# *APPENDIX 6*

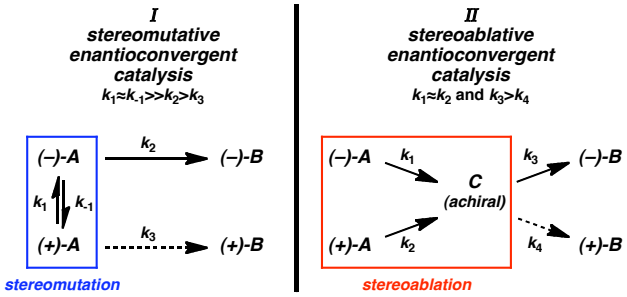
## *Palladium-Catalyzed Decarboxylative Allylic Alkylation of Diastereomeric β-Ketoesters*

### A6.1 INTRODUCTION AND BACKGROUND

We are interested in stereoablative enantioconvergent catalysis, a concept that is illustrated by the use of quaternary β-ketoesters in the palladium-catalyzed decarboxylative allylic alkylation reported by our laboratories.[1] Typical stereomutative enantioconvergent processes, such as dynamic kinetic resolution, require a pre-equilibration epimerization of starting material **A** followed by enantioselective conversion to product **B** (Pathway I, Scheme A6.1). Quaternary stereocenters are not typically epimerizable. Thus, we believe another pathway is operative, wherein both enantiomers of the starting material **A** convert irreversibly to prochiral intermediate **C**. This prochiral intermediate **C** can then preferentially form one enantiomer of product **B** under the influence of the chiral catalyst (Pathway II, Scheme A6.1). This alternate pathway has been termed stereoablative enantioconvergent catalysis. The lability of the

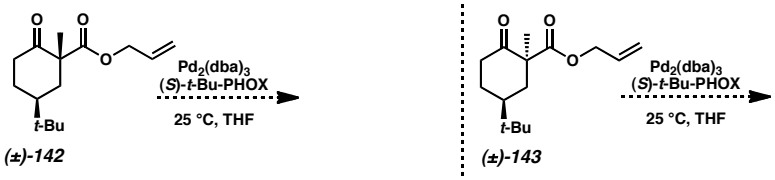
stereogenic center is illustrated with quaternary β-ketoesters, where enolate formation destroys the stereochemical information at the α-position.

*Scheme A6.1 Stereomutative versus stereoablative enantioconvergent catalysis*




To provide evidence for stereoablative enantioconvergent catalysis, we envisioned using diastereomeric β-ketoesters **142** and **143** as substrates for the palladium-catalyzed decarboxylative allylic alkylation (Scheme A6.2). The stereoablative hypothesis is supported if both β-ketoesters afford similar diastereomeric product ratios as the stereochemistry at α-position of the β-ketoester is not expected to influence the outcome of the reaction.

*Scheme A6.2 Proposed experiment to test stereoablation hypothesis*



## A6.2 PALLADIUM-CATALYZED DECARBOXYLATIVE ALLYLIC ALKYLATION OF β-KETOESTERS

### *A6.2.1 Experimental Results*

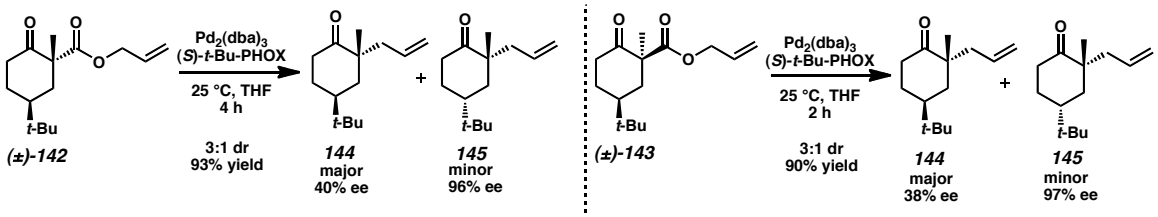
Once the synthesis and stereochemical verification of diastereomeric β-ketoesters **142** and **143** were completed,[2] we treated each β-ketoester with $Pd_2(dba)_3$ and (*S*)-*t*-Bu-PHOX. We observed similar product ratios and enantioselectivities for the asymmetric decarboxylative allylic alkylation of both **142** and **143** (Scheme A6.3). Thus, our results support the formation of an enolate wherein the stereochemistry at the α-position of the β-ketoester starting material does not influence the outcome of the reaction. The relative and absolute stereochemistry of the products **144** and **145** were determined by x-ray crystallography of their corresponding crystalline semicarbazone derivatives obtained from the asymmetric variant of the decarboxylative allylic alkylation (Scheme A6.4).[2]

However, two other interesting observations were made during this experiment. Minor product **145** had a significantly greater enantiomeric excess than that of major product **144** (97% ee versus 39% ee). Furthermore, decarboxylative allylation of **143** was 1.5 times faster than the decarboxylative allylation of **142**, which is surprising because stereoelectronic arguments would predict that **142** should be the faster reacting diastereomer as there is better orbital overlap between the carbonyl carbon and the α-carbon when the carboxyl is in the axial position.

