, 1166, 1123, 1069, 1018, 964, 924, 846 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{22}H_{22}F_3O_3$ $[M+H]^+$: 391.1516, found 391.1517; SFC conditions: 2% IPA, 2.5 mL/min, Chiralpak AD-H column, λ = 254 nm, t_R (min): minor = 5.20, major = 6.68.

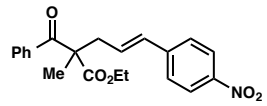
Ethyl (2*R*,3*S*)-2-benzoyl-2-methyl-3-(4-nitrophenyl)pent-4-enoate (112h).



112h

Ketoester **112h** was isolated by silica gel chromatography (5% EtOAc in hexanes) as a colorless oil. 93% ee, $[\alpha]_D^{25}$ +96.8 (*c* 0.64, $CHCl_3$); R_f = 0.3 (10% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13–8.09 (m, 2H), 7.70–7.63 (m, 2H), 7.52–7.48 (m, 1H), 7.46–7.43 (m, 2H), 7.40–7.35 (m, 2H), 6.31 (ddd, *J* = 16.9, 10.2, 8.5 Hz, 1H), 5.23–5.16 (m, 1H), 5.08 (dt, *J* = 17.0, 1.3 Hz, 1H), 4.50 (d, *J* = 8.5 Hz, 1H), 4.10 (qd, *J* = 7.1, 2.4 Hz, 2H), 1.54 (s, 3H), 1.05 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.0, 172.3, 147.4, 146.8, 136.3, 136.1, 132.6, 131.0, 128.4, 128.2, 123.1, 118.8, 61.8, 61.4, 54.3, 20.5, 13.7; IR (Neat Film, NaCl) 3080, 2982, 2942, 1731, 1686, 1682, 1597, 1523, 1519, 1446, 1379, 1346, 1245, 1219, 1111, 1001, 1015, 964, 926, 853 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{21}H_{22}O_5N$ $[M+H]^+$: 368.1492, found 368.1508; SFC conditions: 5% MeOH, 3.0 mL/min, Chiralpak AD-H column, λ = 254 nm, t_R (min): minor = 4.47, major = 5.71.

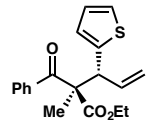
Ethyl (*E*)-2-benzoyl-2-methyl-5-(4-nitrophenyl)pent-4-enoate (113h).



113h

Ketoester **113h** was isolated by silica gel chromatography (5% EtOAc in hexanes) as a yellow solid. 23% ee, $[\alpha]_D^{25}$ +4.7 (*c* 0.96, $CHCl_3$); R_f = 0.3 (10% EtOAc in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 8.15 (dt, *J* = 9.0, 2.5 Hz, 2H), 7.86 (dt, *J* = 8.5, 2.0 Hz, 2H), 7.59–7.49 (m, 1H), 7.47–7.40 (m, 4H), 6.45 (dt, *J* = 15.9, 1.2 Hz, 1H), 6.32 (dt, *J* = 15.7, 7.5 Hz, 1H), 4.12 (qd, *J* = 7.2, 1.1 Hz, 2H), 3.00 (ddd, *J* = 14.2, 7.3, 1.3 Hz, 1H), 2.90 (ddd, *J* = 14.2, 7.7, 1.2 Hz, 1H), 1.58 (s, 3H), 1.05 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.0, 173.6, 146.9, 143.6, 135.4, 133.1, 132.1, 130.0, 128.7, 126.8, 124.1, 61.7, 57.3, 40.6, 21.6, 14.0; IR (Neat Film, NaCl) 2981, 2936, 1732, 1686, 1682, 1596, 1519, 1515, 1446, 1342, 1298, 1267, 1239, 1184, 1108, 973, 857 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{21}H_{22}O_5N$ $[M+H]^+$: 368.1492, found 368.1499; SFC conditions: 10% MeOH, 3.0 mL/min, Chiralpak AD-H column, λ = 254 nm, t_R (min): major = 7.13, minor = 8.06.

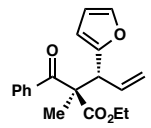
Ethyl (2*R*,3*R*)-2-benzoyl-2-methyl-3-(thiophen-2-yl)pent-4-enoate (112i).



112i

Ketoester **112i** was isolated by silica gel chromatography (gradient elution, 0→1→2% EtOAc in hexanes) as a colorless oil. 95% ee, $[\alpha]_D^{25}$ +53.0 (*c* 1.63, $CHCl_3$); R_f = 0.4 (5% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74–7.68 (m, 2H), 7.51–7.47 (m, 1H), 7.42–7.35 (m, 2H), 7.16 (dd, *J* = 5.1, 1.2 Hz, 1H), 6.89 (dd, *J* = 5.1, 3.5 Hz, 1H), 6.84 (ddd, *J* = 3.5, 1.2, 0.7 Hz, 1H), 6.23 (ddd, *J* = 16.4, 10.6, 9.0 Hz, 1H), 5.23–5.16 (m, 2H), 4.77 (d, *J* = 9.0 Hz, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 1.52 (s, 3H), 1.09 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.5, 172.3, 142.1, 136.8, 136.6, 132.5, 128.5, 128.4, 126.9, 126.2, 124.9, 118.2, 62.2, 61.9, 49.8, 19.4, 13.9; IR (Neat Film, NaCl) 3069, 2981, 2937, 1732, 1687, 1682, 1597, 1580, 1446, 1383, 1298, 1246, 1221, 1107, 1018, 1001, 968, 924, 851, 795, 747 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{19}H_{21}O_3S$ $[M+H]^+$: 329.1206, found 329.1214; SFC conditions: 5% IPA, 2.5 mL/min, Chiralpak IC column, λ = 254 nm, t_R (min): major = 7.92, minor = 11.24.

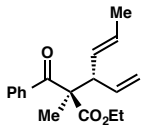
Ethyl (2*R*,3*R*)-2-benzoyl-3-(furan-2-yl)-2-methylpent-4-enoate (112j).



112j

Ketoester **112j** was isolated by silica gel chromatography (gradient elution, 0→1→2% EtOAc in hexanes) as a colorless oil. >99% ee, $[\alpha]_D^{25}$ +67.3 (*c* 1.34, $CHCl_3$); R_f = 0.4 (5% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73–7.67 (m, 2H), 7.52–7.45 (m, 1H), 7.40–7.35 (m, 2H), 7.27 (dd, *J* = 1.8, 0.9 Hz, 1H), 6.25 (dd, *J* = 3.3, 1.8 Hz, 1H), 6.17 (ddd, *J* = 17.0, 10.2, 8.5 Hz, 1H), 6.11 (dt, *J* = 3.3, 0.7 Hz, 1H), 5.19 (ddd, *J* = 10.2, 1.7, 0.8 Hz, 1H), 5.14 (ddd, *J* = 17.0, 1.7, 1.1 Hz, 1H), 4.62 (dd, *J* = 8.5, 0.9 Hz, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 1.52 (s, 3H), 1.10 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.9, 172.1, 152.9, 141.5, 136.6, 134.4, 132.2, 128.3, 128.2, 118.3, 110.1, 108.7, 61.6, 61.4, 47.9, 19.3, 13.8; IR (Neat Film, NaCl) 3081, 2983, 2941, 2904, 1732, 1686, 1597, 1581, 1501, 1446, 1378, 1301, 1246, 1222, 1149, 1096, 1013, 968, 926, 885, 860, 797, 736 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{19}H_{21}O_4$ $[M+H]^+$: 313.1431, found 313.1438; SFC conditions: 5% IPA, 2.5 mL/min, Chiralpak IC column, λ = 254 nm, t_R (min): major = 5.09, minor = 9.14.

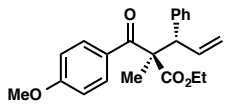
Ethyl (2*R*,3*S*,*E*)-2-benzoyl-2-methyl-3-vinylhex-4-enoate (112k).



