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Iridium-Catalyzed Asymmetric Allylic Substitution Reactions with Unstabilized Enolates and Prochiral Enolates

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Iridium-Catalyzed Asymmetric Allylic Substitution Reactions with Unstabilized Enolates and Prochiral Enolates

By

Xingyu Jiang

A dissertation submitted in partial satisfaction of the

requirements for the degree of

Doctor of Philosophy

in

Chemistry

in the

Graduate Division

of the

University of California, Berkeley

Committee in charge:

Professor John F. Hartwig, Chair
Professor F. Dean Toste
Professor Richmond Sarpong
Professor Phillip B. Messersmith

Fall 2018

Abstract

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Xingyu Jiang

Doctor of Philosophy in Chemistry

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Professor John F. Hartwig, Chair

The following dissertation discuss the development of iridium-catalyzed asymmetric allylic substitution reactions with unstabilized enolates and prochiral enolates. These reactions include the enantioselective allylic substitutions with silyl ketene acetals, diastereo- and enantioselective allylic substitutions with α-alkoxy ketones, and stereodivergent allylic substitutions with aryl acetic acid esters, azaaryl acetamides and azaaryl acetates.

Chapter 1 provides a brief overview of transition-metal-catalyzed asymmetric allylic substitutions with enolates. This overview focused on the mechanism of allylations of enolates catalyzed by palladium complexes and iridium complexes. Additionally, methodologies for asymmetric allylations of unstabilized enolates are discussed in detail. Furthermore, this overview highlights the challenges and the strategies for the control of diastereoselectivity for the allylic substitutions with prochiral enolates.

Chapter 2 describes the development of iridium-catalyzed enantioselective allylic substitution reactions with silyl ketene acetals, the silicon enolates of esters, under relatively neutral conditions. The ester products contain a quaternary carbon atom at the nucleophile moiety and a chiral tertiary carbon atom at the electrophile moiety.

Chapter 3 describes the study on diastereoselective and enantioselective allylic substitution reactions with acyclic α-alkoxy ketones. A metallacyclic iridium complex catalyzes the allylation of unstabilized copper(I) enolates generated *in situ* from acyclic α-alkoxy ketones to form products with contiguous stereogenic centers.

Chapter 4 describes the development of stereodivergent allylic substitutions with aryl acetic acid esters catalyzed synergistically by a metallacyclic iridium complex and a Lewis base co-catalyst. Through permutations of the enantiomers of the two chiral catalysts, all four stereoisomers of the products bearing two adjacent stereocenters are accessible with high diastereoselectivity and enantioselectivity. A stereochemical model is provided to understand the origin of high stereoselectivity.

Chapter 5 describes a combination of catalysts that enable stereodivergent allylic substitution reactions with azaaryl acetamides and acetates. This combination of catalysts comprises a chiral metallacyclic iridium complex and a chiral bisphosphine-ligated copper(I) complex, which individually control the configuration of the electrophilic and nucleophilic carbon atoms, respectively.

Chapter 6 extends from the work discussed in Chapter 5 and demonstrates iridium and copper complexes synergistically catalyze stereodivergent allylations to construct vicinal fully substituted and tertiary stereogenic centers in acyclic structures. In particular, fluorine-containing fully substituted stereocenters are readily constructed from fluorinated acetates.

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Time flies so fast. All of a sudden, it is time to put an end to my PhD study at UC Berkeley. The memory is so fresh that I still remember how thrilled I was when I received my admission letter from UC Berkeley. After living and learning here for four and half years, I feel really spoiled by the open culture, helpful and hard-working environment, lovely weather, and of course, yummy food from different countries. There would definitely be a tough time of adaptation if I leave the bay area. This is part of reason why I chose a local job after graduation.

Life in graduate school is never easy. I could not survive without support and help from all the people around me. First, I would like to thank my PhD advisor, Prof. John Hartwig. John is so knowledgeable that I was astonished every time when he introduced the history of a specific field of organometallic chemistry during catalysis lunch and when he shared with us his understanding on a question. I guess everyone in our group has the same question: how John manages his brain storage. I benefited a lot from brainstorming and problem-solving during the meetings with John. I am also thankful for his guidance on scientific writing and presentation skills. These are invaluable treasures in my future career.

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Finally, I would like to express my sincere gratitude to my family for their kind and selfless support throughout the years. As the only child of the family, my parents have suffered a lot when I am studying abroad. But they support me ceaselessly regardless of the long distance between us. Also, I have to thank my girlfriend, Fangying Jin, for her love. I really look forward to the bright future with her by my side.

CHAPTER 1

Overview of Transition-Metal-Catalyzed Asymmetric Allylic Substitution Reactions with Enolates

1.1 Overview

Transition-metal-catalyzed asymmetric allylic substitution reactions with enolates are one of the most powerful and reliable methods to synthesize enantio-enriched carbonyl compounds with high level of asymmetric induction.[1] In general, these reactions occur through the formation of allyl metal intermediates that react with enolates to form new C–C bonds (Figure 1.1). Products containing a single stereocenter at the α (Figure 1.2, category 1) or β (category 2) position could be obtained from a prochiral enolate as the nucleophile or a prochiral allylic compound as the electrophile. If both nucleophile and electrophile are prochiral, two contiguous stereocenters at α and β positions could be assembled in a single step (category 3).

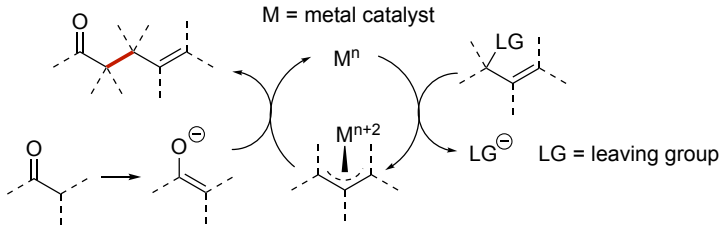

Figure 1.1 general mechanism for transition-metal-catalyzed allylic substitution reactions with enolates

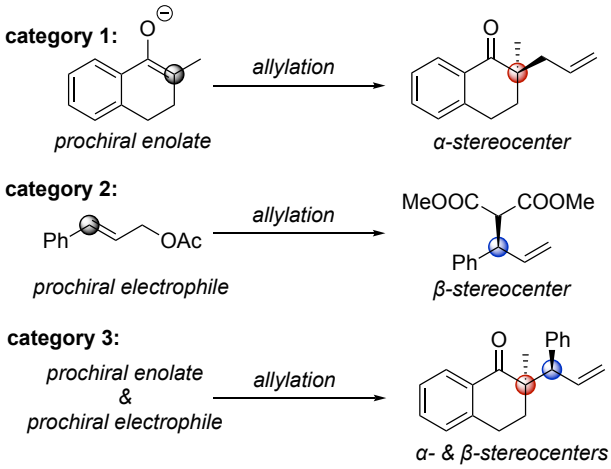

Figure 1.2 allylation products with α and/or β stereocenter(s)

Among all the transition metal catalysts developed for asymmetric allylic substitutions with enolates, palladium complexes have been studied most intensively.[2] Since the first example of palladium-catalyzed enantioselective allylic substitution with enolate was reported in 1977[3], numerous chiral ligands have been designed, synthesized, and employed in combination with palladium precursors to evaluate the level of asymmetric induction in these transformations.[2,4]

It is well-established that with unsymmetrical allylic electrophiles, the reactions catalyzed by palladium complexes usually afford linear products with substitution occurring at less-hindered terminus of the allyl electrophiles (Figure 1.3). However, similar reactions catalyzed by other metal catalysts (Mo, W, Rh, Ir, *etc.*) favor the formation of branched products with substitution occurring at more-hindered terminus of the allyl electrophiles.[5] This observed branched-selectivity,

which complements the linear-selectivity of the venerable palladium catalysis, has stimulated the development of asymmetric allylic substitution reactions with metal catalysts other than palladium complexes.[5-9]

Historically, the enolates of the parent carbonyl compounds that have a pK_a value lower than 25 in DMSO are referred to as the stabilized or "soft" enolates. Correspondingly, the unstabilized or "hard" enolates are the ones whose parent carbonyl compounds have a pK_a value higher than 25 in DMSO. Transition-metal-catalyzed asymmetric allylic substitution reactions with stabilized enolates are well-established in the literature. However, similar transformations with unstabilized enolates of simple ketones, aldehydes and carboxylic acid derivatives are relatively undeveloped. Details will be discussed in section 1.3 of Chapter 1.

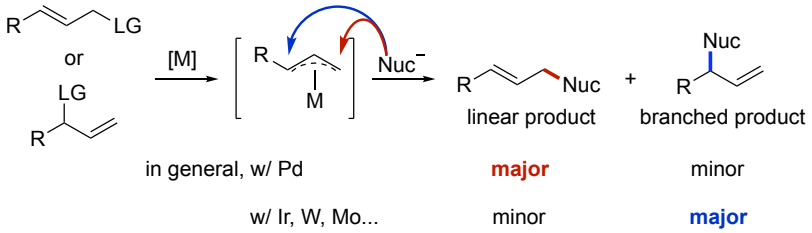

Figure 1.3 general regioselectivity for transition-metal-catalyzed allylic substitution reactions

Besides the development of methodology and meticulous mechanistic investigations of the asymmetric allylic substitutions with enolates catalyzed by transition-metal complexes, the utilities of these reactions have been demonstrated for the syntheses of many natural products and drug molecules.[4,10]

1.2 Mechanism

Although asymmetric allylic substitution reactions with enolates have been developed with many metal catalysts, the palladium-catalyzed and the iridium-catalyzed versions have proven to be exceptionally versatile due to their broad substrate scope, excellent functional group tolerance, and high enantioselectivity.[4] Related mechanistic studies have also been conducted in detail.

1.2.1 Palladium

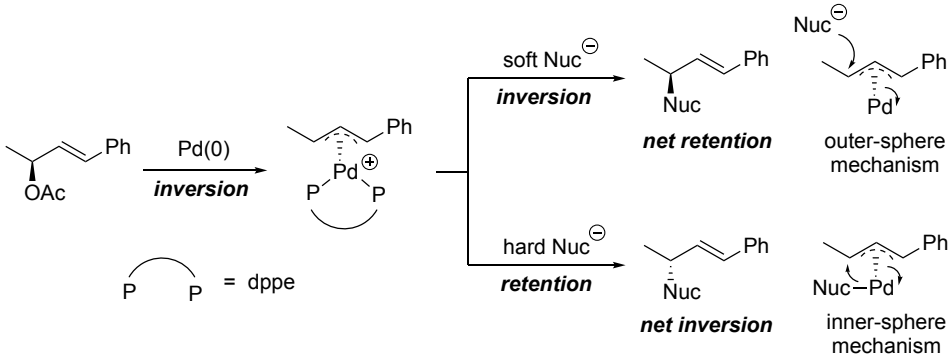

Figure 1.4 mechanism of palladium-catalyzed allylic substitution

The mechanism of palladium-catalyzed allylic substitution reactions with enolates consists of the following steps: 1) oxidative addition step of allyl electrophiles to form the allylpalladium(II) intermediate and 2) reductive elimination of the allylpalladium(II) intermediate to form the product and to regenerate the palladium(0) catalyst.