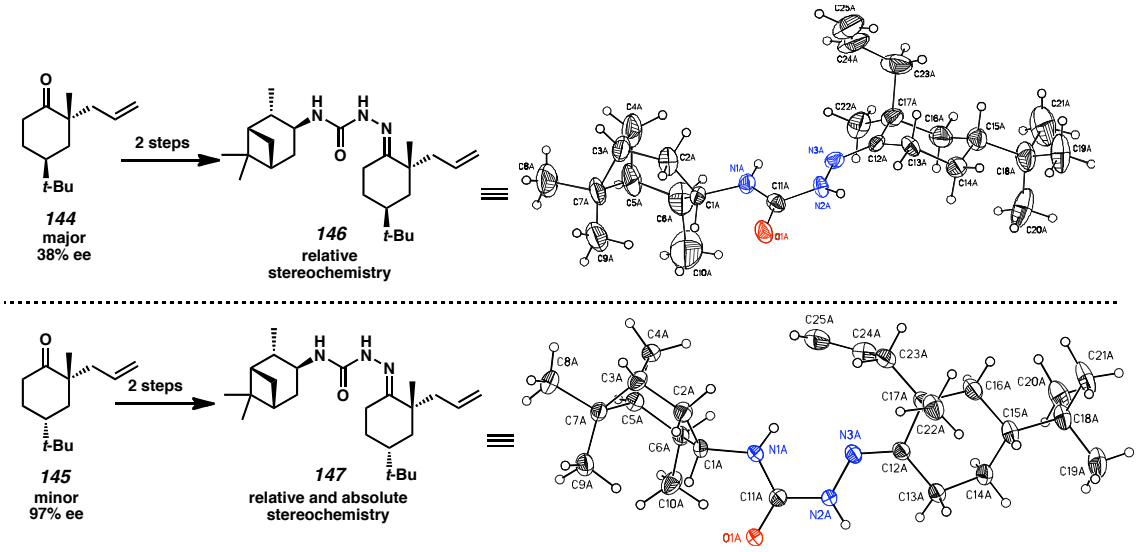
To confirm the observed difference in their relative rates of reaction, **142** and **143** were treated with an achiral catalyst (Scheme A6.5). Decarboxylative allylic alkylation of **142** and **143** using $PPh_3$ as the ligand gave the same major and minor products as those

observed in the enantioselective case. Furthermore, the difference in relative rate of reaction was more dramatic for the $PPh_3$ case; the decarboxylative allylic alkylation of **143** was 15.6 times faster than that observed for **142**.[3]

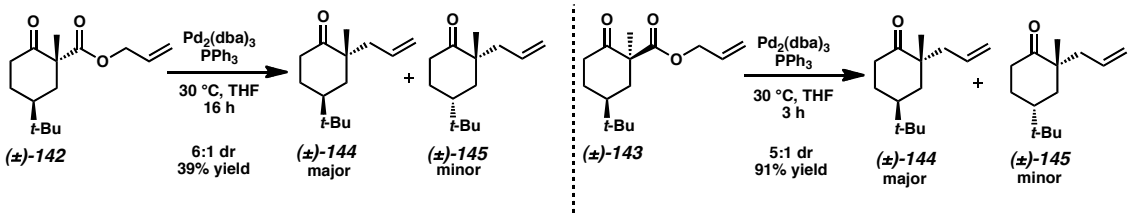
*Scheme A6.3 Asymmetric palladium-catalyzed decarboxylative allylation of β-ketoesters*




*Scheme A6.4 Determination of relative and absolute stereochemistry*



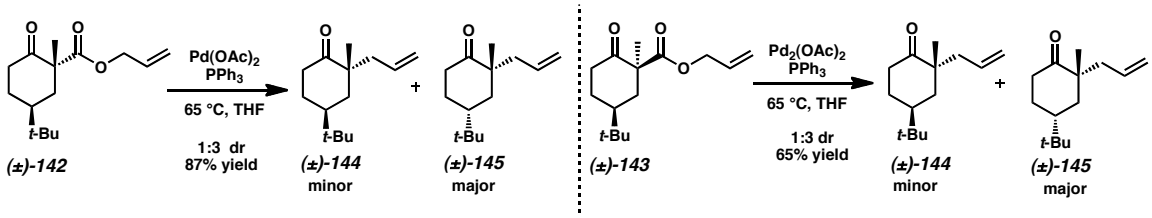

*Scheme A6.5. Racemic palladium-catalyzed decarboxylative allylation of β-ketoesters*




It is important to note that Tsuji has previously reported a nonenantioselective allylation reaction of diastereomeric β-ketoesters **142** and **143** (Scheme A6.6).[4] Tsuji's

assignment of the minor and major products are not in agreement with our results. In Tsuji's report, the yield and product ratios were determined by GC, and Tsuji does not offer any rationale for his assignment of **144** and **145**. Furthermore, Tsuji did not comment on the relative rate of reaction between the two diastereomers.

*Scheme A6.6 Racemic palladium-catalyzed decarboxylative allylic alklylation as reported by Tsuji*

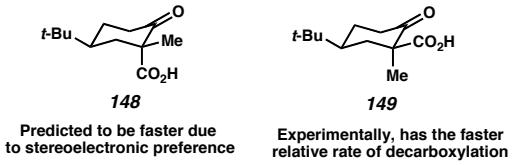



### *A6.2.2 Rationalization for Lack of Stereoelectronic Control in Decarboxylation of Diastereomeric β-Ketoacids*

The surprising observation that β-ketoester **143**, which has the ester group in an equatorial position, is more reactive than β-ketoester **142**, which has the ester group in an axial position, contradicts stereoelectronic control arguments. However, this contradiction has also been observed in the decarboxylation of diastereomeric β-ketoacids.[5]

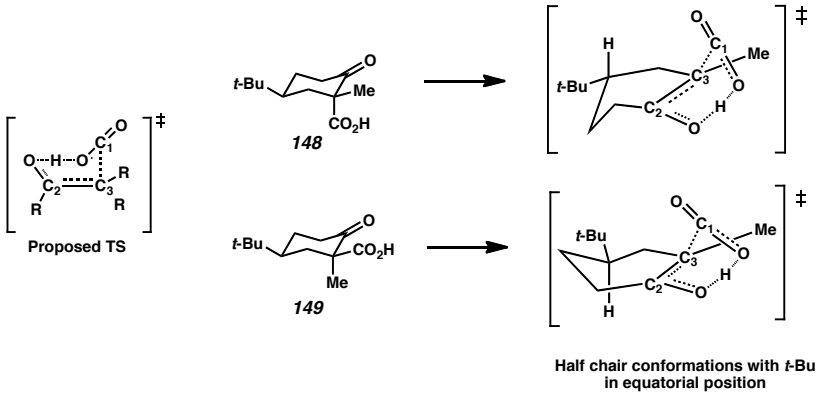
Based on stereoelectronic arguments, β-ketoacid **148** is predicted to be more reactive because having the carboxyl group in the axial position allows for continuous overlap of the incipient p-orbital with the p-orbital on the carbonyl carbon (Figure A6.1). However, Pollack has reported that β-ketoacid **149** decarboxylates 3-fold faster than **148** in acidic media.[5] Under basic conditions, the relative rate of reactions is more striking: β-ketoacid **149** decarboxylates 15- to 20-fold faster than **148**.