112k

Ketoester **112k** was isolated by silica gel chromatography (gradient elution, 0→1→2% EtOAc in hexanes) as a colorless oil. 91% ee, $[\alpha]_D^{25}$ +43.5 (*c* 1.86, $CHCl_3$); R_f = 0.4 (5% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80–7.71 (m, 2H), 7.52–7.46 (m, 1H), 7.42–7.36 (m, 2H), 5.98 (ddd, *J* = 16.9, 10.5, 7.5 Hz, 1H), 5.47–5.27 (m, 2H), 5.15–5.00 (m, 2H), 4.09 (qd, *J* = 7.1, 1.5 Hz, 2H), 3.73–3.69 (m, 1H), 1.65–1.58 (m, 3H), 1.48 (s, 3H), 1.07 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.4, 173.0, 137.2, 136.8, 132.4, 129.0, 128.5, 128.4, 128.3, 117.1, 61.4, 60.5, 51.6, 19.2, 18.2, 14.0; IR (Neat Film, NaCl) 3077, 2981, 2939, 2913, 1732, 1687, 1682, 1597, 1580, 1446, 1377, 1299, 1245, 1221, 1100, 1018, 1001, 970, 921, 859 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{18}H_{23}O_3$ $[M+H]^+$: 287.1642, found 287.1654; SFC conditions: 2% IPA, 2.5 mL/min, Chiralpak AD-H column, λ = 210 nm, t_R (min): minor = 4.40, major = 5.52.

Ethyl (2*R*,3*S*)-2-(4-methoxybenzoyl)-2-methyl-3-phenylpent-4-enoate (112l).

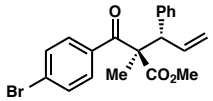


112l

Ketoester **112l** was isolated by silica gel chromatography (4% EtOAc in hexanes) as a colorless oil. 99% ee, $[\alpha]_D^{25}$ +53.9 (*c* 1.51, $CHCl_3$); R_f = 0.3 (10% EtOAc in hexanes);

^{1}H NMR (500 MHz, $CDCl_3$) δ7.76–7.69 (m, 2H), 7.25–7.17 (m, 5H), 6.87–6.82 (m, 2H), 6.36 (ddd, *J* = 17.0, 10.3, 8.1 Hz, 1H), 5.12 (ddd, *J* = 10.3, 1.8, 1.0 Hz, 1H), 5.05 (ddd, *J* = 17.0, 1.8, 1.2 Hz, 1H), 4.39 (dt, *J* = 8.1, 1.2 Hz, 1H), 4.10 (q, *J* = 7.1 Hz, 2H), 3.84 (s, 3H), 1.53 (s, 3H), 1.07 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 195.8, 173.4, 162.9, 139.6, 138.0, 130.8, 130.2, 129.5, 128.1, 127.0, 117.3, 113.6, 61.5, 61.3, 55.5, 54.7, 21.0, 13.9; IR (Neat Film, NaCl) 3083, 2981, 2940, 2842, 1727, 1677, 1600, 1576, 1513, 1454, 1417, 1376, 1310, 1247, 1221, 1176, 1118, 1031, 964, 842 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{22}H_{25}O_4$ $[M+H]^+$: 353.1747, found 353.1752; SFC conditions: 10% IPA, 4.0 mL/min, Chiralpak IC column, λ = 254 nm, t_R (min): major = 2.67, minor = 3.51.

Methyl (2*R*,3*S*)-2-(4-bromobenzoyl)-2-methyl-3-phenylpent-4-enoate (112m).

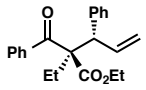


112m

Ketoester **112m** was isolated by silica gel chromatography (gradient elution, 1→2 Et_2O in hexanes) as a colorless oil. >99% ee, $[\alpha]_D^{25}$ +65.9 (*c* 0.50, $CHCl_3$); R_f = 0.3 (10% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51–7.48 (m, 4H), 7.29–7.09 (m, 5H), 6.31 (ddd, *J* = 16.9, 10.3, 8.4 Hz, 1H), 5.21–4.96 (m, 2H), 4.37 (d, *J* = 8.5 Hz, 1H), 3.62 (s, 3H), 1.51 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.6, 173.3, 139.1, 137.3, 135.7, 131.7, 130.0, 129.7, 128.2, 127.5, 127.1, 117.7, 61.8, 54.7, 52.5, 20.8; IR (Neat Film, NaCl) 3355, 3028, 2997, 2948, 1735, 1685, 1584, 1484, 1452, 1395, 1245, 1221, 1117, 1073, 966, 922, 841, 756 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{20}H_{20}BrO_3$ $[M+H]^+$:

387.0590, found 387.0612; SFC conditions: 5% IPA, 2.5 mL/min, Chiralpak AD-H column, λ = 254 nm, t_R (min): major = 5.35, minor = 5.88.

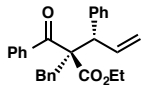
Ethyl (2*R*,3*S*)-2-benzoyl-2-ethyl-3-phenylpent-4-enoate (112n).



112n

Ketoester **112n** was isolated by silica gel chromatography (gradient elution, 0→2 Et_2O in hexanes) as a colorless oil. >99% ee, $[\alpha]_D^{25}$ +77.4 (*c* 0.25, $CHCl_3$); R_f = 0.4 (10% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61–7.51 (m, 2H), 7.48–7.38 (m, 1H), 7.35–7.11 (m, 7H), 6.33 (ddd, *J* = 17.0, 10.3, 7.8 Hz, 1H), 5.07 (ddd, *J* = 10.3, 1.8, 1.1 Hz, 1H), 4.96 (dt, *J* = 17.1, 1.5 Hz, 1H), 4.38 (dd, *J* = 7.9, 1.4 Hz, 1H), 4.06 (qd, *J* = 7.2, 3.3 Hz, 2H), 2.15 (dq, *J* = 15.0, 7.5 Hz, 1H), 1.89 (dq, *J* = 14.9, 7.5 Hz, 1H), 0.99 (t, *J* = 7.1 Hz, 3H), 0.78 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 198.1, 172.9, 139.5, 138.4, 137.9, 132.0, 129.8, 128.2, 128.1, 127.9, 127.0, 116.6, 65.2, 61.0, 52.2, 27.6, 13.6, 8.5; IR (Neat Film, NaCl) 3061, 3028, 2980, 1729, 1679, 1597, 1446, 1386, 1303, 1228, 1208, 1097, 1028, 993, 917, 759 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{22}H_{25}O_3$ $[M+H]^+$: 337.1798, found 337.1813; SFC conditions: 5% MeOH, 2.5 mL/min, Chiralpak AD-H column, λ = 254 nm, t_R (min): major = 2.48, minor = 2.20.

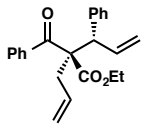
Ethyl (2*R*,3*S*)-2-benzoyl-2-benzyl-3-phenylpent-4-enoate (112o).



112o

Ketoester **112o** was isolated by silica gel chromatography (gradient elution, 1→2 EtOAc in hexanes) as a white solid. >99% ee, $[\alpha]_D^{25}$ +37.1 (*c* 1.29, $CHCl_3$); R_f = 0.4 (5% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33–7.29 (m, 1H), 7.29–7.21 (m, 4H), 7.17–7.10 (m, 8H), 7.04–7.00 (m, 2H), 6.37 (ddd, *J* = 17.0, 10.3, 8.1 Hz, 1H), 5.13 (ddd, *J* = 10.2, 1.8, 1.0 Hz, 1H), 5.02 (dt, *J* = 17.0, 1.5 Hz, 1H), 4.42 (d, *J* = 7.9 Hz, 1H), 3.99 (dq, *J* = 10.7, 7.1 Hz, 1H), 3.80 (dq, *J* = 10.7, 7.1 Hz, 1H), 3.28 (AB, *J* = 15.5, 13.5 Hz, 2H), 0.82 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 200.5, 172.0, 139.7, 139.3, 138.3, 136.8, 131.4, 131.2, 130.0, 128.4, 128.1, 127.7, 127.6, 127.4, 126.9, 117.6, 67.5, 61.0, 56.8, 42.1, 13.4; IR (Neat Film, NaCl) 3063, 3029, 2982, 2929, 1729, 1673, 1600, 1582, 1496, 1448, 1367, 1299, 1241, 1209, 1082, 1066, 1025, 925, 757 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{27}H_{27}O_3$ $[M+H]^+$: 399.1955, found 399.1956; SFC conditions: 4% IPA, 4.0 mL/min, Chiralpak AD-H column, λ = 254 nm, t_R (min): major = 5.06, minor = 8.94.

Ethyl (2*R*,3*S*)-2-allyl-2-benzoyl-3-phenylpent-4-enoate (112p).