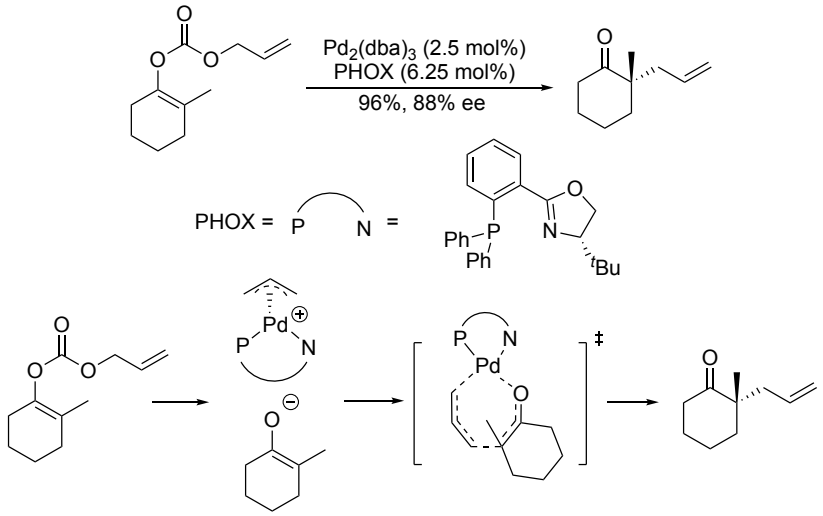

Figure 1.5 inner-sphere mechanism of palladium-catalyzed decarboxylative allylation

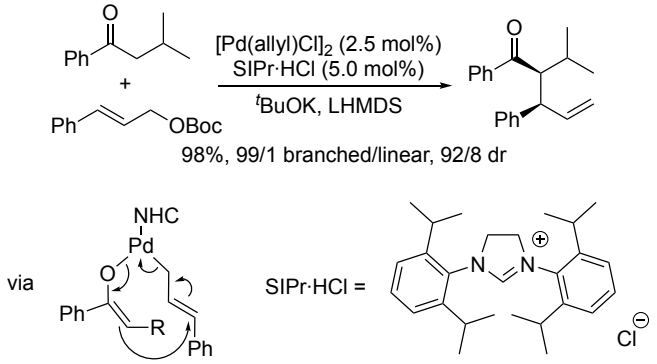

Figure 1.6 inner-sphere mechanism of palladium-catalyzed allylation of ketones

In 1983, Hayashi and co-workers reported that enantio-enriched allylic electrophiles oxidatively added to the palladium(0) complexes ligated by bisphosphine ligands with inversion of configuration (Figure 1.4).[11] They also observed that the resulting allylpalladium(II) intermediates reacted with the sodium enolate of dimethyl malonate (stabilized or "soft" nucleophile) to give the products with inversion of configuration. However, similar transformation with "hard" nucleophiles (phenyl and allyl Grignard reagents) afforded the products with retention of configuration.[12] These results indicate that the reductive elimination occurs through outer-sphere mechanism with soft nucleophiles and through inner-sphere mechanism with hard nucleophiles. Furthermore, the substitution occurred preferentially at the less-hindered terminus of the allyl moiety.

The palladium-catalyzed allylic substitution reactions with enolates usually proceed through the outer-sphere mechanism. However, in some cases, the inner-sphere mechanism was suggested.

In 2012, Goddard, III, Stoltz and co-workers reported their computational studies on understanding the mechanism of enantioselective decarboxylative allylation of enolates catalyzed by palladium complexes ligated by phosphino-oxazoline (PHOX) ligands.[13] Three computational schemes using different levels of theory all suggested that inner-sphere reductive elimination involving a 7-centered transition state would be lowered in energy than conventional outer-sphere pathway (Figure 1.5). Similar mechanism was suggested by Hou and co-workers for the palladium-catalyzed allylation of imines[14] and ketones[15] with achiral ligands based on labelling experiments and computational studies. Branched isomers were obtained as the major product when mono-substituted allyl electrophiles were used (Figure 1.6).

1.2.2 Iridium

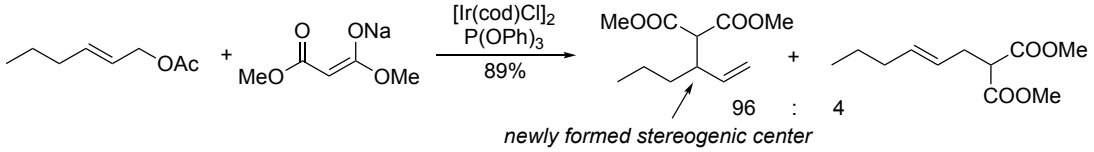

Figure 1.7 first iridium-catalyzed allylic substitution reaction reported by Takeuchi

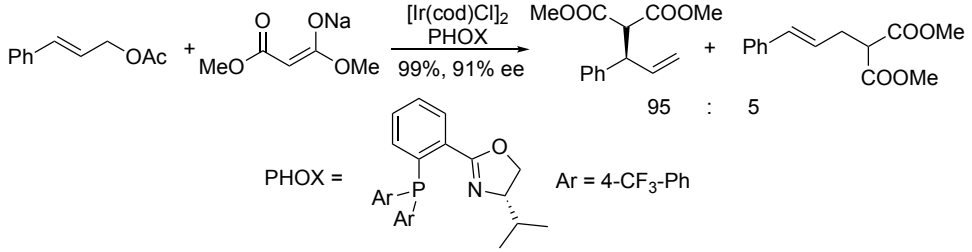

Figure 1.8 first enantioselective iridium-catalyzed allylic substitution reaction reported by Helmchen

In contrast to the linear-selectivity observed in most palladium-catalyzed allylic substitution reactions, branched-selectivity was usually observed in allylic substitutions catalyzed by iridium complexes. Takeuchi and co-workers disclosed the first iridium-catalyzed allylic substitution reaction with $[Ir(cod)Cl]_2$ as the precursor and triphenyl phosphite as the ligand (Figure 1.7).[16] In this report, branched products with newly formed stereogenic centers were obtained starting from linear allyl electrophiles, allowing development of stereoselective allylic substitution reactions. Shortly afterward, Helmchen and co-workers reported an enantioselective version by introducing PHOX ligands (Figure 1.8).[17]

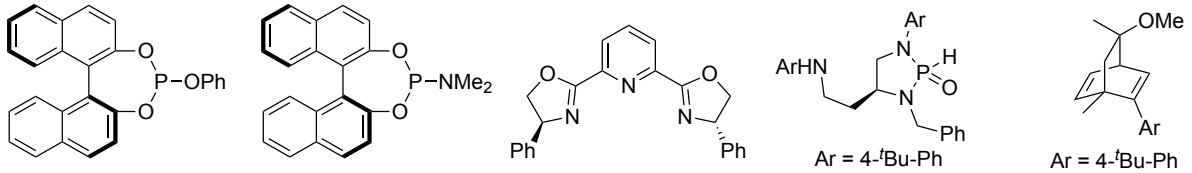

Figure 1.9 Examples of ligands for iridium-catalyzed enantioselective allylic substitution reactions

Besides PHOX ligands, several other types of chiral ligands were developed for iridium-catalyzed enantioselective allylic substitutions (Figure 1.9).[18-22] Among them, phosphoramidite ligands (**L1**) shown in the Figure 1.10 are the most versatile ones.[6,10] Reactions catalyzed by iridium complexes ligated by these phosphoramidite ligands occur with a variety of carbon and heteroatom nucleophiles to afford the branched products with excellent regio- and enantioselectivity (Figure 1.10).

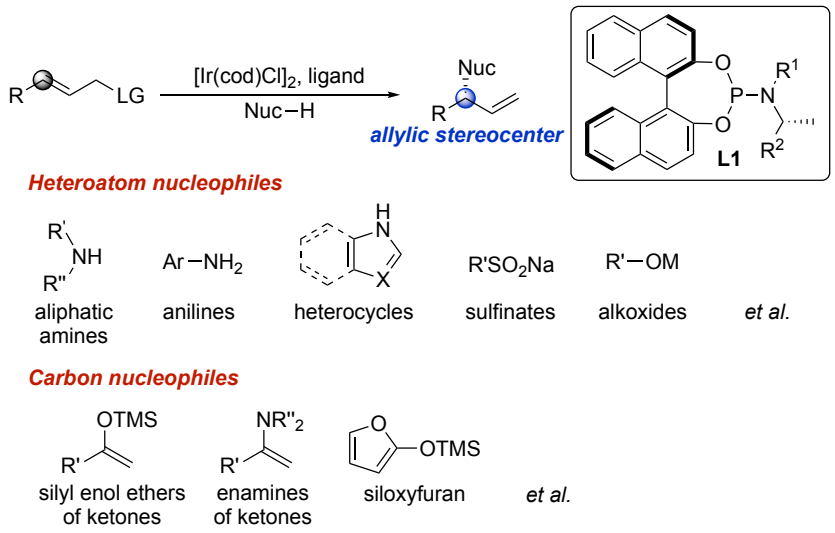

Figure 1.10 iridium-catalyzed enantioselective allylic substitution reactions with **L1**

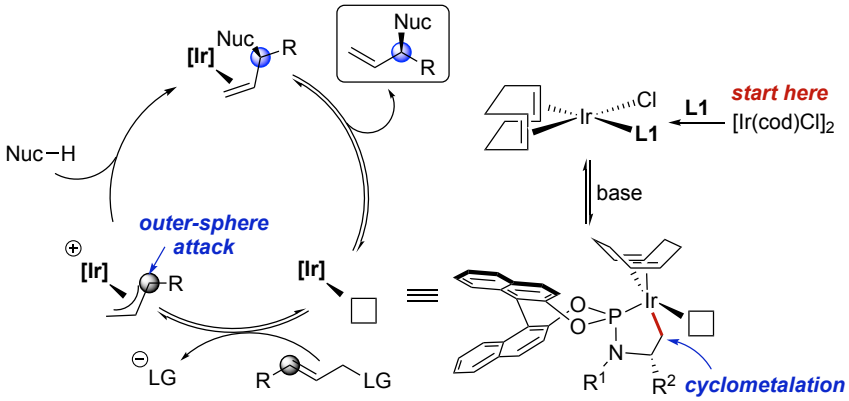

Figure 1.11 mechanism of for iridium-catalyzed enantioselective allylic substitution reactions with **L1**

Detailed mechanistic investigations performed by Hartwig and co-workers demonstrated that the active catalyst in these reactions is not the square-planar complex formed by coordination of the phosphoramidite to $[Ir(cod)Cl]_2$.[23-26] Instead, the phosphoramidite on the iridium center undergoes cyclometalation under basic conditions to form a rigid 5-membered iridacycle (Figure 1.11). The resulting iridium complex has an open coordination site that activates the allyl electrophile through the formation of the allyl iridium intermediate (oxidative addition step). Thereafter, a suitable nucleophile attacks selectively at the more-hindered terminus of the allyl moiety through the outer-sphere mechanism to form the allylation product (reductive elimination step).[27]