*Figure A6.1 Kinetic experiments on rates of decarboxylation of β-ketoacids*



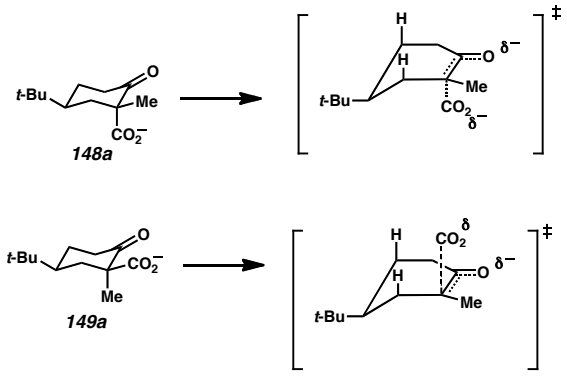

Under acidic conditions, Pollack has proposed that the transition state for decarboxylation is a six-membered intermediate, in which the O–H bond is in the same plane as the original C(3)–C(2)=O bond (Figure A6.2).[5] The C(1)–C(3) bond that is broken is perpendicular to this plane, which allows for the continuous overlap of the incipient p-orbital with the $\pi^*$ of the carbonyl bond. The proposed transition states for β-ketoacids **148** and **149** are shown in Figure A6.2, where the cyclohexene is shown in a half chair conformation with the *tert*-butyl group in the equatorial position and the methyl group in the plane of the carbon–carbon double bond. If the energies of the transition states are similar, then the relative rate of decarboxylation is determined by the relative stabilities of β-ketoacids **148** and **149**. Based on A values derived from cyclohexanes (Me = 1.70 kcal/mol, COOH = 1.35 kcal/mol), β-ketoacid **149** is higher in energy; therefore, it should be more reactive.

*Figure A6.2 Proposed transition states under acidic conditions*



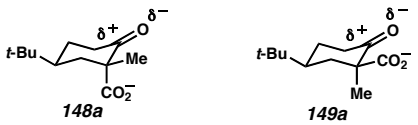
Rationalization of the relative rate of decarboxylation of β-ketoacids **148** and **149** under basic conditions is based on a similar argument. Decarboxylation of the carboxylate anions of β-ketoacids has not been investigated thoroughly, but studies on the decarboxylation of benzoylacetic acids have suggested that the transition state is late on the reaction coordinate; thus, the transition state resembles the enolate product (Figure A6.3).[6] We can apply this observation to the decarboxylation of carboxylates **148a** and **149a**. If steric interactions with the axial hydrogens are ignored in the transition states shown in Figure A6.3, these two transition states should have similar energies, and the relative rates of reaction reflect the differences in energy of carboxylates **148a** and **149a**.

*Figure A6.3 Proposed transition states under basic conditions*




To predict the relative energy of **148a** and **149a**, the dipole-dipole repulsions between the carboxylate and the carbonyl oxygen should be considered (Figure A6.4). For **149a**, the dipole-dipole repulsion is more significant; hence, **149a** is less stable and will decarboxylate more readily. Evidence that this dipole-dipole interaction is significant can be found in the $pK_a$ values of **148** and **149**. Acid **149** has a higher $pK_a$ than **148** (5.79 versus 5.29 in 70% MeOH in water at 0 °C).[6]

*Figure A6.4 Dipole-dipole repulsions*




### *A6.2.3 Rationalization for the Faster Relative Rate of Reaction for β-Ketoesters*

A possible explanation for the increased reactivity of β-ketoester **143** relative to its diastereomer assumes that the palladium π-allyl complex is formed prior to decarboxylation, and that both of these events occur in a stepwise fashion. It is proposed that formation of a carboxylate intermediate occurs and that unfavorable dipole-dipole repulsion, such as those shown in Figure A6.4 for the carboxylate derived from **143** would make it the more reactive diastereomer. The formation of a palladium carboxylate intermediate in our decarboxylative allylic alkylation has been supported by subsequent mechanistic studies performed by our laboratories.[7]

### *A6.2.4 Rationale for Greater Enantioselectivity in Minor Product*

The second interesting observation made in our asymmetric decarboxylative allylation of diastereomeric β-ketoesters is that the minor product **145** had a much greater enantiomeric excess than major product **144**. We believe that this observation can be attributed to competing modes of control. To help illustrate our point, we must consider all four possible products and their relative abundance for the asymmetric decarboxylative allylic alkylation of β-ketoester **142** (Scheme A6.3). The diastereomers and their enantiomers are shown in Figure A6.5, and the relative percentages of each of the products are shown in Figure A6.6.

*Figure A6.5 All possible products from asymmetric decarboxylative allylic alkylation of β-ketoester* ***142***

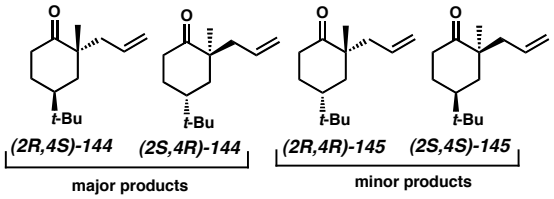
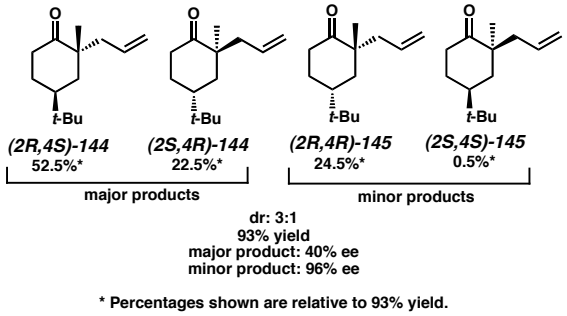