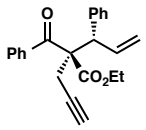


112p

Ketoester **112p** was isolated by silica gel chromatography (2% EtOAc in hexanes) as a colorless oil. >99% ee, $[\alpha]_D^{25}$ +80.7 (*c* 0.31, $CHCl_3$); R_f = 0.4 (5% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54–7.49 (m, 2H), 7.43 (ddt, *J* = 7.7, 7.0, 1.2 Hz, 1H),

7.33–7.27 (m, 2H), 7.25–7.19 (m, 3H), 7.18–7.13 (m, 2H), 6.36 (ddd, *J* = 17.0, 10.3, 8.0 Hz, 1H), 5.71 (dddd, *J* = 17.0, 10.2, 7.8, 7.0 Hz, 1H), 5.10 (ddd, *J* = 10.3, 1.8, 1.1 Hz, 1H), 5.03 (ddt, *J* = 10.2, 2.1, 1.0 Hz, 1H), 4.99 (ddd, *J* = 17.0, 1.8, 1.2 Hz, 1H), 4.92 (dq, *J* = 17.1, 1.7 Hz, 1H), 4.35 (dt, *J* = 8.0, 1.2 Hz, 1H), 4.14–3.96 (m, 2H), 2.86 (ddt, *J* = 14.6, 7.0, 1.3 Hz, 1H), 2.63 (ddt, *J* = 14.6, 7.7, 1.2 Hz, 1H), 0.99 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 198.0, 172.4, 139.4, 138.3, 138.2, 132.5, 132.1, 130.1, 128.3, 128.14, 128.12, 127.2, 119.5, 117.2, 65.2, 61.2, 53.4, 39.4, 13.7; IR (Neat Film, NaCl) 3079, 3029, 2981, 2933, 1728, 1679, 1638, 1597, 1581, 1493, 1446, 1367, 1257, 1216, 1181, 1144, 1045, 1023, 1001, 921, 758 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{23}H_{25}O_3$ $[M+H]^+$: 349.1808, found 349.1808; SFC conditions: 3% IPA, 4.0 mL/min, Chiralpak IC column, λ = 254 nm, t_R (min): major = 7.16, minor = 8.60.

Ethyl (2*R*,3*S*)-2-benzoyl-3-phenyl-2-(prop-2-yn-1-yl)pent-4-enoate (112q).

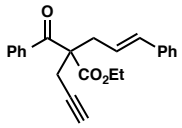


112q

Ketoester **112q** was isolated by silica gel chromatography (2% EtOAc in hexanes) as a colorless oil. >99% ee, $[\alpha]_D^{25}$ +57.7 (*c* 0.94, $CHCl_3$); R_f = 0.3 (5% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62–7.55 (m, 2H), 7.46 (ddt, *J* = 8.6, 7.0, 1.2 Hz, 1H), 7.35–7.29 (m, 2H), 7.25–7.23 (m, 5H), 6.37 (ddd, *J* = 17.0, 10.3, 7.8 Hz, 1H), 5.15 (ddd, *J* = 10.3, 1.8, 1.2 Hz, 1H), 5.09 (dt, *J* = 17.0, 1.5 Hz, 1H), 4.58 (dt, *J* = 7.8, 1.3 Hz, 1H), 4.19–4.05 (m, 2H), 2.97 (dd, *J* = 17.4, 2.7 Hz, 1H), 2.69 (dd, *J* = 17.4, 2.7 Hz, 1H), 2.09

(t, *J* = 2.7 Hz, 1H), 1.05 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.0, 171.4, 138.9, 137.6, 137.3, 132.5, 130.1, 128.4, 128.32, 128.27, 127.4, 117.6, 79.3, 72.9, 64.0, 61.7, 52.5, 25.7, 13.8; IR (Neat Film, NaCl) 3288, 3060, 3030, 2981, 1728, 1682, 1597, 1580, 1446, 1255, 1213, 1183, 1046, 1001, 925 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{23}H_{23}O_3$ $[M+H]^+$: 347.1642, found 347.1647; SFC conditions: 5% IPA, 2.5 mL/min, Chiralcel OD-H column, λ = 254 nm, t_R (min): minor = 5.67, major = 6.44.

Ethyl (*E*)-2-benzoyl-5-phenyl-2-(prop-2-yn-1-yl)pent-4-enoate (113q).

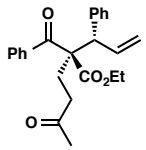


113q

Ketoester **113q** was isolated by silica gel chromatography (2% EtOAc in hexanes) as a colorless oil. 34% ee, $[\alpha]_D^{25}$ -23.4 (*c* 0.42, $CHCl_3$); R_f = 0.3 (5% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88–7.85 (m, 2H), 7.59–7.54 (m, 1H), 7.48–7.42 (m, 2H), 7.30–7.24 (m, 4H), 7.21 (ddd, *J* = 8.7, 4.9, 3.8 Hz, 1H), 6.43 (dt, *J* = 15.6, 1.3 Hz, 1H), 5.90 (dt, *J* = 15.5, 7.7 Hz, 1H), 4.20 (qq, *J* = 7.1, 3.6 Hz, 2H), 3.19 (ddd, *J* = 14.5, 7.9, 1.3 Hz, 1H), 3.11 (ddd, *J* = 14.5, 7.5, 1.4 Hz, 1H), 2.98 (d, *J* = 2.7 Hz, 2H), 2.07 (t, *J* = 2.7 Hz, 1H), 1.13 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 195.2, 171.7, 137.1, 135.7, 134.9, 133.2, 128.8, 128.60, 128.57, 127.6, 126.4, 122.9, 79.0, 72.4, 62.1, 60.6, 36.5, 23.9, 14.1; IR (Neat Film, NaCl) 3287, 3059, 3026, 2979, 2933, 1729, 1679, 1596, 1580, 1446, 1367, 1285, 1270, 1239, 1192, 1180, 1094, 1064, 1023, 966, 937 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{23}H_{23}O_3$ $[M+H]^+$: 347.1642, found 347.1651; SFC

conditions: 5% IPA, 2.5 mL/min, Chiralpak IC column, λ = 254 nm, t_R (min): minor = 9.81, major = 10.67.

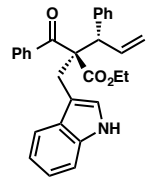
Ethyl (*R*)-2-benzoyl-5-oxo-2-((*S*)-1-phenylallyl)hexanoate (112r).



112r

Ketoester **112r** was isolated by silica gel chromatography (gradient elution, 5→10% EtOAc in hexanes) as a colorless oil. 99% ee, $[\alpha]_D^{25}$ +66.8 (*c* 1.20, $CHCl_3$); R_f = 0.4 (25% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59–7.55 (m, 2H), 7.48–7.43 (m, 1H), 7.37–7.30 (m, 2H), 7.26–7.14 (m, 5H), 6.34 (ddd, *J* = 17.0, 10.3, 8.1 Hz, 1H), 5.09 (ddd, *J* = 10.3, 1.7, 1.0 Hz, 1H), 4.97 (ddd, *J* = 17.0, 1.7, 1.2 Hz, 1H), 4.36–4.32 (m, 1H), 4.13–3.99 (m, 2H), 2.46–2.38 (m, 1H), 2.34–2.29 (m, 2H), 2.25–2.17 (m, 1H), 1.99 (s, 3H), 1.00 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 206.9, 198.0, 172.4, 139.1, 137.9, 137.8, 132.4, 129.7, 128.4, 128.3, 128.0, 127.3, 117.2, 64.2, 61.3, 53.2, 38.3, 29.9, 28.0, 13.7; IR (Neat Film, NaCl) 3063, 3030, 2981, 2905, 1733, 1717, 1681, 1637, 1596, 1582, 1495, 1446, 1419, 1367, 1243, 1214, 1137, 1093, 1029, 1002, 925, 860, 761 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{24}H_{27}O_3$ $[M+H]^+$: 379.1904, found 379.1911; SFC conditions: 5% IPA, 2.5 mL/min, Chiralcel OD-H column, λ = 254 nm, t_R (min): minor = 8.00, major = 10.08.

Ethyl (2*R*,3*S*)-2-((1*H*-indol-3-yl)methyl)-2-benzoyl-3-phenylpent-4-enoate (112s).