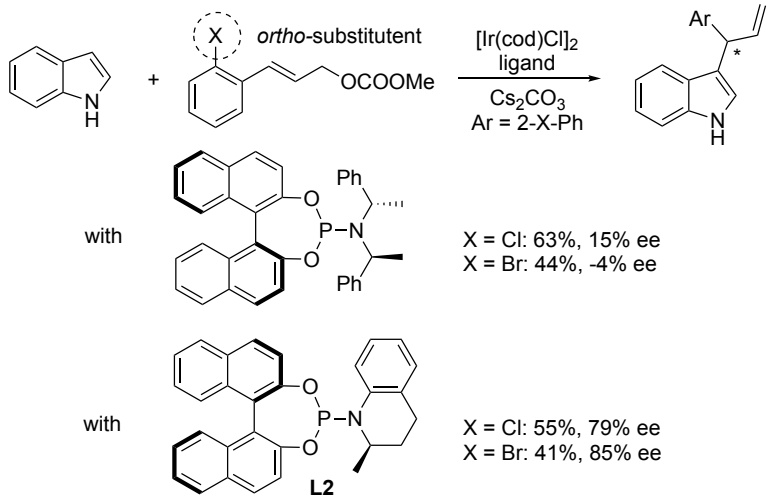

Figure 1.12 comparison between **L1** and **L2** in iridium-catalyzed enantioselective allylic substitution reactions

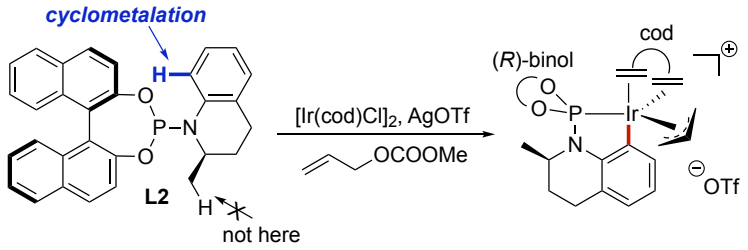

Figure 1.13 active catalyst in iridium-catalyzed enantioselective allylic substitution reactions with **L2** as ligand

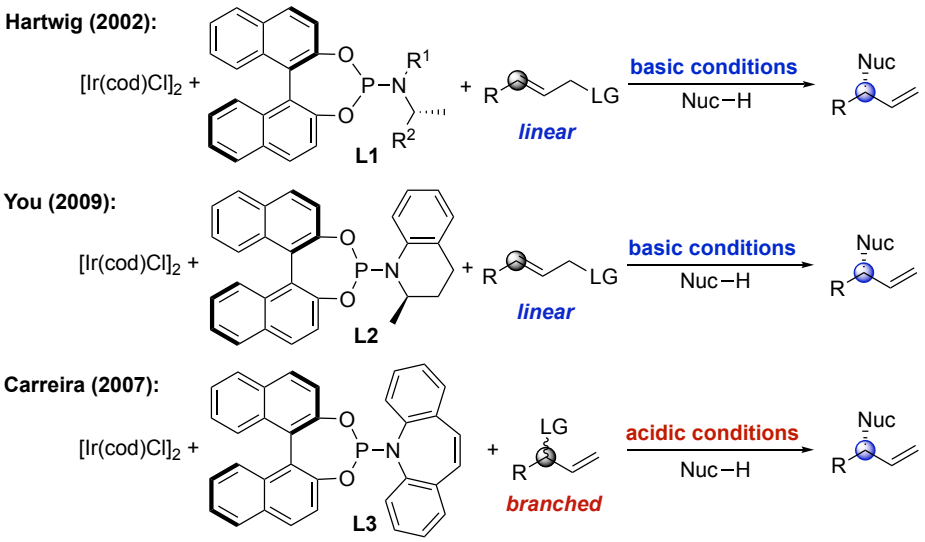

Figure 1.14 three systems for iridium-catalyzed enantioselective allylic substitution reactions

In some iridium-catalyzed enantioselective allylic substitution reactions with **L1** type ligands, the reactions conducted with *ortho*-substituted cinnamyl electrophiles afforded the allylation products with low to modest enantioselectivity.[28-31] In 2009, You and co-workers reported the synthesis of an related phosphoramidite ligand (**L2**) and demonstrated that when using *ortho*-substituted

cinnamyl electrophiles, reactions conducted with **L2** gave products with higher enantioselectivity than those with **L1** (Figure 1.12).[32] Later, **L2** was employed as the ligand in the iridium-catalyzed asymmetric allylic dearomatization reactions.[33,34]

In 2012, the same group reported the synthesis and characterization of the active iridium catalysts derived from **L2**.[35,36] This ligand undergoes cyclometalation at the C(sp^2) position of the N-aryl moiety instead of the C(sp^3) position of the methyl group to form a rigid 5-membered iridacycle (Figure 1.13).

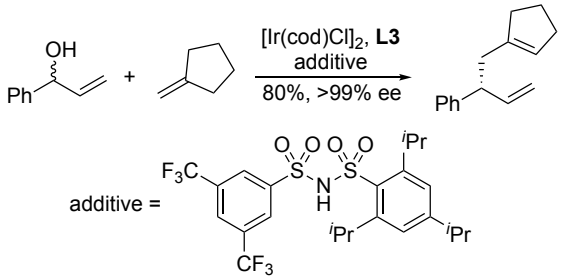

Figure 1.15 allylation of olefins reported by Carreira

The iridium-catalyzed enantioselective allylic substitutions with **L1** and **L2** as ligands usually operate under basic conditions to generate the active catalysts *in situ* and with linear allylic alcohol derivatives as electrophiles. In 2007, Carreira and co-workers reported phosphoramidite ligand **L3** for iridium-catalyzed enantioselective allylic substitution reactions that operated under acidic conditions and with racemic branched secondary alcohols or their derivatives as electrophiles (Figure 1.14).[37] An example is shown in Figure 1.15.[38]

To elucidate the mechanism of the iridium-catalyzed allylation reactions with **L3** as the ligand, Sunoj and co-workers disclosed a detailed computational study.[39] Very recently, Carreira and co-workers isolated substrate-bound complexes that were catalytically and kinetically competent to be intermediates in the previously reported allylation reactions with **L3** as the ligand.[40] In the proposed mechanism, in contrast to **L1** and **L2**, **L3** does not undergo cyclometalation with iridium (Figure 1.16).

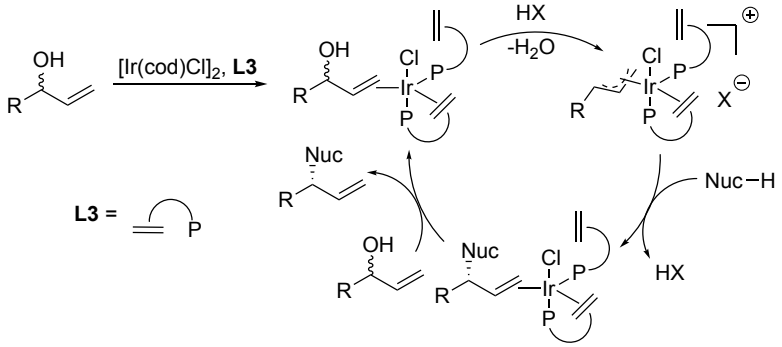

Figure 1.16 mechanism of iridium-catalyzed enantioselective allylic substitution reactions with **L3** as ligand

1.3 Asymmetric Allylic Substitution Reactions with Unstabilized Enolates

Transition-metal-catalyzed asymmetric allylic substitution reactions with stabilized enolates are well-established in the literature. For example, the allylation reactions of malonates with 1,3-diphenylallyl acetate are the benchmark reaction to measure the level of asymmetric induction for chiral ligands on palladium catalysts.[2] Other stabilized enolates, such as the enolates of β-ketoesters, 1,3-diketones, and malononitrile, have also been well-studied.[4]

Similar transformations with unstabilized enolates of simple ketones and aldehydes have been reported.[1] For example, Trost and co-workers reported that the tin enolate of 2-methyl-1-tetralone formed *in situ* underwent palladium-catalyzed allylic substitution to afford the product in 99% yield and with 88% ee (Figure 1.17).[41] List and co-workers reported the first highly enantioselective direct allylation of branched aldehydes with allylic alcohols as electrophiles (Figure 1.18). The reaction occurred presumably through the formation of the corresponding enamines that served as nucleophiles to attack the allyl palladium intermediate. Enantioselectivity was realized through the incorporation of a chiral phosphate anion within the transition state.[42]

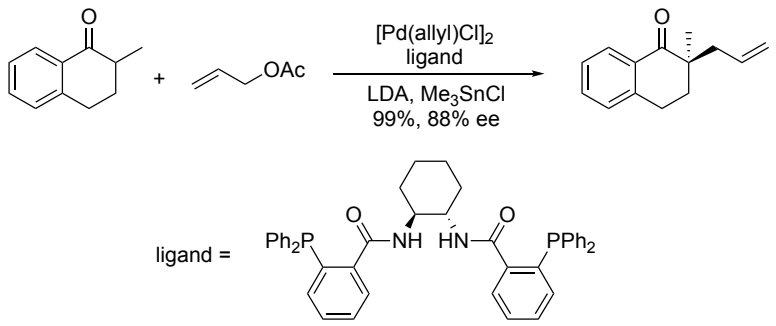

Figure 1.17 palladium-catalyzed enantioselective allylic substitution reactions with tetralones

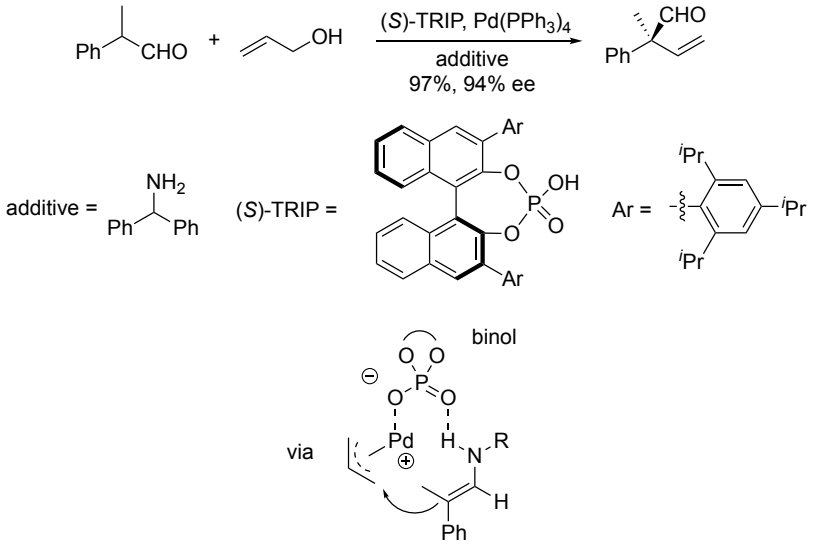

Figure 1.18 enantioselective allylic substitution reactions with aldehydes

In contrast, transition-metal-catalyzed asymmetric allylic substitution reactions with unstabilized enolates derived from carboxylic acid derivatives remain undeveloped. Although carboxylic acid derivatives with additional carbanion-stabilizing functional groups (cyano[43], heteroatom functionality[44], aromatic substituent[45], *etc*.) have been reported to undergo stereoselective allylic substitutions, similar transformation with simple aliphatic esters and lactones are rare.[46]