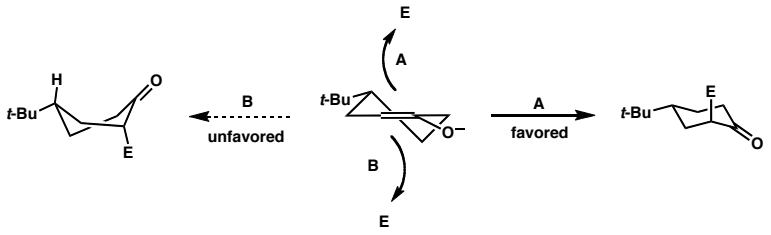

*Figure A6.6 Product distribution asymmetric decarboxylative allylic alkylation of β-ketoester* ***142***




One type of control believed to be operative is demonstrated in the non-enantioselective alkylation of 4-*tert*-butylcyclohexanone enolates, which are known to have an innate selectivity for one product. As shown in Scheme A6.7, the electrophile can be attacked by enolate from either its top face or bottom face. Studies by House and coworkers have shown that the electrophile and the *t*-butyl group have a trans relationship in the major product.[8] Approach from the bottom face will force the cyclohexane ring into a twist boat conformation and will install the electrophile on the same face as the *t*-butyl group. On the other hand, approach from the top face will install the electrophile trans to the *t*-butyl group and will lead directly to the product's chair conformation. The rationale for the favored trans relationship between the electrophile and the *t*-butyl group is that the chair-like transition state is lower in energy than the transition state in a twist boat conformation. Furthermore, although the cis relationship

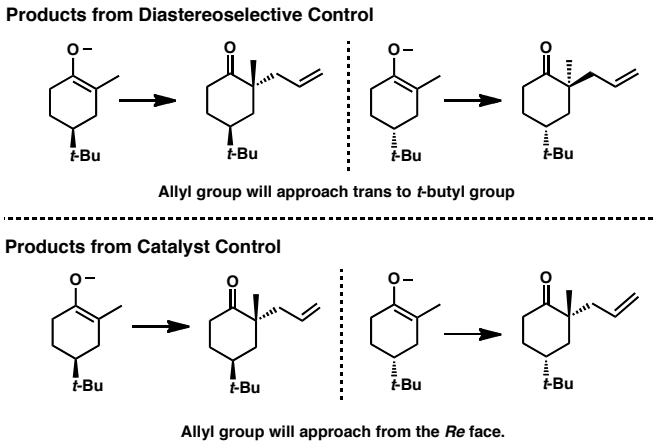
between the electrophile and *t*-butyl group affords a more thermodynamically stable product because both groups will be in equatorial positions, this reaction is under kinetic control. Thus, if we apply this diastereoselective model to β-ketoesters **142** and **143**, then the preferred products should have the allyl group trans to the *t*-butyl group (Scheme A6.8), a general trend that is observed for our decarboxylative allylic alkylation with $PPh_3$ (Scheme A6.5).

*Scheme A6.7 Stereoselective alkylation of t-butylcyclohexanones*




The other source of control is from our catalyst. From our experiments, we have found that (*S*)-*t*-Bu PHOX will incorporate the allyl group from the *Re* face;[1] the predicted products are shown in Scheme A6.8.

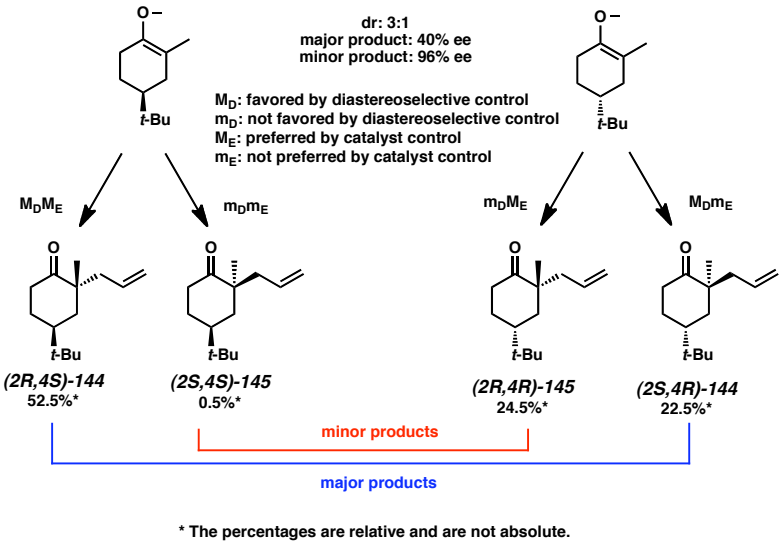
*Scheme A6.8 Predicted products as dictated by mode of control*




The high enantioselectivity observed for the minor product can be explained by considering the relative amount of each product and the competing modes of control

(Figure A6.7). Ketone (2*R*,4*S*)-**144** comprises half of the product mixture and is the product that is favored by both catalyst and diastereoselective controls. Ketone (2*S*,4*S*)-**145** is less than 1% of the product mixture and is favored neither by diastereoselective or by catalyst control. Ketone (2*R*,4*R*)-**145**, the major enantiomer of the minor product, is approximately 24% of the product mixture and is only favored by catalyst control. Ketone (2*S*,4*R*)-**144** is 22% of the product mixture and is only favored by diastereoselective control. Thus, the competition of these two types of control, one dictated by the catalyst and one dictated by the substrate, impart excellent enantioselectivity to the minor product but only moderate enantioselectivity to the major product.

*Figure A6.7 Distribution of products as governed by two competing modes of control*




From our studies of the asymmetric decarboxylative allylic alkylation of β-ketoesters derived 4-*tert*-butylcyclohexanone, we observe a case where the two types of control are closely matched. This conclusion is supported by the observation that the relative ratios of the products that are favored by only one type of control ((2*R*,4*R*)-**145** and (2*S*, 4*R*)-

**144**) are similar. It is because the substrate control and catalyst control are matched that we observed a situation where the major product has moderate ee while the minor product has high ee.