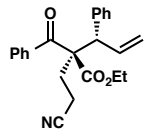


112s

Ketoester **112s** was isolated by silica gel chromatography (gradient elution, 5→10% EtOAc in hexanes) as a colorless oil. >99% ee, $[\alpha]_D^{25}$ –7.7 (*c* 1.60, $CHCl_3$); R_f = 0.4 (25% EtOAc in hexanes); ^{1}H NMR (300 MHz, C_6D_6) δ 7.70–7.65 (m, 1H), 7.36 (dd, *J* = 7.2, 1.8 Hz, 2H), 7.24–7.16 (m, 2H), 7.08–6.93 (m, 5H), 6.90–6.63 (m, 6H), 6.56 (br s, 1H), 5.17–5.12 (m, 1H), 5.10 (t, *J* = 1.0 Hz, 1H), 4.82 (d, *J* = 7.8 Hz, 1H), 3.82–3.63 (m, 3H), 3.62–3.45 (m, 1H), 0.40 (td, *J* = 6.7, 1.3 Hz, 3H); ^{13}C NMR (126 MHz, C_6D_6) δ 199.7, 172.2, 139.7, 139.6, 138.9, 135.5, 130.8, 130.2, 128.4, 128.1, 127.9, 127.8, 127.6, 126.9, 124.3, 121.6, 119.7, 119.2, 116.9, 110.5, 66.6, 60.4, 56.0, 31.9, 12.9; IR (Neat Film, NaCl) 3411, 3060, 1724, 1673, 1456, 1241, 1216, 1096, 1012, 923, 747 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{29}H_{28}NO_3$ $[M+H]^+$: 438.2064, found 438.2070; SFC conditions: 10% MeOH, 2.5 mL/min, Chiralpak IC column, λ = 254 nm, t_R (min): minor = 8.26, major = 9.30.

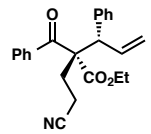
Ethyl (2*R*,3*S*)-2-benzoyl-2-(2-cyanoethyl)-3-phenylpent-4-enoate (112t) and ethyl (2*S*,3*S*)-2-benzoyl-2-(2-cyanoethyl)-3-phenylpent-4-enoate (112t').

Products **112t** and **112t'** were isolated by silica gel chromatography (5% EtOAc in hexanes) as a mixture of diastereomers (3:1), which were separated by preparative HPLC (20% EtOAc in hexanes).



112t

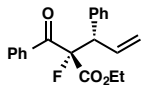
The major diastereomer **112t** was isolated as a white solid, >99% ee, $[\alpha]_D^{25}$ +59.1 (*c* 1.81, $CHCl_3$); R_f = 0.2 (10% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52–7.44 (m, 3H), 7.36–7.30 (m, 2H), 7.26–7.20 (m, 3H), 7.15–7.11 (m, 2H), 6.33 (ddd, *J* = 17.0, 10.2, 8.2 Hz, 1H), 5.14 (ddd, *J* = 10.2, 1.6, 1.0 Hz, 1H), 5.01 (dt, *J* = 17.0, 1.3 Hz, 1H), 4.32 (dt, *J* = 8.0, 1.0 Hz, 1H), 4.15–4.06 (m, 2H), 2.50–2.36 (m, 2H), 2.28 (td, *J* = 8.0, 0.8 Hz, 2H), 1.01 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.2, 171.8, 138.3, 137.5, 137.1, 132.8, 129.7, 128.7, 128.5, 128.1, 127.7, 119.1, 118.1, 64.0, 61.9, 53.6, 30.6, 13.7, 13.1; IR (Neat Film, NaCl) 3061, 3027, 2981, 2248, 1729, 1675, 1596, 1580, 1446, 1243, 1214, 1185, 1085, 1017, 971, 924, 757 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{23}H_{24}NO_3$ $[M+H]^+$: 362.1751, found 362.1766; SFC conditions: 5% IPA, 2.5 mL/min, Chiralpak AD-H column, λ = 254 nm, t_R (min): major = 9.77, minor = 11.61.



112t'

The minor diastereomer was isolated as a white solid, >99% ee, $[\alpha]_D^{25}$ +22.3 (*c* 0.11, $CHCl_3$); R_f = 0.2 (10% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69–7.63 (m, 2H), 7.55–7.47 (m, 1H), 7.41–7.32 (m, 2H), 7.31–7.22 (m, 4H), 7.22–7.16 (m, 1H), 6.29 (dt, *J* = 16.8, 10.2 Hz, 1H), 5.21–5.11 (m, 2H), 4.35 (d, *J* = 10.3 Hz, 1H), 4.03 (dq, *J* = 10.8, 7.2 Hz, 1H), 3.84 (dq, *J* = 10.8, 7.2 Hz, 1H), 2.74–2.63 (m, 1H), 2.46–2.28 (m, 2H), 2.14–2.02 (m, 1H), 0.81 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.0, 171.3, 139.7, 136.7, 136.0, 133.0, 129.7, 128.7, 128.5, 128.3, 127.4, 119.2, 118.9, 63.8, 61.7, 53.0, 30.7, 13.3, 12.9; IR (Neat Film, NaCl) 3062, 3029, 2982, 2248, 1728, 1678, 1596, 1580, 1494, 1446, 1367, 1275, 1242, 1215, 1093, 1018, 972, 928, 757 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{23}H_{24}NO_3$ $[M+H]^+$: 362.1751, found 362.1757; SFC conditions: 5% IPA, 2.5 mL/min, Chiralpak AD-H column, λ = 254 nm, t_R (min): major = 10.65, minor = 12.02.

Ethyl (2*S*,3*S*)-2-benzoyl-2-fluoro-3-phenylpent-4-enoate (112u).

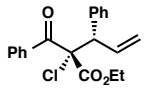


112u

Ketoester **112u** was isolated by silica gel chromatography (gradient elution, 1→2% EtOAc in hexanes) as a colorless oil. 95% ee, $[\alpha]_D^{25}$ +82.0 (*c* 1.19, $CHCl_3$); R_f = 0.4 (5% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (ddt, *J* = 7.6, 2.0, 1.2 Hz, 2H), 7.49 (ddt, *J* = 7.7, 7.0, 1.3 Hz, 1H), 7.38–7.30 (m, 4H), 7.31–7.14 (m, 3H), 6.20 (ddd, *J* = 17.0, 10.2, 9.4 Hz, 1H), 5.27 (ddt, *J* = 17.0, 1.5, 0.8 Hz, 1H), 5.23 (ddd, *J* = 10.1, 1.5, 0.6

Hz, 1H), 4.65 (dd, J = 33.3 ($J_{H\text{-}F}$), 9.4 Hz, 1H), 4.31 (ddq, J = 39.5, 10.8, 7.2 Hz, 2H), 1.30 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 192.6 (d, J = 27.1 Hz), 166.3 (d, J = 26.4 Hz), 137.4, 134.9 (d, J = 3.5 Hz), 134.5 (d, J = 4.0 Hz), 133.6, 129.9 (d, J = 2.6 Hz), 129.5 (d, J = 6.7 Hz), 128.5, 128.4, 127.4, 119.1, 103.1 (d, J = 208.4 Hz), 63.1, 54.4 (d, J = 18.3 Hz), 14.2; ^{19}F NMR (282 MHz, $CDCl_3$) δ -169.39 (d, J = 33.2 Hz); IR (Neat Film, NaCl) 3062, 3030, 2982, 2934, 1749, 1694, 1597, 1454, 1447, 1367, 1230, 1187, 1129, 1038, 929, 856, 743 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{20}H_{20}FO_3$ $[M+H]^+$: 327.1391, found 327.1401; SFC conditions: 5% IPA, 4.0 mL/min, Chiralpak IC column, λ = 254 nm, t_R (min): major = 2.02, minor = 3.18.

Ethyl (2*S*,3*S*)-2-benzoyl-2-chloro-3-phenylpent-4-enoate (112v).

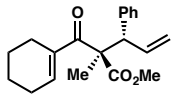


112v

Ketoester **112v** was isolated by silica gel chromatography (gradient elution, 2→3% EtOAc in hexanes) as a colorless oil. >99% ee, $[\alpha]_D^{25}$ +93.8 (*c* 1.43, $CHCl_3$); R_f = 0.4 (5% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84–7.78 (m, 2H), 7.54–7.47 (m, 1H), 7.47–7.40 (m, 2H), 7.40–7.33 (m, 2H), 7.33–7.18 (m, 3H), 6.36 (ddd, J = 16.9, 10.2, 8.7 Hz, 1H), 5.20 (ddd, J = 10.2, 1.5, 0.8 Hz, 1H), 5.15 (ddd, J = 16.9, 1.6, 1.0 Hz, 1H), 4.66 (d, J = 8.6 Hz, 1H), 4.18 (q, J = 7.1 Hz, 2H), 1.12 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 189.8, 167.3, 138.0, 135.9, 134.8, 133.1, 130.7, 129.3, 128.3, 128.0, 127.5, 118.7, 77.3, 63.4, 55.8, 13.8; IR (Neat Film, NaCl) 3062, 3029, 2982, 1754, 1696,

1597, 1581, 1446, 1367, 1299, 1239, 1207, 1186, 1094, 1075, 1025, 1007, 928, 749 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{20}H_{20}ClO_3$ $[M+H]^+$: 343.1095, found 343.1099; SFC conditions: 10% MeOH, 2.5 mL/min, Chiralpak IC column, λ = 254 nm, t_R (min): major = 2.52, minor = 2.77.