Possible challenges come from the low acidity of α hydrogen atoms of aliphatic esters and the instability of the ester-derived enolates (Figure 1.19). Stoichiometric strong bases are required to form the enolates *in situ* without self-condensation; as a result, substrates that bear base-sensitive functionalities are not tolerated, and Claisen condensation between the ester products and the enolates can lead to side products. Finally, cyclopropanation has been shown to compete with the allylation process when palladium catalysts are used.[47]

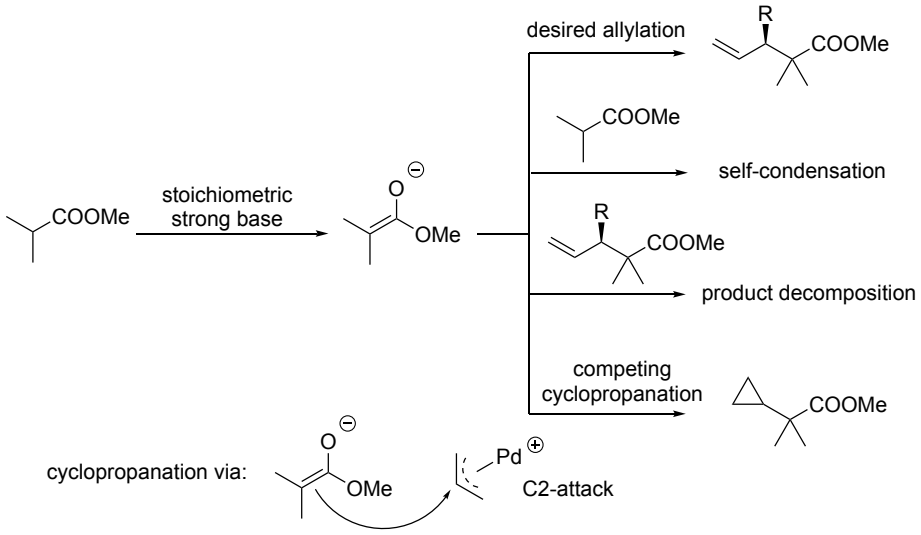

Figure 1.19 challenges of enantioselective allylic substitution reactions with simple esters

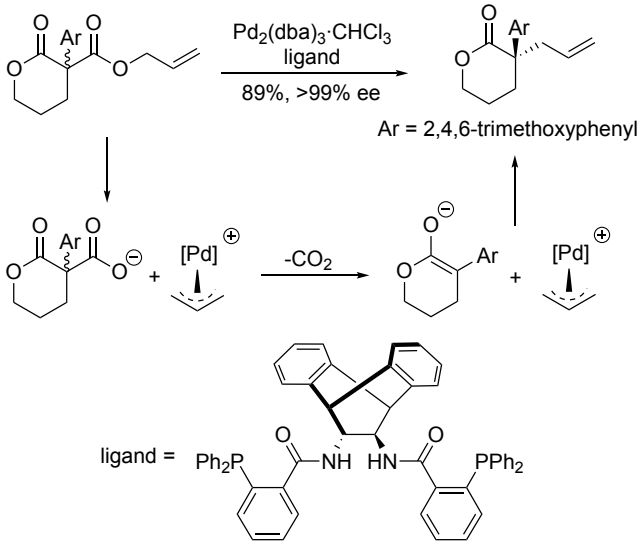

Figure 1.20 palladium-catalyzed enantioselective decarboxylative allylations to afford lactones

To address these challenges, several strategies have been reported. The first strategy is the decarboxylative allylation of allyl enol carbonates to afford the allylated esters as products. For example, Guiry and co-workers reported palladium-catalyzed decarboxylative asymmetric allylic alkylation for sterically hindered α-aryl, β-oxo-allyl ester lactones (Figure 1.20).[48] The enolate intermediates were generated after ionization of the substrates by the palladium catalyst and subsequent decarboxylation, which then reacted quickly with the allyl palladium intermediate to afford the products. The decarboxylative strategy avoids the use of strong bases and the accumulation of basic enolates during the allylation reaction, allowing the reaction to occur smoothly and selectively. However, the scope of this strategy is currently limited to cyclic lactone derivatives.[49]

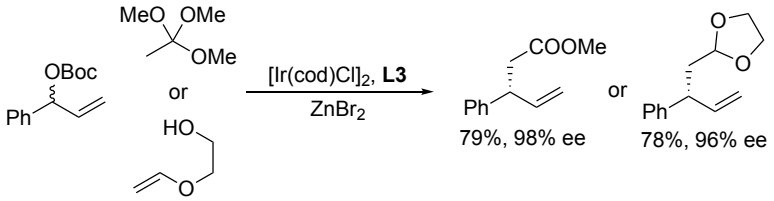

Figure 1.21 iridium-catalyzed enantioselective allylations to afford esters and protected aldehydes

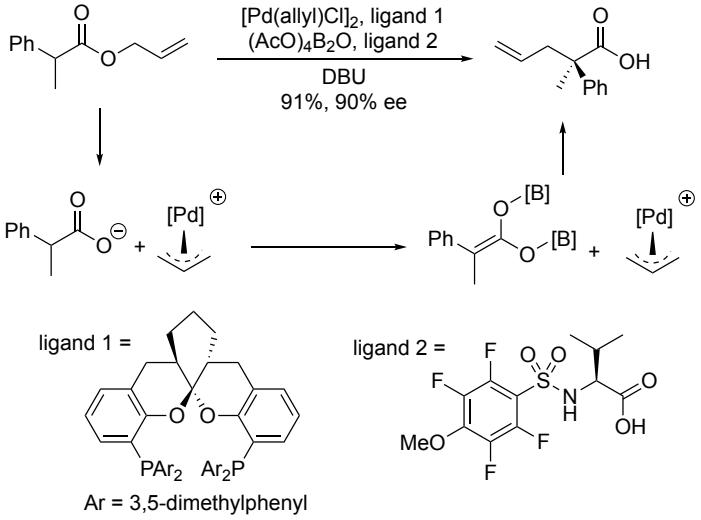

Figure 1.22 enantioselective allyl migration reaction catalyzed synergistically by palladium and boron

The second strategy is to use enolate equivalents that are less basic than the enolates generated *in situ* by direct deprotonation of the parent esters. For example, Hartwig and co-workers reported iridium-catalyzed enantioselective allylic substitutions of silyl ketene acetals.[50] The use of silyl ketene acetals in place of the ester enolate avoids the use of strong bases, thus leading to high functional-group tolerance. Details will be discussed in Chapter 2. With the same strategy, Carreira and co-workers reported trimethyl orthoacetate and ethylene glycol mono-vinyl ether as enolate surrogates in enantioselective iridium-catalyzed allylation (Figure 1.21).[51] This method enables the preparation of β-substituted γ,δ-unsaturated esters and protected aldehydes under mild conditions.

The third strategy was disclosed very recently by Kanai and co-workers (Figure 1.22).[52] Similar to the decarboxylative allylation reactions, the first step involves the ionization of substrate in the presence of the palladium catalyst. The resulting carboxylate is activated by the chiral boron co-catalyst to form the boron enolate with mild bases (so-called "soft-enolization"). The boron enolate reacts with the allyl palladium intermediate to afford the product. Although this reaction occurred intramolecularly to afford the product with net allyl migration, the soft-enolization strategy could be applied to intermolecular enantioselective allylation reactions with esters.[53]

1.4 Asymmetric Allylic Substitution Reactions with Prochiral Enolates

In the transition-metal-catalyzed asymmetric allylic substitution reactions, if both the enolate nucleophiles and the allyl electrophiles are prochiral, synthetically valuable dyads containing contiguous stereocenters at both α and β positions could be assembled in a catalytic and stereoselective fashion (category 3 in Figure 1.2).[54] However, transformations of this type are challenging because a new bond needs to be formed between two sterically hindered prochiral carbon atoms with control of both absolute and relative configurations. Figure 1.23 shows the reaction between the enolate and the allyl-metal complex. To obtain high diastereo- and enantioselectivity for the allylation, it is critical to control 1) geometry of the enolate, 2) facial selectivity of the enolate in the reaction, 3) geometry of the allyl moiety, and 4) facial selectivity of the allyl moiety in the reaction.

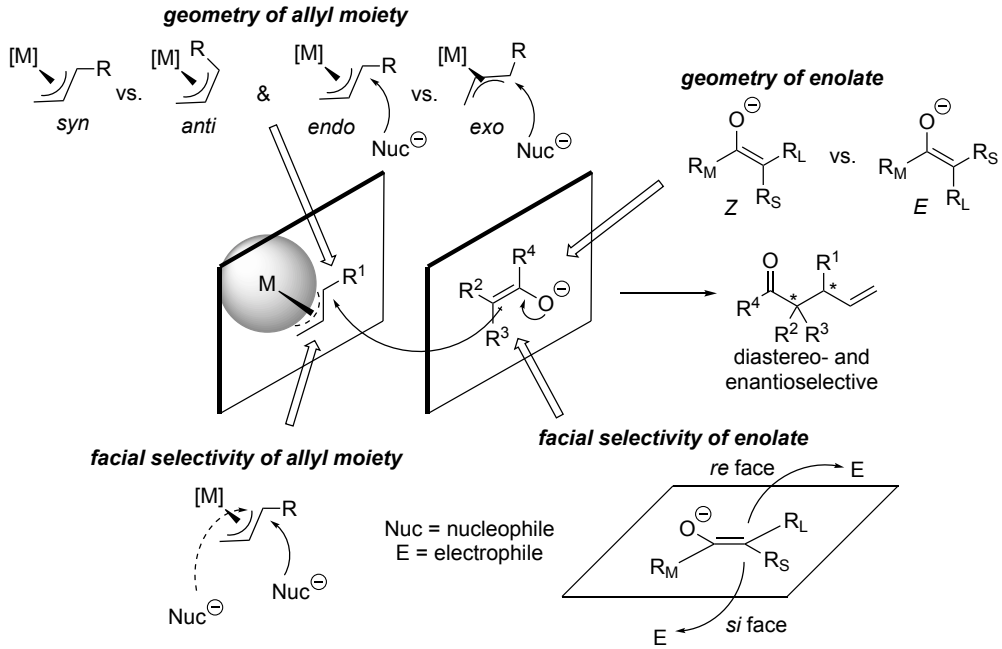

Figure 1.23 important factors in stereoselective allylation of enolates

Metal complexes ligated by chiral ligands are able to dictate the geometry and facial selectivity of the allyl moiety on the metal center in the allylation reactions.[5,55] The geometry of the enolate derived from cyclic substrates is dictated by the ring strain (Figure 1.24).[56] The geometry of the enolate derived from acyclic substrates are usually dictated by inherent steric properties of

the substrate[57] and in some cases, chelation between the substrate and an external Lewis acid (an example of this type will be discussed in Chapter 3).[58]