## A6.3 CONCLUSION

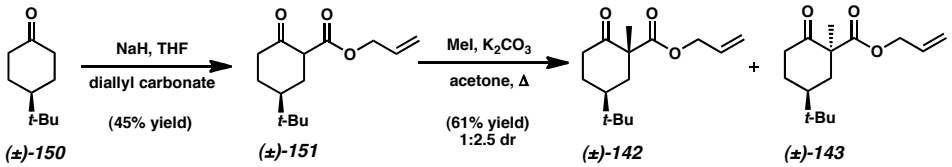
Our studies on the decarboxylative allylic alkylation of diastereomeric β-ketoesters derived from 4-*tert*-butylcyclohexanone support our theory of a stereoablative enantiovergent catalysis. These studies also reveal an interesting example of selectivity that is governed by competing modes of substrate and catalyst control.

## A6.4 EXPERIMENTAL SECTION

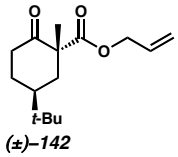
### *A6.4.1 Materials and Methods*

Unless otherwise stated, reactions were performed at ambient temperature (typically 20 to 23 °C) in flame-dried glassware under a nitrogen or argon atmosphere using dry, deoxygenated solvents. Solvents were dried by passage through an activated alumina column under argon. Brine solutions are saturated aqueous sodium chloride solutions. All commercially obtained reagents were used as received. Reaction temperatures were controlled by an IKAmag temperature modulator. Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV, anisaldehyde, permanganate, or CAM staining. ICN silica gel (particle size 0.032-0.063 mm) was used for flash chromatography. $^{1}$H and $^{13}$C NMR spectra were recorded on a Varian Mercury 300 (at 300 MHz and 75 MHz respectively) spectrometer and are reported relative to $Me_4Si$ (δ 0.0). Data for $^{1}$H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz), and integration. Data for $^{13}$C NMR spectra are reported in terms of chemical shift. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in frequency of absorption ($cm^{-1}$). High-resolution mass spectra were obtained from the Caltech Mass Spectral Facility.

### *A6.4.2 Synthesis of β-Ketoesters*

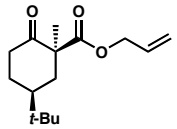



4-*t*-butylcyclohexanone (**150**) (1.094 g, 7.098 mmol) in THF (2.2 mL) was added dropwise to a cooled suspension of NaH (0.7098 g, 17.75 mmol, 60% dispersion in mineral oil) in THF (10 mL). Upon warming to room temperature, diallyl carbonate (1.5 mL, 10.65 mmol) was added. After 18 hours, the reaction was quenched with saturated aqueous $NH_4Cl$ solution and 1 N HCl to give a pH of 4. The phases were separated and the aqueous phase was extracted with EtOAc (7 x 12 ml). The organic layers were combined, dried with sodium sulfate, and concentrated to afford a yellow oil. The resulting oil was purified by flash chromatography (5 cm by 11.5 cm $SiO_2$, 10 % ether in pentane) to afford the β-ketoester **151** as a yellow oil (0.770 g, 45.5%). The β-ketoester **151** was then added to $K_2CO_3$ (1.96 g, 14.20 mmol) in acetone (10 mL). Iodomethane (0.89 mL, 14.20 mmol) was added dropwise, and the reaction was heated at 50 °C for 14 hours. The reaction was filtered and the solids were rinsed with acetone. The resulting organics were collected and purified by column chromatography (10% → 50% ether in pentane), which allowed for the separation of **142** and **143** (494 mg, 60% yield, 1:2.5 dr (**142**:**143**)).




**β-ketoester 142**

$^1$H NMR (300 MHz, $CDCl_3$) δ 5.89 (m, *J* = 10.2 Hz, 16.2 H, 1H), 5.32 (m, *J* = 7.4 Hz, 1.2 Hz, 1H), 5.25 (m, *J* =10.2 Hz, 1.5 Hz), 4.62 (m, 2H), 2.49 (m, 3H), 2.02 (m,1H), 1.57-1.18 (comp. m, 6H), 1.29 (s, 3H), 0.90 (s, 9H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 208.6, 173.2, 131.7, 119.2, 66.0, 56.5, 44.4, 40.6, 39.9, 32.5, 28.6, 27.7, 21.8; IR (Neat Film, NaCl) 2961, 2865, 1717, 1229, 1140 cm$^{-1}$; HRMS *m/z* calc'd for $C_{15}H_{24}O_3$ $[M]^+$: 252.1726, found 252.1714.

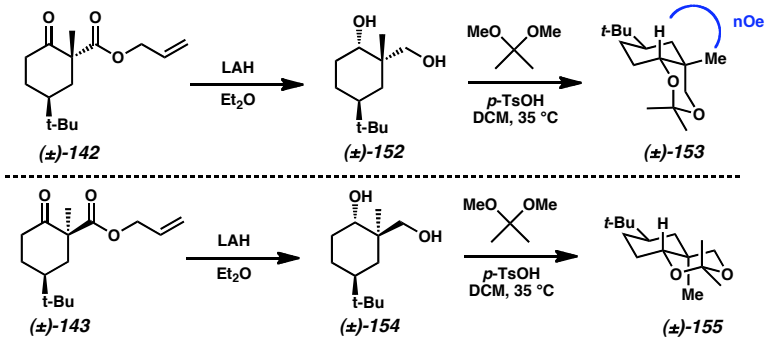



*(±)–143*

**β-ketoester 143**

$^1$H NMR (300 MHz, $CDCl_3$) δ 5.92 (dddd, *J* = 17.4 Hz, 10.5 Hz, 5.7 Hz, 5.7 Hz, 1H), 5.33 (dq, *J* = 17.4 Hz, 1.2 Hz, 1H), 5.23 (dq, *J* = 10.5 Hz, 1.2 Hz, 1H), 4.65 (dt, *J* = 5.7 Hz, 1.2 Hz, 2H), 2.45 (m, 2H), 2.21 (t, *J* = 12.6, 1H), 2.02 (m, 1H), 1.84 (dt, *J* =13.5 Hz, 3.3 Hz, 1H), 1.59 (m, 1H), 1.46 (s, 3H), 0.93 (s, 9H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 210.5, 173.2, 132.2, 118.3, 66.0, 57.4, 41.9, 38.0, 37.0, 32.6, 27.6, 26.8, 21.0; IR (Neat Film, NaCl) 2958, 2876, 1740, 1712, 1459, 1367, 1249, 1227, 1165, 1112 cm$^{-1}$; HRMS *m/z* calc'd for $C_{15}H_{24}O_3$ $[M]^+$: 252.1726, found 252.1718.