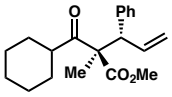
Ethyl (2*R*,3*S*)-2-(cyclohex-1-ene-1-carbonyl)-2-methyl-3-phenylpent-4-enoate (112w).



112w

Ketoester **112w** was isolated by silica gel chromatography (1% EtOAc in hexanes) as a colorless oil. 99% ee, $[\alpha]_D^{25}$ +80.8 (*c* 1.00, $CHCl_3$,); R_f = 0.3 (10% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33–7.13 (m, 5H), 6.47 (td, *J* = 3.9, 2.0 Hz, 1H), 6.25 (ddd, *J* = 16.8, 10.3, 8.0 Hz, 1H), 5.09 (dt, *J* = 10.2, 1.4 Hz, 1H), 5.00 (dt, *J* = 16.9, 1.4 Hz, 1H), 4.29 (dd, *J* = 8.0, 1.4 Hz, 1H), 3.68 (d, *J* = 0.8 Hz, 3H), 2.24–2.03 (m, 3H), 1.97–1.81 (m, 1H), 1.55 (tq, *J* = 7.0, 4.0, 2.3 Hz, 4H), 1.43 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 198.1, 173.8, 139.4, 138.3, 137.9, 137.2, 130.0, 128.0, 126.8, 117.1, 61.1, 54.5, 52.2, 25.9, 24.3, 22.0, 21.3, 20.7; IR (Neat Film, NaCl) 2938, 1732, 1671, 1636, 1452, 1433, 1234, 1113, 984, 917, 703 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{20}H_{25}O_3$ $[M+H]^+$: 313.1798, found 313.1785; SFC conditions: 5% MeOH, 4.0 mL/min, Chiralpak IC column, λ = 254 nm, t_R (min): minor = 5.83, major = 6.55.

Methyl (2*R*,3*S*)-2-(cyclohexanecarbonyl)-2-methyl-3-phenylpent-4-enoate (112x).

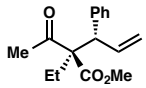


112x

Ketoester **112x** was isolated by silica gel chromatography (5% EtOAc in hexanes) as a mixture of diastereomers (4:1 dr). *For the major isomer*: 96% ee, $[\alpha]_D^{25}$ +57.7 (*c* 1.54, $CHCl_3$, measured with 4:1 dr mixture); R_f = 0.3 (5% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29–7.18 (m, 5H), 6.26 (ddd, *J* = 17.0, 10.2, 8.5 Hz, 1H), 5.08 (ddd, *J* = 10.2, 1.8, 0.9 Hz, 1H), 5.00 (ddd, *J* = 17.0, 1.8, 1.1 Hz, 1H), 4.18 (dt, *J* = 8.5, 1.0 Hz, 1H), 3.71 (s, 3H), 2.50 (tt, *J* = 11.4, 3.2 Hz, 1H), 1.79–1.56 (m, 5H), 1.53–1.46 (m, 1H), 1.33 (s, 3H), 1.32–1.11 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 210.3, 172.4, 139.6, 137.8, 129.9, 128.3, 127.0, 117.4, 64.7, 54.1, 52.2, 48.4, 30.3, 29.6, 25.8, 25.73, 25.71, 18.7; IR (Neat Film, NaCl) 2933, 2854, 1729, 1708, 1635, 1495, 1453, 1432, 1380, 1315, 1228, 1144, 1101, 989, 919 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{20}H_{26}O_3$ $[M+H]^+$: 315.1955, found 315.1955; SFC conditions: 100% CO_2, 4.0 mL/min, Chiralcel OJ-H column, λ = 210 nm, t_R (min): minor = 7.28, major = 7.96.

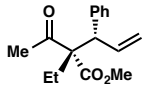
Methyl (2*R*,3*S*)-2-acetyl-2-ethyl-3-phenylpent-4-enoate (112y) and methyl (2*S*,3*S*)-2-acetyl-2-ethyl-3-phenylpent-4-enoate (112y').

Ketoesters **112y** and **112y'** were isolated by silica gel chromatography (gradient elution, 0→4% EtOAc in hexanes) as mixture of two diastereomers (1.5:1 dr). The diastereomers were separated by preparative HPLC (gradient elution, 60→70% MeCN in H_2O).



112y

The major diastereomer **112y** was isolated as a colorless oil. 90% ee, $[\alpha]_D^{25}$ +72.7 (*c* 0.60, $CHCl_3$); R_f = 0.4 (5% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32–7.25 (m, 2H), 7.25–7.18 (m, 1H), 7.17–7.07 (m, 2H), 6.28 (ddd, *J* = 17.0, 10.2, 8.4 Hz, 1H), 5.08 (ddd, *J* = 10.2, 1.7, 0.9 Hz, 1H), 4.97 (ddd, *J* = 17.0, 1.7, 1.1 Hz, 1H), 4.03 (d, *J* = 8.5 Hz, 1H), 3.76 (s, 3H), 2.06 (s, 3H), 1.86–1.68 (m, 2H), 0.77 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 205.8, 172.4, 139.5, 137.7, 129.3, 128.4, 127.3, 117.3, 68.2, 53.5, 51.9, 29.8, 27.4, 9.1; IR (Neat Film, NaCl) 3083, 3029, 2978, 2950, 2883, 1709, 1601, 1494, 1434, 1385, 1353, 1301, 1220, 1116, 1029, 993, 919, 755 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{16}H_{21}O_3$ $[M+H]^+$: 261.1485, found 261.1492; SFC conditions: 0.5% IPA, 2.5 mL/min, Chiralcel OJ-H column, λ = 210 nm, t_R (min): minor = 4.79, major = 7.02.

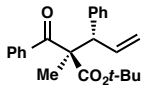


112y'

The minor diastereomer **112y'** was isolated as a colorless oil. 91% ee, $[\alpha]_D^{25}$ +25.3 (*c* 0.26, $CHCl_3$); R_f = 0.4 (5% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26–7.23 (m, 2H), 7.21–7.17 (m, 1H), 7.17–7.13 (m, 2H), 6.31 (ddd, *J* = 16.9, 10.2, 9.3 Hz, 1H), 5.15 (ddd, *J* = 10.2, 1.6, 0.7 Hz, 1H), 5.10 (ddd, *J* = 17.0, 1.7, 1.0 Hz, 1H), 4.11 (d, *J* = 9.4 Hz, 1H), 3.63 (s, 3H), 2.12 (s, 3H), 2.09–1.98 (m, 1H), 1.80 (dq, *J* = 14.8, 7.5 Hz, 1H), 0.77 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 205.3, 172.3, 140.1, 137.3,

129.4, 128.2, 127.0, 117.6, 68.0, 52.5, 51.9, 30.1, 26.9, 8.8; IR (Neat Film, NaCl) 3063, 3030, 2962, 2925, 2850, 1710, 1600, 1446, 1354, 1286, 1260, 1223, 1182, 1118, 1095, 1023, 921, 864, 801 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{16}H_{21}O_3$ $[M+H]^+$: 261.1485, found 261.1494; SFC conditions: 0.5% IPA, 2.5 mL/min, Chiralcel OJ-H column, λ = 210 nm, t_R (min): minor = 6.29, major = 7.02.

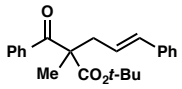
tert-Butyl (2*R*,3*S*)-2-benzoyl-2-methyl-3-phenylpent-4-enoate (112z).