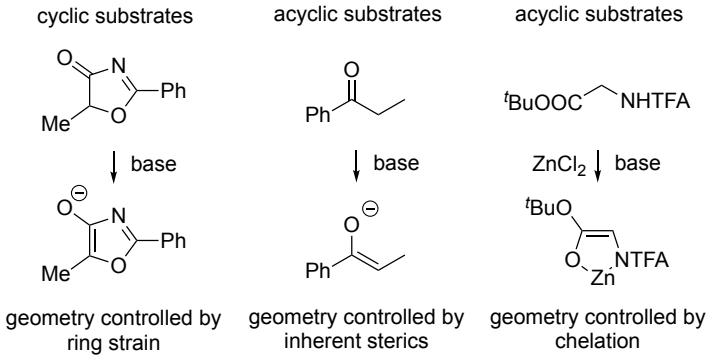

Figure 1.24 strategies to control the geometry of enolates

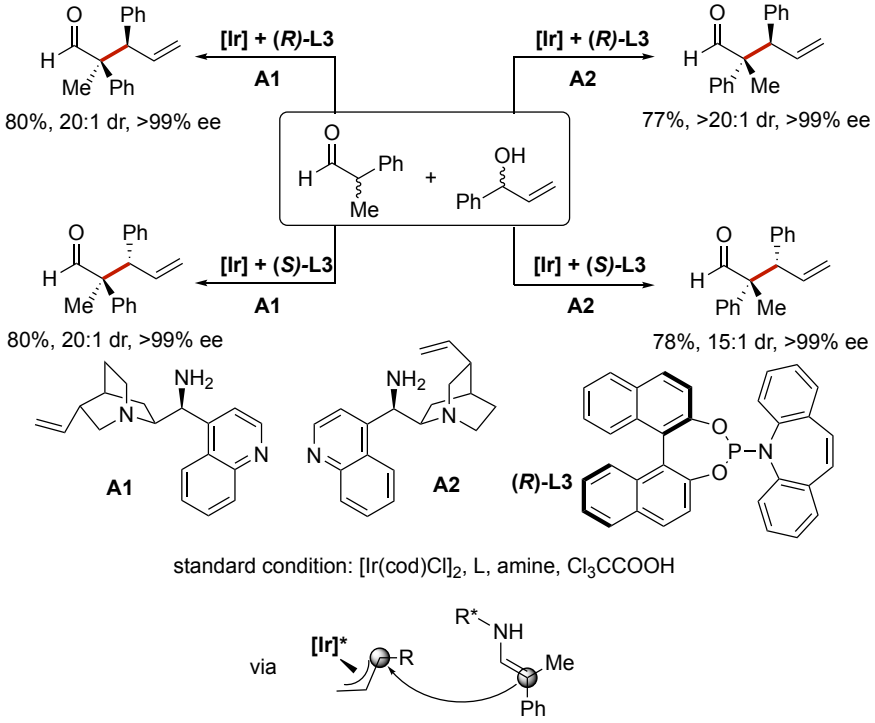

Figure 1.25 stereodivergent allylation of aldehydes

Although high diastereo- and enantioselectivities have been obtained in some allylation reactions with prochiral enolates, understanding of the facial selectivity of the enolates in asymmetric allylation reactions remain elusive. Because most of the allylic substitution reactions with enolates occur through the outer-sphere mechanism as discussed above, the key bond-forming event occurs outside of the coordination sphere of the metal center. Subsequently, there is little possibility for the ligand to interact with the incoming enolate. Ligands with large bite angles have been reported to interact with the incoming enolate in some cases,[4] But the facial selectivity of the enolate in the allylation reaction mainly relies on steric repulsions between substituents on the allyl moiety and

those on the enolate. The aggregation state of the enolates has been proposed to play a key role in the stereoselective event.[59,60]

To exert complete control over the geometry and facial selectivity of the enolate in the asymmetric allylation reactions, Carreira and co-workers developed a dual-catalysis strategy (Figure 1.25).[61] Besides the iridium catalyst to form the chiral allyl iridium intermediate, a second amine catalyst was introduced to react with the aldehyde to form the chiral enamine intermediate. The reaction between the chiral allyl iridium intermediate and the chiral enamine intermediate occurred with high facial selectivity to afford the allylation product with high diastereo- and enantioselectivity. Furthermore, the iridium complex and the amine catalyst could dictate the configurations of the two stereogenic centers of the product arising from the electrophile and the nucleophile, respectively. Thus, all four possible stereoisomers of the product were obtained by simple permutations of the enantiomers of the two catalysts (so-called "stereodivergent catalysis", Figure 1.26).[62]

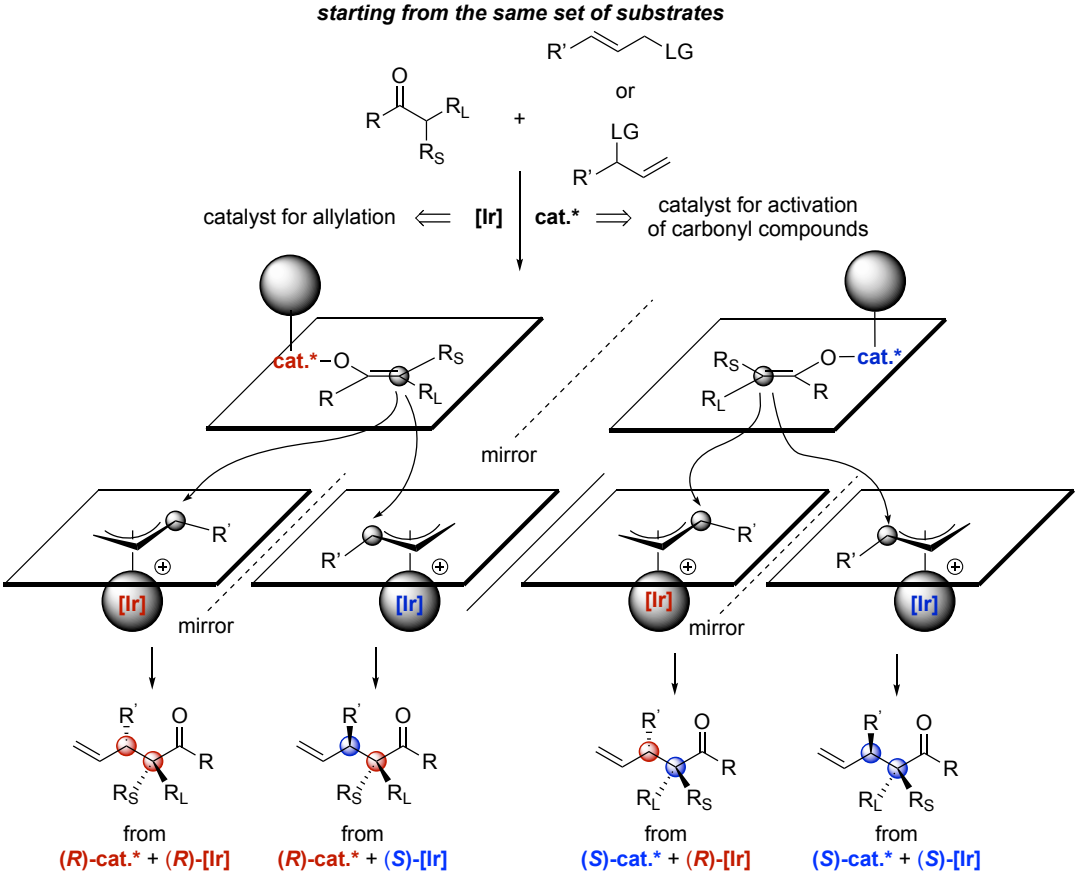

Figure 1.26 stereodivergent allylation by dual catalysis

As discussed above, the iridium-catalyzed allylic substitution reactions with **L3** as the ligand (Carreira's system) usually operate under acidic conditions. In general, enamines are also generated under acidic conditions. Therefore, Carreira and co-workers were able to combine their iridium catalysis with enamine catalysis to realize the stereodivergent allylation reactions of aldehydes.

There are many published activation modes for catalytic asymmetric functionalizations of enolates that operate under basic conditions (Lewis base catalysis, Lewis acid catalysis, *etc.*). These activation modes are unlikely to be compatible with Carreira's system but are likely to work synergistically with the iridium catalysts from **L1** that also operate under basic conditions (Hartwig's system). By introducing a Lewis base or a Lewis acid as the co-catalyst that reacts with pronucleophiles to form the chiral enolates *in situ*, Hartwig and co-workers developed iridium-catalyzed stereodivergent allylic substitution reactions with aryl acetic acid esters and azaaryl compounds.[63] Details will be discussed in Chapter 4, Chapter 5, and Chapter 6.

Following the same strategy, Zhang, Wang and their co-workers recently reported stereodivergent allylic substitution reactions of α-hydroxy ketones and amino acid derivatives by combining Hartwig's iridium system for allylation with a Lewis acid catalyst, indicating the generality of this dual catalysis strategy.[64]

1.5 Summary

Transition-metal-catalyzed asymmetric allylic substitution reactions with enolates have been studied intensively for decades. These studies have encompassed methodology development, mechanistic investigation, and synthetic applications. Early development focused on the identification of catalytic systems for the enantioselective allylation of stabilized enolates derived mainly from 1,3-dicarbonyl compounds. Recently, remarkable progress has been made on similar transformations with unstabilized enolates derived from ketones, aldehydes, and carboxylic acid derivatives. The most recent, major advance has been the stereodivergent construction of two contiguous stereogenic centers by these reactions, especially those from reactions with acyclic substrates. The development of synergistic catalysis (or dual catalysis) in this field not only allows allylation reactions to occur with substrates that are inherently inactive under mild conditions, but also renders the control of both absolute and relative configurations of products containing two stereogenic centers straightforward and predictable. As the field continues to grow, these methods will provide new, powerful tools to construct C–C bonds with high stereoselectivity.