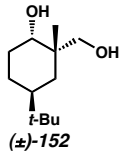
### *A6.4.3 Confirmation of Relative Stereochemistries of β-Ketoesters 142 and 143 via Acetonide Formation*




**General Procedure**

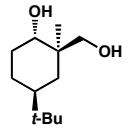
β-ketoester **143** (50 mg, 0.21 mmol) in ether (0.4 mL) was added slowly to LAH (23.9 mg, 0.63 mmol) in 0.5 mL ether at -78 °C. The reaction was allowed to warm to room temperature and was stirred for 20 minutes. The workup procedure was carried out as reported by Fieser and Fieser.[9] Water (24 μL), 15% aqueous NaOH (24 μL), and water (72 μL) were added to reaction at 0°C. A white precipitate was observed, and the reaction was allowed to stir for 30 minutes before filtration. The ether layer was washed with brine (2 x 2 mL) and saturated $NaHCO_3$ (2 x 2 ml). The ether layer was collected, dried with sodium sulfate, and concentrated to give a white solid.

Diol **154** (27.1 mg, 0.136 mmol) was dissolved in DCM (2 mL). *p*-TsOH monohydrate (~2 mg) and diomethoxypropane (33 μL, 0.2706 mmol) were added to the reaction. After 24 hours, the reaction mixture was concentrated and purified by column chromatography (2 cm x 20 cm $SiO_2$, 10% ether in hexanes) to afford a light yellow oil.



**Diol 152.**

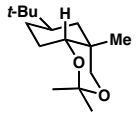
(29.8 mg, 70.9% yield): $^{1}$H NMR (300 MHz, $CDCl_3$) δ 4.26 (d, *J* =10.8 Hz, 1H), 3.46 (dd, *J* = 11.4 Hz, 4.2 Hz, 1H), 3.27 (d, *J* = 11.1 Hz, 1H), 2.74 (bs, 2H), 1.73 (m, 2H), 1.44 (dt, *J* = 13.5 Hz, 2.7 Hz, 1H), 1.30 (m, 2H), 1.19 (s, 3H), 0.81 (s, 9H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 80.0, 68.0, 42.3, 38.9, 37.9, 32.3, 31.7, 27.6, 26.3, 24.9; IR (KBr pellet) 3272, 2958, 2868, 1459, 1365, 1064, 1039, 1019, 999 cm$^{-1}$; HRMS *m/z* calc'd for $C_{12}H_{25}O_2$ $[M+H]^+$: 201.1855, found 201.1854.



*(±)-154*

**Diol 154.**

(36.5 mg, 85.7% yield): $^{1}$H NMR (300 MHz) δ 3.58 (dd, *J* =11.4 Hz, 3.6 Hz, 1H), 3.50 (d, *J* = 9.3 Hz, 1H), 3.42 (dd, *J* = 10.5 Hz, 4.8 Hz), 2.84 (bs, 1H), 2.78 (bs, 1H), 1.74 (m, 1H), 1.41 (m, 2H), 1.23 (m, 2H), 0.99-0.78 (m, 2H), 0.99 (s, 3H), 0.82 (s, 9H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 77.5, 75.6, 41.7, 39.4, 34.7, 32.2, 31.0, 27.7, 25.6, 14.2; IR (KBr pellet) 3325, 2936, 2868, 1462, 1365, 1066, 1039, 991, 687 cm$^{-1}$; HRMS *m/z* calc'd for $C_{12}H_{25}O_2$ $[M+H]^+$: 201.1855, found 201.1847.

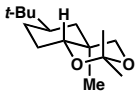


*(±)-153*

**Acetonide 153.**

(40 mg, 45% yield): $^{1}$H NMR (300 MHz, $C_6D_6$) δ 3.64 (d, *J* = 11.1 Hz, 1H), 3.47 (dd, *J* = 4.5 Hz, 5.1 Hz, 1H), 3.05 (d, *J* = 11.1 Hz, 1H), 1.65 (comp. m, 3H), 1.48 (s, 1H), 1.37 (s, 3H), 1.36 (s, 3H), 1.14 (m, 1H), 0.94 (m, 1H), 0.89 (s, 3H), 0.78 (s, 9H), 0.69 (m, 1H),

$^{13}$C NMR (75 MHz, $C_6D_6$) δ 99.6, 74.0, 67.2, 40.3, 35.5, 33.8, 32.7, 27.6, 26.5, 26.3, 25.9, 25.1, 21.4; IR (Neat Film, NaCl) 2951, 2870, 1463, 1365, 1225, 1084, 1067 cm$^{-1}$; HRMS *m/z* calc'd for $C_{15}H_{28}O_2$ [M+H]$^+$: 241.2168, found 241.2173.