112z

Ketoester **112z** was isolated by silica gel chromatography (gradient elution, 0→2→5% EtOAc in hexanes) as a colorless oil. >99% ee, $[\alpha]_D^{25}$ +67.4 (*c* 1.54, $CHCl_3$); R_f = 0.4 (5% EtOAc in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 7.74–7.70 (m, 2H), 7.49–7.46 (m, 1H), 7.39–7.34 (m, 2H), 7.25–7.16 (m, 5H), 6.34 (ddd, *J* = 17.0, 10.3, 7.9 Hz, 1H), 5.12 (ddd, *J* = 10.3, 1.8, 1.1 Hz, 1H), 5.03 (dt, *J* = 17.0, 1.6 Hz, 1H), 4.42 (dt, *J* = 7.9, 1.2 Hz, 1H), 1.50 (s, 3H), 1.29 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 198.1, 171.8, 139.7, 138.1, 137.3, 132.2, 130.4, 128.5, 128.3, 128.1, 126.9, 117.1, 82.6, 62.1, 54.6, 27.8, 21.0; IR (Neat Film, NaCl) 3061, 3027, 2978, 2934, 1728, 1716, 1687, 1682, 1598, 1454, 1446, 1251, 1155, 1115, 961, 918, 844 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{23}H_{27}O_3$ $[M+H]^+$: 351.1955, found 351.1955; SFC conditions: 5% IPA, 2.5 mL/min, Chiralpak IC column, λ = 254 nm, t_R (min): major = 4.14, minor = 5.80.

tert-Butyl (_E_)-2-benzoyl-2-methyl-5-phenylpent-4-enoate (113z).

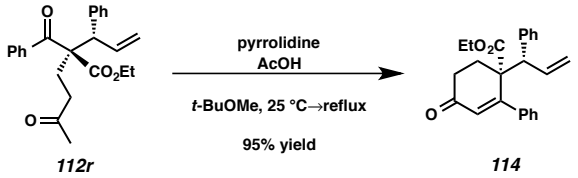


113z

Ketoester **113z** was isolated by silica gel chromatography (gradient elution, 0→2→5% EtOAc in hexanes) as a colorless oil. 38% ee, $[\alpha]_D^{25}$ +3.9 (*c* 0.74, $CHCl_3$); R_f = 0.4 (5% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92–7.89 (m, 2H), 7.56–7.51 (m, 1H), 7.46–7.41 (m, 2H), 7.33–7.27 (m, 4H), 7.23–7.18 (m, 1H), 6.39 (dt, *J* = 15.8, 1.3 Hz, 1H), 6.16–6.06 (m, 1H), 2.93 (ddd, *J* = 14.2, 7.5, 1.4 Hz, 1H), 2.84 (ddd, *J* = 14.2, 7.7, 1.3 Hz, 1H), 1.55 (s, 3H), 1.28 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.8, 172.8, 137.3, 135.9, 133.9, 132.7, 128.8, 128.6, 128.5, 127.4, 126.3, 124.7, 82.2, 58.0, 40.7, 27.8, 21.5; IR (Neat Film, NaCl) 3058, 3026, 2977, 2933, 1728, 1686, 1682, 1597, 1579, 1447, 1368, 1249, 1212, 1152, 1111, 970, 845 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{23}H_{27}O_3$ $[M+H]^+$: 351.1955, found 351.1949; SFC conditions: 5% IPA, 2.5 mL/min, Chiralpak IC column, λ = 254 nm, t_R (min): major = 9.88, minor = 8.48.

4.6.5 Procedures for derivatization of allylic alkylation products and spectroscopic data of derivatives

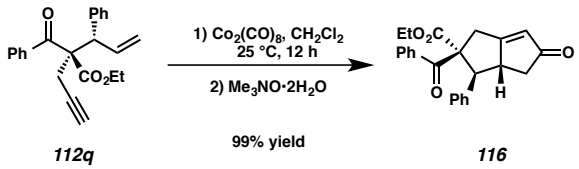
Synthesis of cyclohexenone 114:



112r *114*

To a solution of ketoester **112r** (60.4 mg, 0.6 mmol) in *t*-BuOMe (2 mL) was added pyrrolidine (13.7 mg, 0.19 mmol) and AcOH (11.6 mg, 0.19 mmol). The mixture was stirred for 12 h at 25 °C then heated to reflux for 4 h. The solvent was removed under reduced pressure and the residue was subjected to column chromatography on silica gel (gradient elution, 10→25% EtOAc in hexanes) to give cyclohexenone **114** (55.1 mg, 95% yield) as a colorless oil. $[\alpha]_D^{25}$ +151.4 (*c* 1.19, $CHCl_3$); R_f = 0.5 (25% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34–7.28 (m, 1H), 7.25–7.19 (m, 2H), 7.13–7.04 (m, 3H), 7.04–6.97 (m, 2H), 6.69–6.63 (m, 2H), 6.33 (ddd, *J* = 16.9, 10.2, 7.8 Hz, 1H), 6.07 (s, 1H), 5.10 (ddd, *J* = 10.2, 1.6, 1.0 Hz, 1H), 4.87 (dt, *J* = 17.0, 1.5 Hz, 1H), 4.31 (q, *J* = 7.1 Hz, 2H), 4.26 (dt, *J* = 7.5, 1.5 Hz 1H), 2.91–2.77 (m, 1H), 2.62–2.53 (m, 3H), 1.32 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 198.5, 173.2, 161.6, 139.5, 139.2, 138.0, 131.9, 129.8, 128.7, 128.2, 128.1, 128.0, 126.7, 118.1, 62.0, 54.0, 53.8, 34.7, 30.9, 14.3; IR (Neat Film, NaCl) 3058, 3030, 2981, 1725, 1673, 1602, 1492, 1444, 1326, 1240, 1214, 1170, 1016, 921, 882 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{24}H_{25}O_3$ $[M+H]^+$: 361.1798, found 361.1798.

Synthesis of bicyclic enone 116:

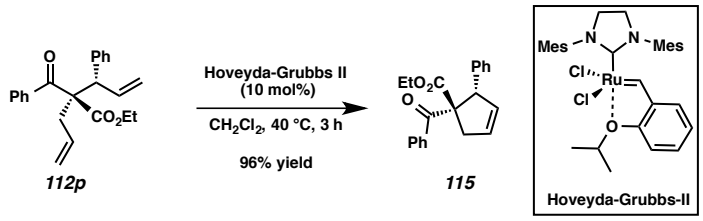


112q *116*

A dried flask was charged with a solution of enyne **112q** (8.6 mg, 0.025 mmol) and $Co_2(CO)_8$ (11.8 mg, 0.034 mmol) in CH_2Cl_2 (2 mL) and the mixture was stirred at room temperature for 12 h under an atmosphere of argon. After full consumption of **112q** was observed by TLC analysis, $Me_3NO{\bullet}2H_2O$ (7.6 mg, 0.068 mmol) was added. The mixture was stirred for 20 min and an additional portion of $Me_3NO{\bullet}2H_2O$ (30.1 mg, 0.27 mmol) was added. Stirring was continued until complete consumption of the cobalt-alkyne complex was observed by TLC analysis (about 4 h). The mixture was filtered through a celite pad, washed with CH_2Cl_2, the solvent removed under reduced pressure, and the residue subjected to column chromatography on silica gel (25% EtOAc in hexanes) to give the bicyclic enone **116** (9.3 mg, 99% yield) as a colorless oil. The relative stereochemistry of **116** was assigned by 2D-NOESY. $[\alpha]_D^{25}$ -178.8 (*c* 0.79, $CHCl_3$); R_f = 0.3 (25% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33–7.26 (m, 1H), 7.26–7.18 (m, 4H), 7.13–7.02 (m, 5H), 6.03 (td, *J* = 2.2, 1.1 Hz, 1H), 4.11–3.91 (m, 3H), 3.82 (d, *J* = 12.3 Hz, 1H), 3.73–3.63 (m, 1H), 3.01 (dq, *J* = 18.2, 1.1 Hz, 1H), 2.54 (ddd, *J* = 18.0, 6.4, 0.8 Hz, 1H), 2.14 (ddd, *J* = 18.0, 2.5, 1.7 Hz, 1H), 0.86 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 209.3, 197.1, 183.8, 173.3, 137.1, 136.7, 132.4, 129.5, 128.5, 128.3, 127.9, 127.8, 126.1, 68.6, 62.0, 55.8, 50.4, 41.7, 39.2, 13.6; IR (Neat Film, NaCl) 3034, 2979, 2927, 1733, 1714, 1668, 1636, 1600, 1583, 1449, 1409, 1255, 1211, 1183,

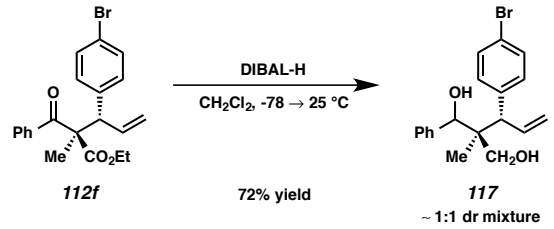
1071, 1043, 927, 914, 819 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{24}H_{23}O_4$ $[M+H]^+$: 375.1596, found 375.1592.