1.6 References

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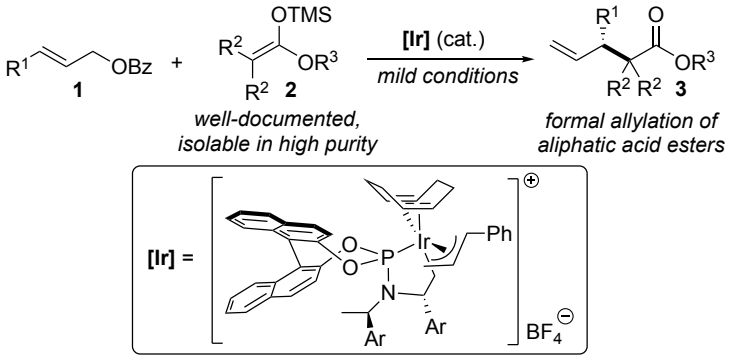
CHAPTER 2

Iridium-Catalyzed Enantioselective Allylic Substitutions of Aliphatic Esters via Silyl Ketene Acetals

2.1 Introduction

Catalytic asymmetric allylic substitutions with enolates form C–C bonds reliably with high enantioselectivity.[1] Such reactions with enolates derived from ketones and aldehydes form products bearing α-stereogenic centers,[2] β-stereogenic centers,[3] or both.[4] These reactions of stabilized enolates generated from carboxylic acid derivatives containing proximal electron-withdrawing groups (such as acyl, carboxyalkyl, nitro or cyano groups),[5] heteroatom functionalities,[6] or aromatic substituents[7] also occur. However, analogous transformations of the unstabilized enolates derived from aliphatic esters are rare. Reported enantioselective examples are limited to palladium-catalyzed reactions of lactones or ester equivalents with symmetrical allylic electrophiles, and one recently reported example of a ruthenium-catalyzed process.[8,9]

The low acidity of the α hydrogens of the aliphatic esters and the instability of the ester-derived enolates make allylation of ester enolates challenging. Stoichiometric strong bases are required to form the enolates *in situ* without self-condensation, substrates that bear base-sensitive functionalities (for example, acetoxyl group) are not tolerated, and Claisen condensation between the ester products and the enolates can lead to side products. Finally, cyclopropanation has been shown to compete with the allylation process when palladium catalysts are used.[10]



Scheme 2.1 Iridium-catalyzed enantioselective allylic substitution reactions with silyl ketene acetals

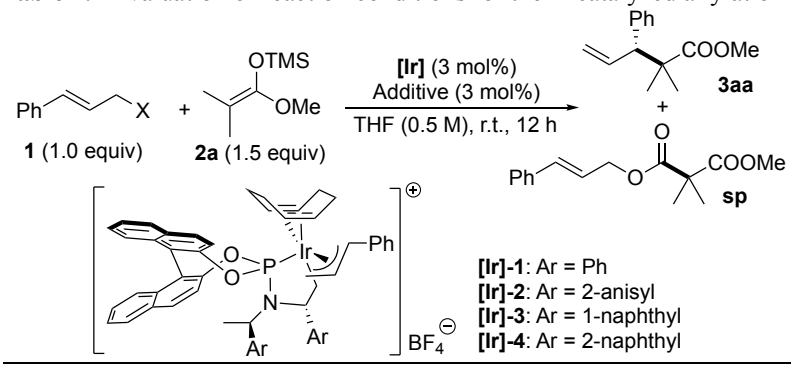
To develop a general method for the enantioselective allylation of aliphatic esters under mild conditions, we envisioned that silyl ketene acetals, the silicon enolates of esters, could be employed as the nucleophiles because they are significantly less basic than the alkali metal enolates formed *in situ* by deprotonation. Iridium complexes **[Ir]** (Scheme 2.1) developed in our group could catalyze this proposed transformation because they enable enantioselective allylic substitution reactions with various nucleophiles under relatively neutral conditions, without competing formation of cyclopropanes.[11]

The allylation of silyl ketene acetals containing *gem*-dialkyl groups would be particularly valuable because the resulting enantioenriched α-allyl esters containing a quaternary α-carbon and a tertiary β-stereocenters are inaccessible by asymmetric Michael additions or asymmetric hydrogenations of the α,β-unsaturated esters. Furthermore, the enantioselective allylations of stabilized malonate-type nucleophiles followed by fragmentation (desulfonylation and decarboxylation) would not afford these highly substituted products.[12]

Herein we report enantioselective allylations of silyl ketene acetals catalyzed by a metallocyclic iridium complex (Scheme 2.1) to form the allylated aliphatic esters with high regio- and enantioselectivity under mild conditions. Due to the versatility of the ester functionality in organic synthesis, these products are readily transformed to primary alcohols, carboxylic acids, amides, isocyanates, carbamates, tetrahydrofuran (THF) derivatives and γ-butyrolactone derivatives without erosion of enantiomeric purity.

2.2 Results and Discussion

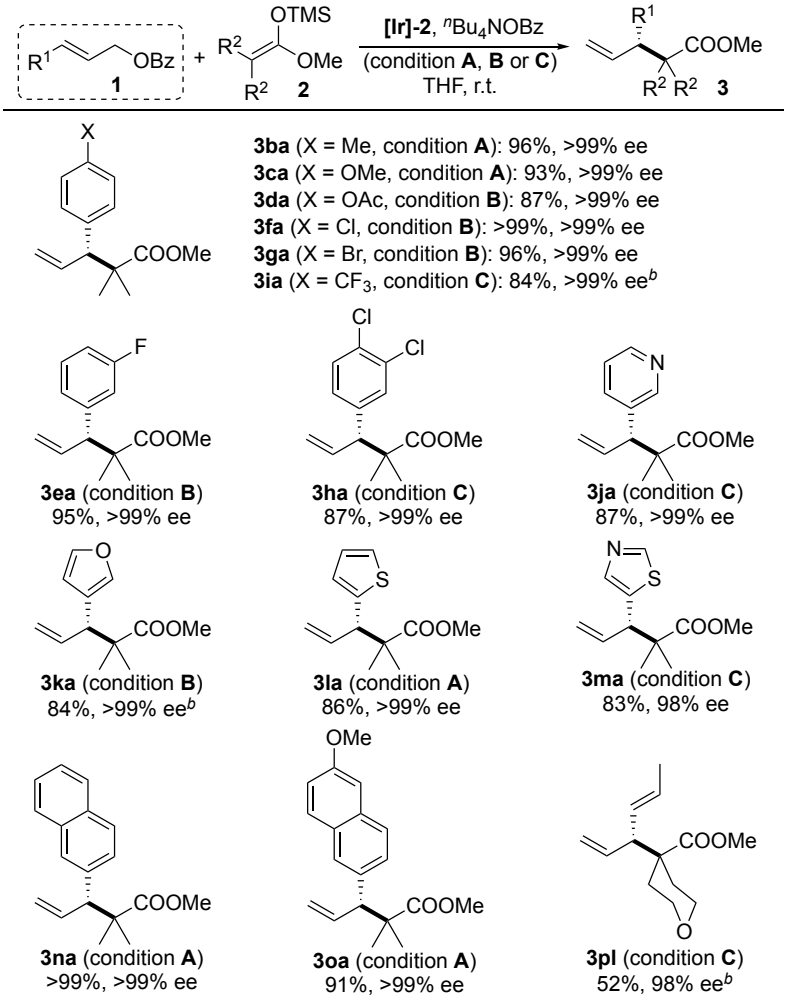
Table 2.1 Evaluation of reaction conditions for the Ir-catalyzed allylation[a]



Entry	X	[Ir]	Additive	b:l[b]	Yields/%[c]		*ee*/%[d]
					3aa	**sp**	**3aa**
1	OCOOMe	**[Ir]-1**	^{n}Bu$_4$NOAc	19:1	17	32	n.d
2	OCOOMe	**[Ir]-2**	^{n}Bu$_4$NOAc	>20:1	50	33	98
3	OCOOMe	**[Ir]-3**	^{n}Bu$_4$NOAc	17:1	23	55	n.d.
4	OCOOMe	**[Ir]-4**	^{n}Bu$_4$NOAc	>20:1	17	33	n.d.
5	OTroc	**[Ir]-2**	^{n}Bu$_4$NOAc	>20:1	16	20	n.d.
6	OBoc	**[Ir]-2**	^{n}Bu$_4$NOAc	>20:1	97	0	98
7	OPO(OEt)$_2$	**[Ir]-2**	^{n}Bu$_4$NOAc	>20:1	23	-	n.d.
8	OAc	**[Ir]-2**	^{n}Bu$_4$NOAc	>20:1	62	-	>99
9	OPiv	**[Ir]-2**	^{n}Bu$_4$NOAc	>20:1	69	-	99
10	OBz	**[Ir]-2**	^{n}Bu$_4$NOAc	>20:1	96	-	>99
11[e]	OBz	**[Ir]-2**	^{n}Bu$_4$NOAc	>20:1	68	-	>99
12	OBz	**[Ir]-2**	^{n}Bu$_4$NOBz	>20:1	>99 (>99)	-	>99
13	OBoc	**[Ir]-2**	^{n}Bu$_4$NOBz	>20:1	96 (94)	0	98
14	OBz	**[Ir]-2**	none	-	0	-	-

[a]Reaction conditions: **1** (0.20 mmol, 1.0 equiv), **2a** (1.5 equiv), **[Ir]** (3 mol%), additive (3 mol%), THF (0.4 mL), r.t., 12 h. The absolute configuration of **3aa** was assigned by analogy. [b]The branched/linear selectivities were determined by ^{1}H NMR analysis of the crude mixtures. [c]Determined by ^{1}H NMR analysis of the crude mixtures with mesitylene as an internal standard. The yields within parentheses are that of the branched isomer and the linear isomer isolated. [d]Determined by chiral supercritical fluid chromatography (SFC) analysis of the branched isomer. [e]0.5 equiv of ^{n}Bu$_4$NOAc was added. n.d. = not determined.

Table 2.2 Iridium-catalyzed allylations of silyl ketene acetals: scope of the allyl benzoates[a]

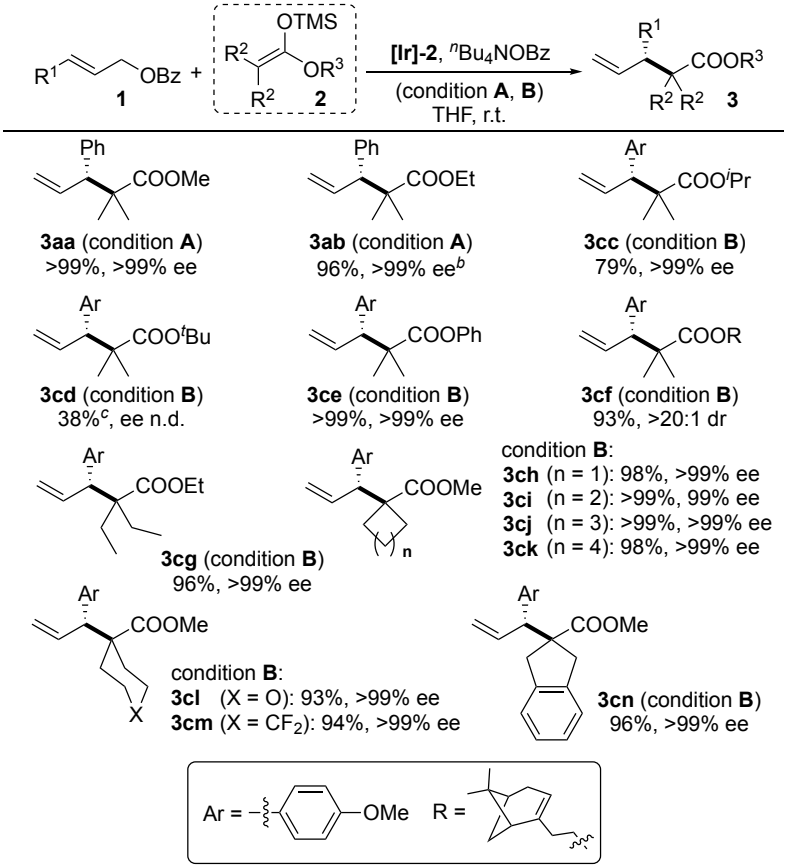


[a]Condition **A**: **[Ir]-2** (3 mol%), ^{n}Bu$_4$NOBz (3 mol%), THF (0.5 M); condition **B**: **[Ir]-2** (4 mol%), ^{n}Bu$_4$NOBz (4 mol%), THF (0.25 M); condition **C**: **[Ir]-2** (3 mol%), ^{n}Bu$_4$NOBz (3 mol%), THF (0.5 M), then another batch of **[Ir]-2** (3 mol%), ^{n}Bu$_4$NOBz (3 mol%) and THF were added after 12 h. The absolute configurations were assigned by analogy. [b]The enantiomeric excesses were determined after further transformations of the products.