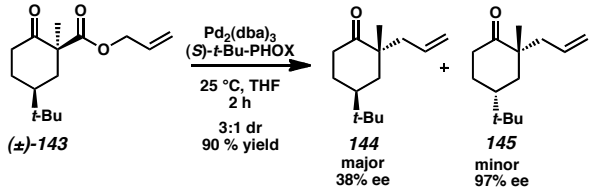



*(±)-155*

**Acetonide 155.**

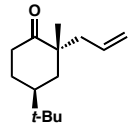
(40 mg, 71.8% yield): $^1$H NMR (300 MHz, $CDCl_3$) δ 3.57 (d, *J* = 10.5 Hz, 1H), 3.50 (dd, *J* = 11.4 Hz, 4.2 Hz, 1H), 3.33 (d, *J* = 10.8 Hz, 1H), 1.84 (m, 1H), 1.62-1.04 (m, 6H), 1.45 (s, 3H), 1.42 (s, 3H), 1.10 (s, 3H), 0.83 (s, 9H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 99.6, 76.0, 73.6, 41.5, 34.5, 33.8, 32.4, 30.2, 27.8, 27.2, 26.0, 19.4 15.9; IR (Neat Film, NaCl) 2992, 2944, 2870, 1462, 1384, 1366, 1270, 1235, 1204, 1104, 1084, 1040 cm$^{-1}$; HRMS *m/z* calc'd for $C_{15}H_{28}O_2$ [M+H]$^+$: 241.2168, found 241.2177.

### *A6.4.4 General Procedures for Pd-Catalyzed Decarboxylative Allylic Alkylation of Diastereomeric β-Ketoesters*




$Pd_2(dba)_3$ (67 mg, 0.0733 mmol) and (*S*)-*t*-BuPHOX (73.8 mg, 0.19045 mmol) were combined in a round bottom flask. The vial was evacuated for 10 minutes prior to addition of THF (88 mL). The reaction was allowed to stir for 30 minutes prior to addition of β-ketoester **143** (739 mg, 2.93 mmol) via syringe. The reaction was monitored by TLC. Once the reaction was complete, the reaction was concentrated.

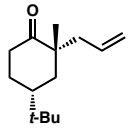
Isolation of products was accomplished by multiple flash chromatography (3 cm x 24 cm $SiO_2$, 10 % ether in pentane).




*(±)-144*

**Major product 144.**

$^1$H NMR (300 MHz) δ 5.64 (m, 1H), 5.04 (m, 2H), 2.38-2.23 (m, 4H), 2.03 (m, 1H), 1.84 (m, 1H), 1.70 (m, 1H), 1.42-1.13 (m, 2H), 1.00 (s, 3H), 0.89 (s, 9H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 216.0, 133.0, 118.5, 48.2, 42.0, 40.1, 38.5, 32.4, 28.3, 27.7, 22.7 ; IR (Neat Film, NaCl) 2962, 2870, 1709, 1366, 912 cm$^{-1}$; HRMS *m/z* calc'd for $C_{14}H_{24}O$ [$M^+$]: 208.1827, found 208.1825; $[\alpha]_D^{25.6}$ –30.00° (*c* 1.08, hexane).

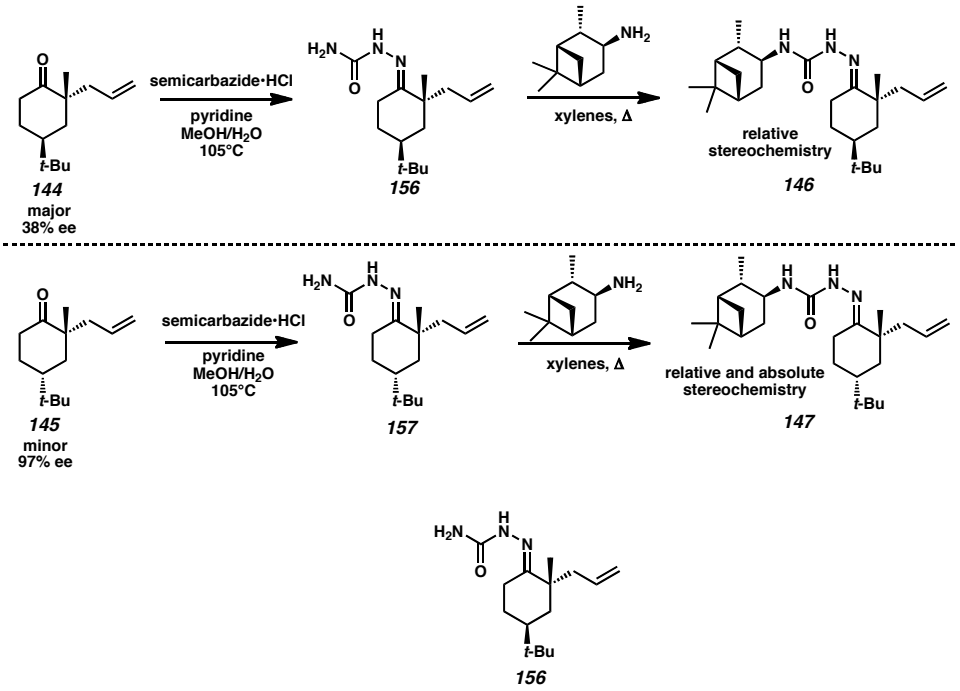



*(±)-145*

**Minor product 145.**

$^1$H NMR (300 MHz) δ 5.77 (m, 1H), 5.03 (m, 2H), 2.50 (m, 1H), 2.28 (m, 2H), 2.16 (m, 1H), 2.00 (m, 1H), 1.64 (m, 2H), 1.42 (m, 2H), 1.14 (s, 3H), 0.89 (s, 9H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 216.2, 135.0, 117.9, 47.3, 43.3, 42.3, 38.9, 38.5, 32.5, 27.8, 27.7, 24.2; IR (Neat Film, NaCl) 2963, 2870, 1709, 1366, 912 cm$^{-1}$; HRMS *m/z* calc'd for $C_{14}H_{24}O$ [$M^+$]: 208.1827, found 208.1836; $[\alpha]_D^{25.7}$ +77.81° (*c* 0.105, hexane).