Synthesis of compound 115:



To a flame-dried Schlenk flask was added a solution of **112p** (20.8 mg, 0.06 mmol in 1.5 mL of CH_2Cl_2) and Hoveyda-Grubbs II catalyst (3.7 mg, 10 mol%). The reaction mixture was stirred for 3 h at 40 °C, filtered through a short silica pad and purified by silica gel chromatography (gradient elution, 1→5% EtOAc in hexanes) to give ketoester **115** (18.3 mg, 96% yield) as a white solid. $[\alpha]_D^{25}$ -613.7 (*c* 0.94, $CHCl_3$); R_f = 0.4 (5% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61–7.55 (m, 2H), 7.38 (ddt, *J* = 8.6, 7.1, 1.2 Hz, 1H), 7.28–7.21 (m, 2H), 6.97–6.93 (m, 3H), 6.89–6.83 (m, 2H), 5.90 (ddt, *J* = 6.1, 2.6, 1.8 Hz, 1H), 5.75 (dtd, *J* = 5.5, 2.6, 1.5 Hz, 1H), 4.92 (q, *J* = 2.3 Hz, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 4.03 (dtd, *J* = 18.0, 2.6, 1.9 Hz, 1H), 2.73 (ddd, *J* = 18.0, 2.6, 1.6 Hz, 1H), 1.00 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 194.2, 174.4, 138.4, 136.6, 133.8, 132.5, 129.5, 128.5, 128.1, 128.0, 127.4, 127.0, 68.3, 61.9, 58.0, 41.5, 13.8; IR (Neat Film, NaCl) 3060, 3028, 2959, 2932, 2871, 1736, 1732, 1686, 1682, 1598, 1582, 1492, 1447, 1365, 1258, 1243, 1220, 1157, 1087, 1048, 1004, 966, 922, 876, 761 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{21}H_{21}O_3$ $[M+H]^+$: 321.1485, found 321.1489.

4.6.6 Determination of the absolute confirmation of compound 112f



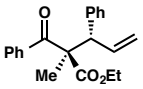
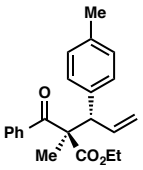
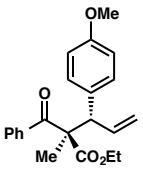
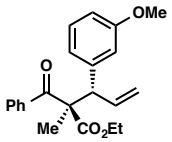
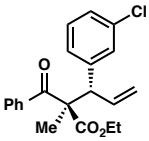
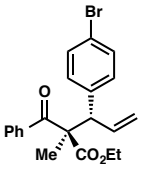
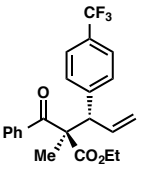
112f 72% yield *117* ~ 1:1 dr mixture

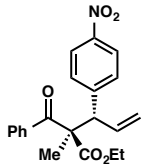
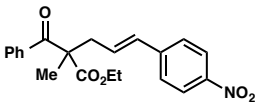
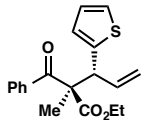
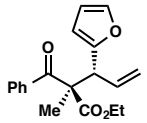
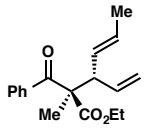
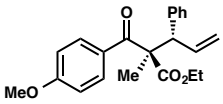
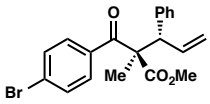
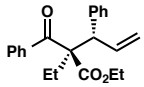
To a flame-dried flask was added **112f** (98% ee, 62.1 mg, 0.16 mmol), CH_2Cl_2 (5 mL) and this solution was cooled to -78 °C. DIBAL-H (0.62 mL, 1.0 M solution in hexane) was added dropwise by syringe. The mixture was stirred for 2 h at -78 °C, then allowed to warm to 25 °C and stirred for an additional 12 h. The reaction was then cooled to 0 °C, and another 0.62 mL of DIBAL-H solution was added, followed by stirring at 25 °C for 3 h. The reaction mixture was then quenched with saturated aqueous Rochelle's salt (20 mL) and stirred for another 3 h. The aqueous layer was partitioned with a total of 100 mL of CH_2Cl_2 and the combined organic phases washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (gradient elution, 5→20% EtOAc in hexanes) to give 40.2 mg (72% yield) of **117** as white solid mixture (1:1 dr). The diastereomers were separated by preparative HPLC (gradient elution, 60→90% MeCN in H_2O). *For isomer a*: white solid, $[\alpha]_D^{25}$ +58.9 (*c* 0.47, $CHCl_3$); R_f = 0.4 (25% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ7.46–7.39 (m, 4H), 7.36–7.31 (m, 2H), 7.31–7.27 (m, 1H), 7.27–7.23 (m, 2H), 6.79 (dt, *J* = 16.9, 10.1 Hz, 1H), 5.20–5.10 (m, 2H), 5.07 (s, 1H), 3.67 (d, *J* = 10.1 Hz, 1H), 3.34 (d, *J* = 11.2 Hz, 1H), 3.11 (dd, *J* = 11.1, 0.7 Hz, 1H), 1.56 (br s, 2H), 0.72 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.5, 141.0, 140.4, 131.6, 131.4, 128.04, 128.79,

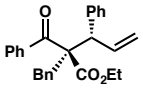
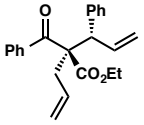
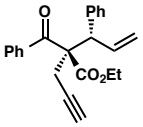
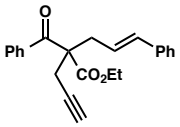
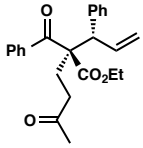
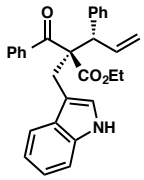
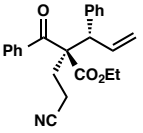
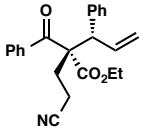
127.8, 120.5, 116.5, 76.0, 66.6, 55.8, 46.2, 15.3; IR (Neat Film, NaCl) 3423, 3070, 2969, 2923, 1486, 1452, 1403, 1342, 1074, 1012, 916, 827 cm^{-1}; HRMS (ESI+) *m/z* calc'd for fragment $C_{19}H_{18}Br$ $[M-H_4O_2+H]^+$: 325.0586, found 325.0585. *For isomer b*: white solid, $[\alpha]_D^{25}$ +53.4 (*c* 0.43, $CHCl_3$); R_f = 0.4 (24% EtOAc in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 7.50–7.45 (m, 2H), 7.35–7.27 (m, 5H), 7.25–7.20 (m, 2H), 6.30 (dt, *J* = 16.8, 10.0 Hz, 1H), 5.35 (ddd, *J* = 16.8, 1.9, 0.8 Hz, 1H), 5.24 (ddd, *J* = 10.0, 1.9, 0.5 Hz, 1H), 4.39 (d, *J* = 10.0 Hz, 1H), 4.26 (s, 1H), 3.64 (d, *J* = 11.6 Hz, 1H), 3.51 (dd, *J* = 11.6, 1.8 Hz, 1H), 1.58 (br s, 2H), 0.48 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.0, 140.2, 137.2, 131.7, 131.3, 128.02, 127.97, 127.8, 120.6, 118.3, 80.0, 65.6, 49.7, 44.5, 15.5; IR (Neat Film, NaCl) 3372, 2973, 2938, 2888, 1637, 1486, 1473, 1454, 1402, 1348, 1266, 1203, 1101, 1077, 1024, 1010, 921, 894, 831, 782 cm^{-1}; HRMS (ESI+) *m/z* calc'd for fragment $C_{19}H_{18}Br$ $[M-H_4O_2+H]^+$: 325.0586, found 325.0588.