We began our studies on enantioselective allylic substitutions of aliphatic silyl ketene acetals by examining the reactions between cinnamyl methyl carbonate and ketene acetal **2a** in the presence of a series of metallacyclic iridium complexes containing a series of aryl substituents on the ligands (Table 2.1, entry 1–4). A catalytic amount of tetrabutylammonium acetate (^{n}Bu$_4$NOAc) was added to activate the silicon enolate because our previous studies demonstrated that carboxylates could activate silyl enol ethers in related iridium-catalyzed allylation reactions.[3f,13] The reaction conducted with iridium catalyst **[Ir]-2** bearing two 2-anisyl substituents on the ligand gave the ester product **3aa** in 50% yield with >20:1 branched/linear selectivity and 98% ee. The yield was modest because side product **sp** (33%) was formed from competitive nucleophilic acyl substitution of **2a** with the carbonyl group of cinnamyl methyl carbonate. To suppress the formation of **sp**, we studied reactions of allylic esters containing the 2,2,2-trichloroethyl carbonate (OTroc)

and the *t*-butyl carbonate (OBoc) groups that are more hindered than the methyl carbonate. Reaction of the 2,2,2-trichloroethyl carbonate gave **3aa** in a low yield of 16% and **sp** in 20% yield (entry 5), as well as an additional product in 54% yield from the allylation of 2,2,2-trichloroethoxide generated from oxidative addition of the carbonate and decarboxylation of the resulting anion. However, reaction of the *t*-butyl carbonate formed **3aa** as a single product in 97% yield with 98% ee (entry 6).

Table 2.3 Iridium-catalyzed allylations of silyl ketene acetals: scope of the silyl ketene acetals[a]



[a]Condition **A**: **[Ir]-2** (3 mol%), ^{n}Bu$_4$NOBz (3 mol%), THF (0.5 M); condition **B**: **[Ir]-2** (4 mol%), ^{n}Bu$_4$NOBz (4 mol%), THF (0.25 M). The absolute configurations were assigned by analogy. [b]The enantiomeric excess was determined after further transformation of the product. [c]NMR yield.

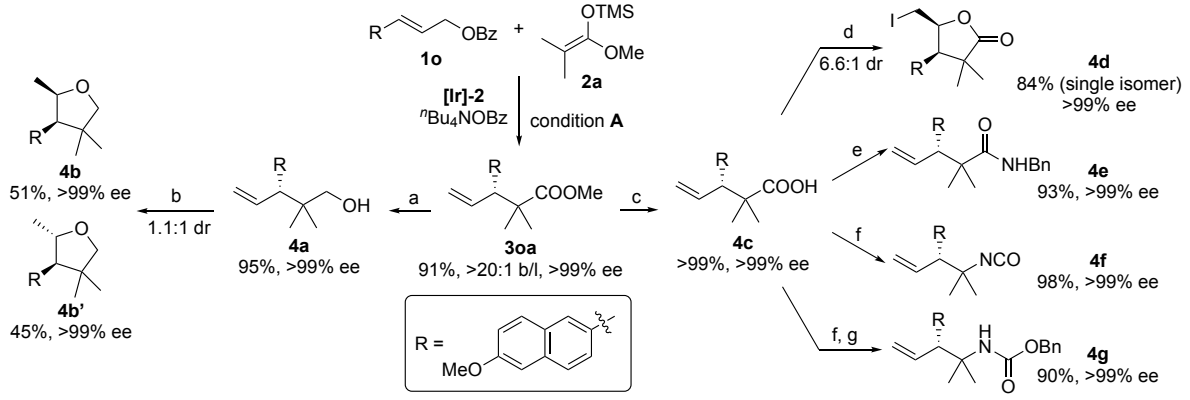
Further investigation of the effect of leaving groups included reactions of the ethyl phosphate, acetate, pivalate and benzoate derivatives of cinnamyl alcohol (entry 7–10). The reaction of cinnamyl benzoate **1a** (entry 10) delivered **3aa** in almost quantitative (96%) yield with excellent ee (>99%). However, a small amount of cinnamyl acetate (<5%) was observed, presumably from reaction of the allyl iridium intermediate and ^{n}Bu$_4$NOAc.[11d] This hypothesis was supported by the result of the reaction conducted with 0.5 equiv of ^{n}Bu$_4$NOAc (entry 11), which gave **3aa** in a lower yield of 68% and cinnamyl acetate in 26% yield, which was higher than that from the reaction with 3 mol % of ^{n}Bu$_4$NOAc in entry 10. To avoid the formation of cinnamyl acetate, tetrabutylammonium benzoate (^{n}Bu$_4$NOBz) was used instead of ^{n}Bu$_4$NOAc as the carboxylate additive, and this

reaction occurred to afford **3aa** in quantitative yield with >99% ee (entry 12). The reaction with cinnamyl *t*-butyl carbonate occurred similarly to give **3aa** in 94% yield with 98% ee (entry 13). No reaction occurred in the absence of a carboxylate additive (entry 14) or with the TBS analog of **2a**.

Table 2.2 shows the scope of allyl benzoates that underwent the allylation process. The reactions with various cinnamyl benzoates bearing electron-neutral (**3aa**, **3ba**), electron-donating (**3ca**, **3da**), and electron-withdrawing (**3ea**–**3ia**) substituents on the aryl rings all afforded the corresponding products in ≥84% yield with >99% ee. Benzoate **1d** bearing a base-sensitive acetoxy substituent at the *para*-position of the phenyl ring underwent allylation cleanly to give **3da** in 87% yield with >99% ee, highlighting the mild conditions of these reactions. In general, the reactions of electron-deficient cinnamyl benzoates required a higher catalyst loading of 4 mol % (condition **B** for **3ea**–**3ga**) or 6 mol % (condition **C** for **3ha**, **3ia**), instead of 3 mol % (condition **A** for **3aa**–**3ca**), to reach full conversion of the allyl benzoate.

This reaction also occurred with allyl benzoates bearing heteroaryl, naphthyl, and alkenyl substituents. Allyl benzoates containing pyridyl (**1j**), furyl (**1k**), thienyl (**1l**), thiazolyl (**1m**), naphthyl (**1n**), and 6-methoxy naphthyl (**1o**) groups underwent the allylations to form products **3ja**–**3oa** in ≥83% yield with ≥98% ee. Sorbyl benzoate **1p** reacted with silyl ketene acetal **2l** to give the allylation product **3pl** in 52% yield with 98% ee.

Table 2.3 shows the scope of silyl ketene acetals that underwent the allylation process. Silyl ketene acetals generated from methyl (**2a**), ethyl (**2b**), isopropyl (**2c**) and phenyl (**2e**) isobutyrate reacted to form products **3aa**, **3ab**, **3cc**, and **3ce** in ≥79% yield with >99% ee. The reactivity of the silyl ketene acetal derived from *t*-butyl isobutyrate (**2d**) was lower, and **3cd** was obtained in 38% yield with 39% of **1c** unconverted. Silyl ketene acetal **2f** derived from (-)-nopol that bears a chiral hydrocarbon motif also reacted to give **3cf** in 93% yield with >20:1 dr.



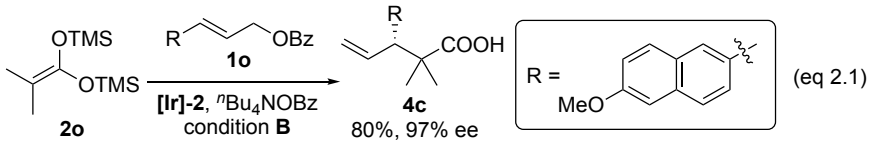
Scheme 2.2 Derivatizations. Steps: a) $LiAlH_4$ (1.5 equiv), THF, 0 °C to r.t.; b) AgOTf (10 mol%), DCE, 80 °C; c) NaOH (4.0 equiv, 2 M aq), MeOH, 80 °C; d) I_2 (1.3 equiv), $NaHCO_3$ (1.4 equiv), KI (1.3 equiv), $MeCN/H_2O$ (1:1), 0 °C to r.t.; e) $SOCl_2$ (5.0 equiv), PhH, 80 °C then $BnNH_2$ (2.0 equiv), DMAP (20 mol%), Et_3N (2.0 equiv), DCE, 80 °C; f) diphenylphosphoryl azide (1.05 equiv), Et_3N (1.7 equiv), DCE, 80 °C; g) BnOH (4.0 equiv) added to the mixture after step f, 80 °C.

In addition to the silyl ketene acetals derived from isobutyrates, *gem*-diethyl silyl ketene acetal **2g** reacted to afford **3cg** in 96% yield with >99% ee. Exocyclic *gem*-dialkyl silyl ketene acetals

bearing exocyclic double bonds on 4- (**2h**), 5- (**2i**, **2n**),6- (**2j**) and 7-membered (**2k**) rings all reacted with benzoate **1c** to give products **3ch**–**3ck**, and **3cn** in ≥96 yields with ≥99% ee. Exocyclic silyl ketene acetals containing oxygen atoms or a difluoromethylene unit on the ring structure reacted similarly to give the products (**3cl**, **3cm**) in ≥93% yield with >99% ee.

To illustrate the synthetic utility of this allylation reaction, various transformations of allylation product **3oa** were conducted. For example, **3oa** was readily converted to the primary alcohol **4a** and carboxylic acid **4c** without erosion of ee after reduction and hydrolysis, respectively. The acid **4c** was further transformed into the enantioenriched amide **4e**, isocyanate **4f**, and carbamate **4g**. The terminal alkene functionality was also derivatized. An intramolecular hydroalkoxylation of the olefin moiety on alcohol **4a** occurred with silver triflate[14] as the catalyst, giving enantioenriched tetrahydrofuran derivatives **4b** and **4b**'. Although the diastereoselectivity was low (1.1:1), each diastereomer was isolated in pure form with >99% ee. Carboxylic acid **4c** underwent iodolactonization[15] to afford lactone **4d** in 84% yield as a single isomer with >99% ee.