### *A6.4.5 Determination of the Relative Stereochemistry for the Products from the Asymmetric Pd-Catalyzed Decarboxylative Allylic Alkylation*

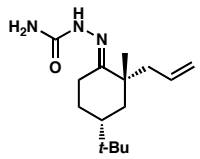






**Major Semicarbazone 156.**

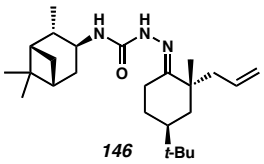
Prepared as reported by Behenna and Stoltz.[10] 131.7 mg, 69.1% yield; $^{1}$H NMR (300 MHz) δ 7.66 (bs, 1H), 5.63 (m, 1H), 5.02 (m, 2H), 2.55 (m, 1H), 2.07 (m, 2H), 1.93 (m, 2H), 1.72 (m, 1H), 1.51-1.06 (m, 3H), 1.10 (s, 3H), 0.86 (s, 9H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 158.3, 157.3, 134.0, 117.8, 42.8, 41.9, 41.9, 40.0, 32.5, 31.2, 27.0, 25.0, 22.8; IR (Neat Film, NaCl) 3470, 3194, 2963, 1689, 1583, 1475, 1366, 1078, 913, 770 cm$^{-1}$; HRMS *m/z* calc'd for $C_{15}H_{27}N_3O$ [$M^+$]: 265.2154, found 265.2149; $[\alpha]_D^{25.7}$ –8.23° (*c* 0.305, methanol).




***157***

**Minor Semicarbazone 157.**

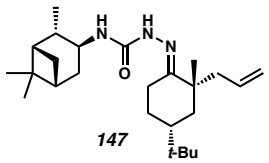
Prepared as reported by Behenna and Stoltz.[10] 103.7 mg, 81.4% yield; $^{1}$H NMR (300 MHz) δ 7.96 (bs, 1H), 5.89 (m, 1H), 5.03 (app. d, 2H), 2.56 (m, 1H), 2.36 (m, 2H), 1.94 (m, 2H), 1.53 (m, 2H), 1.20-1.11 (m, 2H), 1.11 (s, 3H), 0.85 (s, 9H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 158.9, 157.5, 136.0, 117.0, 45.2, 42.3, 41.3, 39.0, 32.5, 27.6, 26.8, 25.8, 23.1; IR (Neat Film, NaCl) 3473, 3199, 2963, 1694, 1578, 1473, 1366, 1101, 912 cm$^{-1}$; HRMS *m/z* calc'd for $C_{15}H_{27}N_3O$ [$M^+$]: 265.2154, found 265.2163; $[\alpha]_D^{25.9}$ –6.67° (*c* 0.995, methanol).




***146***

**Major (isopinocampheylamine)-semicarbazone 146.**

Prepared as reported by Behenna and Stoltz.[10] 40.1 mg, 66.2% yield; $^{1}$H NMR (300 MHz) δ 7.83 (bs, 1H), 6.08 (d, *J* = 9 Hz, 1H), 5.65 (m, 1H), 5.05 (m, 2H), 4.17 (m, 1H), 2.68 – 1.46 (comp m., 13H), 1.22 (s, 3H), 1.08 (d, *J* = 7.2 Hz, 1H); 1.10 (s, 3H), 1.054 (s, 3H), 0.88 (d, 1H, *J* = 9.9 Hz), 0.85 (s, 9H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 156.8, 156.0, 134.1, 117.8, 48.3, 48.2, 48.0, 47.1, 42.7, 41.9, 41.8, 39.8, 38.6, 38.1, 35.5, 32.5, 28.2, 27.6, 27.0, 25.0, 23.6, 22.6, 21.0; IR (Neat Film, NaCl) 3406, 3194, 3075, 2962, 1672, 1526 cm$^{-1}$, [M+H]$^+$: 402.3484, found 402.3487.




147

**Minor (isopinocampheylamine)-semicarbazone 147.**

Prepared as reported by Behenna and Stoltz.[10] 64.1 mg, 84.9% yield; $^{1}$H NMR (300 MHz) δ 8.42 (bs, 1H), 6.08 (d, *J* = 9 Hz, 1H), 5.94 (m, 1H), 5.04 (m, 2H), 4.17 (m, 1H), 2.707 (m, 2H), 2.37 (m, 3H), 1.91 (m, 5H), 1.55 (m, 3H), 1.21 (s, 3H), 1.12 (d, *J* = 7.5, 3H), 1.10 (s, 3H), 1.04 (s, 3H), 0.87 (d, *J* = 9.9 Hz, 1H), 0.84 (s, 9H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 157.3, 156.1, 136.4, 116.6, 48.2, 46.9, 45.1, 42.3, 41.9, 41.3, 39.4, 38.6, 38.0, 35.5, 32.5, 28.2, 27.6, 26.9, 25.6, 23.6, 22.9, 21.0; IR (Neat Film, NaCl) 3400, 3194, 2952, 2873, 1672, 1526 $cm^{-1}$; HRMS *m/z* calc'd for $C_{25}H_{43}N_3O$ $[M+H]^+$: 402.3484, found 402.3491; $[\alpha]_D^{25.1}$ +29.73° (*c* 0.2550, hexane).

## A6.5 NOTES AND REFERENCES

(1) Mohr, J. T.; Behenna, D. C.; Harned, A. M.; Stoltz, B. M. *Angew. Chem. Int. Ed.* **2005**, *44*, 6924–6927.

(2) Please see Experimental Section for details.

(3) The relative rate of consumption of starting material was determined by comparing the negative slopes of ln[β-ketoester] versus time for β-ketoesters **142** and **143**.

(4) Tsuji, J.; Yamada, T.; Minami, L.; Yuhara, M.; Nisar, M.; Shimizu, I. *J. Org. Chem.* **1987**, *52*, 2988–2995.

(5) Kayser, R. H.; Brault, M.; Pollack, R. M.; Bantia, S.; Sadoff, S. F. *J. Org. Chem.* **1983**, *48*, 4497–4502.

(6) Pollack, R.M. In "Transition States of Biochemical Processes"; Gandour, R. D., Schowen, R. L., Eds.; Plenum: New York, 1978; p. 467.

(7) Please refer to Appendix 5 for references.

(8) House, H. O.; Tefertiller, B. A.; Olmstead, H. D. *J. Org. Chem.* **1968**, *33*, 935–942.

(9) Fieser, L.F.; Fieser, M. *Reagents for Organic Synthesis* **1967**, 581–595.

(10) Behenna, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2004**, *126*, 15044–15055.