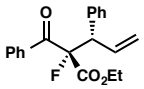
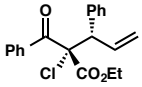
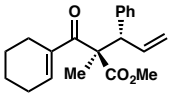
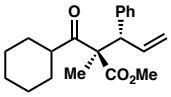
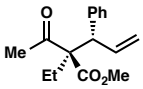
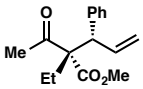
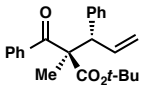
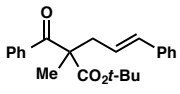
4.6.7 Determination of enantiomeric excess

Table 4.6.7.1. *Determination of enantiomeric excess*

entry	compound	SFC analytic conditions	ee (%)
1	 ***112a***	Chiralpak IC, λ = 254 nm 5% IPA/CO_2, 2.5 mL/min t_R (min): major 4.12, minor 6.14	98
2	 ***112b***	Chiralpak IC, λ = 254 nm 5% IPA/CO_2, 2.5 mL/min t_R (min): major 6.71, minor 9.45	>99
3	 ***112c***	Chiralcel OJ-H, λ = 254 nm 4% IPA/CO_2, 2.5 mL/min t_R (min): minor 5.64, major 6.84	>99
4	 ***112d***	Chiralpak IC, λ = 254 nm 2% MeOH/CO_2, 2.5 mL/min t_R (min): major 12.24, minor 13.50	>99
5	 ***112e***	Chiralpak IC, λ = 254 nm 10% IPA/CO_2, 4.0 mL/min t_R (min): major 1.59, minor 1.77	99
6	 ***112f***	Chiralpak AD-H, λ = 254 nm 10% IPA/CO_2, 4.0 mL/min t_R (min): minor 2.95, major 3.17	>99
7	 ***112g***	Chiralpak AD-H, λ = 254 nm 2% IPA/CO_2, 2.5 mL/min t_R (min): minor 5.20, major 6.68	>99

entry	compound	SFC analytic conditions	ee (%)
8	 ***112h***	**Chiralpak AD-H, λ = 254 nm 5% MeOH/CO_2, 3.0 mL/min t_R (min): minor 4.47, major 5.71**	**93**
9	 ***113h***	**Chiralpak AD-H, λ = 254 nm 10% MeOH/CO_2, 3.0 mL/min t_R (min): major 7.13, minor 8.06**	**23**
10	 ***112i***	**Chiralpak IC, λ = 254 nm 5% IPA/CO_2, 2.5 mL/min t_R (min): major 7.92, mino 11.24**	**95**
11	 ***112j***	**Chiralpak IC, λ = 254 nm 5% IPA/CO_2, 2.5 mL/min t_R (min): major 5.09, minor 9.14**	**>99**
12	 ***112k***	**Chiralpak AD-H, λ = 210 nm 2% IPA/CO_2, 2.5 mL/min t_R (min): minor 4.40, major 5.52**	**91**
13	 ***112l***	**Chiralpak IC, λ = 254 nm 10% IPA/CO_2, 4.0 mL/min t_R (min): major 2.67, minor 3.51**	**99**
14	 ***112m***	**Chiralpak AD-H, λ = 254 nm 5% IPA/CO_2, 2.5 mL/min t_R (min): major 5.35, minor = 5.88**	**>99**
15	 ***112n***	**Chiralpak AD-H, λ = 254 nm, 5% MeOH/CO_2, 2.5 mL/min, t_R (min): major = 2.48, minor = 2.20**	**>99**

entry	compound	SFC analytic conditions	ee (%)
16	 ***112o***	**Chiralpak AD-H, λ = 254 nm** **4% MeOH/CO_2, 4.0 mL/min** **t_R (min): major 5.06, minor 8.94**	**>99**
17	 ***112p***	**Chiralpak IC, λ = 254 nm** **3% IPA/CO_2, 4.0 mL/min** **t_R (min): major 7.16, minor 8.60**	**>99**
18	 ***112q***	**Chiralcel OD-H, λ = 254 nm** **5% IPA/CO_2, 2.5 mL/min** **t_R (min): minor 5.67, major 6.44**	**>99**
19	 ***113q***	**Chiralpak IC, λ = 254 nm** **5% IPA/CO_2, 2.5 mL/min** **t_R (min): major 10.67, minor 9.81**	**34**
20	 ***112r***	**Chiralcel OD-H, λ = 254 nm** **5% IPA/CO_2, 2.5 mL/min** **t_R (min): minor 10.8, major 8.0**	**99**
21	 ***112s***	**Chiralpak IC, λ = 254 nm** **10% MeOH/CO_2, 2.5 mL/min** **t_R (min): major 8.26, minor 9.30**	**>99**
22	 ***112t***	**Chiralpak AD-H, λ = 254 nm** **5% IPA/CO_2, 2.5 mL/min** **t_R (min): major 9.77, minor 11.60**	**>99**
23	 ***112t'***	**Chiralpak AD-H, λ = 254 nm** **5% IPA/CO_2, 2.5 mL/min** **t_R (min): major 10.65, minor 12.00**	**>99**

entry	compound	SFC analytic conditions	ee (%)
24	 ***112u***	**Chiralpak IC, λ = 254 nm** **5% IPA/CO_2, 4.0 mL/min** **t_R (min): major 2.02, minor 3.18**	**95**
25	 ***112v***	**Chiralpak IC, λ = 254 nm** **10% IPA/CO_2, 2.5 mL/min** **t_R (min): major 2.52, minor 2.76**	**>99**
26	 ***112w***	**Chiralpak IC, λ = 254 nm** **5% MeOH/CO_2, 4 mL/min** **t_R (min): major 6.56, minor 5.83**	**99**
27	 ***112x***	**Chiralcel OJ-H, λ = 210 nm** **100% CO_2, 4.0 mL/min** **t_R (min): minor 7.28, major 7.96**	**96**
28	 ***112y***	**Chiralcel OJ-H, λ = 210 nm** **0.5% IPA/CO_2, 2.5 mL/min** **t_R (min): minor 4.79, major 5.33**	**90**
29	 ***112y'***	**Chiralcel OJ-H, λ = 210 nm** **0.5% IPA/CO_2, 2.5 mL/min** **t_R (min): minor 6.29, major 7.02**	**91**
30	 ***112z***	**Chiralpak IC, λ = 254 nm** **5% IPA/CO_2, 2.5 mL/min** **t_R (min): major 4.14, minor 5.80**	**>99**
31	 ***113z***	**Chiralpak IC, λ = 254 nm** **5% IPA/CO_2, 2.5 mL/min** **t_R (min): major 9.88, minor 8.48**	**38**

4.7 REFERENCES AND NOTES

(97) For the first example see reference 75; for reviews see references 76.

(98) Zhuo, C.-X.; Wu, Q.-F.; Zhao, Q.; Xu, Q.-L.; You, S.-L. *J. Am. Chem. Soc.* **2013**, *135*, 8169.

(99) See references 80, 81 and: Bartels, B.; García-Yebra, C.; Helmchen, G. *Eur. J. Org. Chem.* **2003**, 1097.

(100) Chen, W.; Chen, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2014**, *136*, 15825.

(101) Absolute configuration of product **112f** determined by x-ray analysis of a derivative structure, see appendix A7 for detail. Absolute configuration of all other products determined by analogy. Relative configuration of product derivative **116** was determined by 2D NMR studies, see SI below and appendix A6 for details. The relative configurations of all other products determined by anaolgy.

(102) (a) Xia, J.-B.; Liu, W.-B.; Wang, T.-M.; You, S.-L. *Chem. Eur. J.* **2010**, *16*, 6442. (b) Farwick, A.; Engelhart, J. U.; Tverskoy, O.; Welter, C.; Umlauf, Q. A.; Rominger, F.; Kerr, W. J.; Helmchen, G. *Adv. Synth. Catal.* **2011**, *353*, 349.

(103) (a) González, D. F.; Brand, J. P.; Waser, J. *Chem. Eur. J.* **2010**, *16*, 9457. (b) Bartoli, G.; Bosco, M.; Bellucci, M. C.; Marcantoni, E.; Sambri, L.; Torregiani, E. *Eur. J. Org. Chem.* **1999**, 617. (c) Stavber, G.; Zupan, M.; Stavber, S. *Tetrahedron Lett.* **2007**, *48*, 2671. (d) Meshram, H. M.; Reddy, P. N.; Sadashiv, K.; Yadav, J. S. *Tetrahedron Lett.* **2005**, *46*, 623. (e) Turner, J. A.; Jacks, W. S. *J. Org. Chem*, **1989**, *54*, 4229.