Finally, to extend the scope of this allylation method to form α-allyl carboxylic acids directly, the silyl-protected enolate of isobutyric acid (**2o**) was tested (eq 2.1). The reaction between **1o** and **2o** formed carboxylic acid **4c** in 80% yield with >97% ee.



(eq 2.1)

2.3 Conclusions

In summary, we have developed enantioselective allylic substitutions with aliphatic silyl ketene acetals catalyzed by a metallacyclic iridium complex. These reactions are rare allylations of enolates derived from aliphatic esters that occur in high enantioselectivity under mild conditions. The use of silyl ketene acetals avoids the use of strong bases, leading to high functional-group tolerance; a catalytic amount of carboxylate additive (^{n}Bu$_4$NOBz) induced reactivity, presumably by activating the silyl ketene acetals. The allylated esters were obtained with excellent regio- and enantioselectivity and were readily converted to the primary alcohols, carboxylic acids, amides, isocyanates, carbamates, THF derivatives and γ-butyrolactone derivatives with preservation of enantiomeric purity. Studies to achieve the regio-, diastereo- and enantioselective allylations of unsymmetrical aliphatic acid and their derivatives are ongoing in our laboratories.[16,17]

2.4 Experimental

2.4.1 General Experimental Details

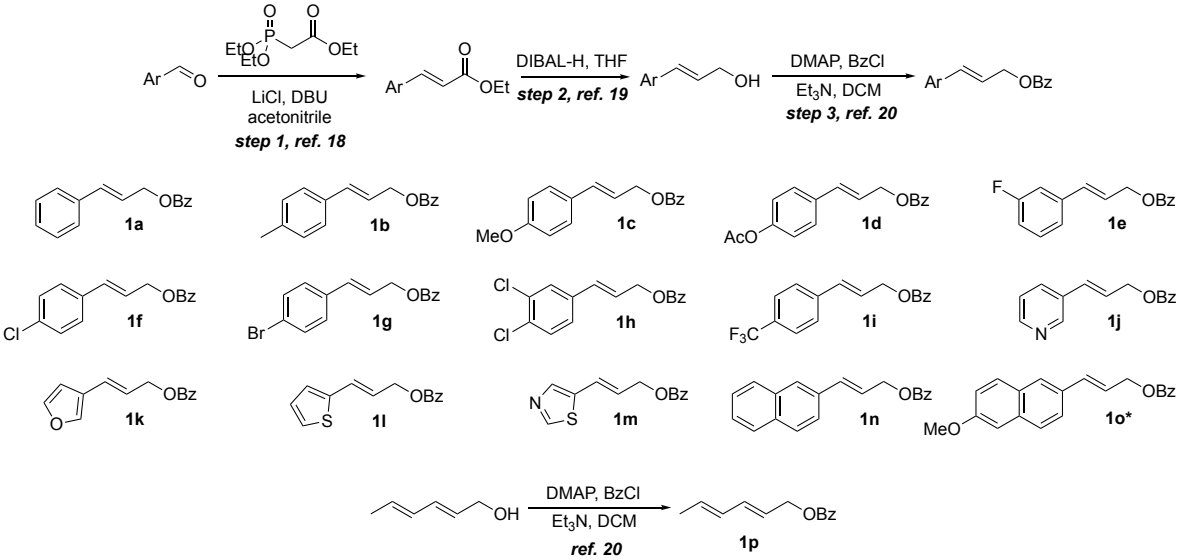
All air-sensitive manipulations were conducted under inert atmosphere in a nitrogen-filled glovebox or by standard Schlenk techniques. Tetrahydrofuran (THF) was purified by passing it through a column composed of activated A-1 alumina and degassing by freeze-pump-thaw methods. [Ir(cod)Cl]$_2$ was obtained from Johnson-Matthey and used without further purification. Both

enantiomers of 2-methoxy-α-methylbenzylamine, the precursors to prepare the corresponding phosphoramidite ligands and the catalyst **[Ir]-2** and *ent*-**[Ir]-2**, were obtained from BASF.

Chiral supercritical fluid chromatography (SFC) analysis was conducted on a JASCO SF-2000 integrated analytical SFC system. Proton nuclear magnetic resonance (^{1}H NMR) spectra were acquired on commercial instruments (300, 400, 500 and 600 MHz) at the NMR facility of University of California, Berkeley. Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were acquired at 100, 126 and 151 MHz. Fluorine-19 nuclear magnetic resonance (^{19}F NMR) spectra were acquired at 376 MHz. The proton signal for the residual non-deuterated solvent (δ 7.26 for $CDCl_3$, δ 7.16 for C_6D_6) was used as an internal reference for ^{1}H NMR spectra. For ^{13}C NMR spectra, chemical shifts are reported relative to the δ 77.16 resonance of $CDCl_3$ and relative to the δ 128.06 resonance of C_6D_6. For ^{19}F NMR spectra, chemical shifts are reported relative to the δ -113.15 resonance of PhF as an external reference. Coupling constants are reported in Hz. Optical rotations were measured on a Perkin Elmer 241 Automatic Polarimeter. High-resolution mass spectra were recorded on a commercial high-resolution mass spectrometer at the QB3/Chemistry Mass Spectrometry Facility at UC Berkeley.

Analytical thin layer chromatography (TLC) was performed on Kieselgel 60 F_{254} glass plates pre-coated with a 0.25 mm thickness of silica gel. The TLC plates were visualized with UV light and/or by staining with $KMnO_4$. For the purification of allylation products, column chromatography was generally performed on a Teledyne Isco Combiflash® R_f system with Redi*Sep* Gold™ columns. Silia*Flash*® T60 silica gel (particle size 5-20 μm) was used to fill the cartridge for Combiflash® system. For the purification of substrates, column chromatography was generally performed using Kieselgel 60 (230-400 mesh) silica gel, typically with a 50-100:1 weight ratio of silica gel to the crude products.

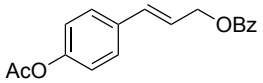
2.4.2 Synthesis of Allylic Benzoates



Scheme 2.3 Synthesis of allylic benzoates: for the synthesis of **1o** in **step 3**, 1:1 THF/DCM was used as the reaction solvent instead of pure DCM due to the low solubility of the corresponding allylic alcohol in DCM.

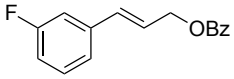
In general, the allylic benzoates were prepared according to published procedures (Scheme 2.3).[18-20]

(*E*)-3-(4-acetoxyphenyl)allyl benzoate (1d)



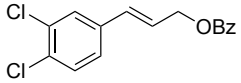
The title compound was isolated (starting from 1.4 mmol of the corresponding allylic alcohol; 390 mg, 1.32 mmol, 94%) as a white solid.
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.14 – 8.05 (m, 2H), 7.60 – 7.52 (m, 1H), 7.50 – 7.36 (m, 4H), 7.11 – 7.01 (m, 2H), 6.73 (dt, *J* = 15.8, 1.4 Hz, 1H), 6.37 (dt, *J* = 15.9, 6.4 Hz, 1H), 4.98 (dd, *J* = 6.4, 1.4 Hz, 2H), 2.30 (s, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 169.6, 166.5, 150.5, 134.2, 133.4, 133.2, 130.3, 129.8, 128.5, 127.8, 123.7, 121.9, 65.6, 21.3.
HRMS (EI): *m/z* for $C_{18}H_{16}O_4$ $[M]^+$ calcd.: 296.1049, found: 296.1050.

(E)-3-(3-fluorophenyl)allyl benzoate (1e)



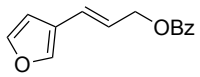
The title compound was isolated (starting from 2.0 mmol of the corresponding allylic alcohol; 384 mg, 1.50 mmol, 75%) as a colorless oil.
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.11 – 8.07 (m, 2H), 7.61 – 7.53 (m, 1H), 7.49 – 7.44 (m, 2H), 7.32 – 7.27 (m, 1H), 7.21 – 7.15 (m, 1H), 7.12 (d, J = 10.1, 2.0 Hz, 1H), 6.96 (td, J = 8.4, 2.5 Hz, 1H), 6.71 (d, J = 15.9 Hz, 1H), 6.42 (dt, J = 15.9, 6.2 Hz, 1H), 4.99 (dd, J = 6.3, 1.4 Hz, 2H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 166.5, 163.2 (d, *J* = 245.6 Hz), 138.7 (d, *J* = 8.2 Hz), 133.2, 133.0 (d, *J* = 2.7 Hz), 130.3, 130.2 (d, *J* = 6.1 Hz), 129.8, 128.6, 124.9, 122.7 (d, *J* = 2.8 Hz), 115.0 (d, *J* = 21.4 Hz), 113.2 (d, *J* = 22.0 Hz), 65.3.
^{19}F NMR (376 MHz, $CDCl_3$) δ -113.4 – -113.5 (m, 1F).
HRMS (EI): *m/z* for $C_{16}H_{13}FO_2$ $[M]^+$ calcd.: 256.0900, found: 256.0901.

(*E*)-3-(3,4-dichlorophenyl)allyl benzoate (1h)



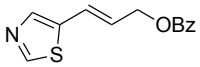
The title compound was isolated (starting from 4.3 mmol of the corresponding allylic alcohol; 1.07 g, 3.50 mmol, 81%) as a white solid.
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.10 – 8.07 (m, 2H), 7.60 – 7.56 (m, 1H), 7.49 (d, *J* = 2.1 Hz, 1H), 7.48 – 7.44 (m, 2H), 7.39 (d, *J* = 8.3 Hz, 1H), 7.23 (dd, *J* = 8.3, 2.1 Hz, 1H), 6.64 (dt, *J* = 15.9, 1.5 Hz, 1H), 6.41 (dt, *J* = 15.9, 6.2 Hz, 1H), 4.98 (dd, *J* = 6.2, 1.5 Hz, 2H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 166.4, 136.5, 133.3, 133.0, 131.9, 131.6, 130.7, 130.2, 129.8, 128.6, 128.5, 125.9, 125.6, 65.1.
HRMS (EI): *m/z* for $C_{16}H_{12}Cl_2O_2$ $[M]^+$ calcd.: 306.0214, found: 306.0215.

(*E*)-3-(furan-3-yl)allyl benzoate (1k)



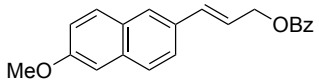
The title compound was isolated (starting from 2.0 mmol of the corresponding allylic alcohol; 370 mg, 1.63 mmol, 81%) as a colorless oil.
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.10 – 8.06 (m, 2H), 7.60 – 7.54 (m, 1H), 7.47 – 7.43 (m, 3H), 7.38 – 7.36 (m, 1H), 6.62 (d, *J* = 15.8 Hz, 1H), 6.57 – 6.54 (m, 1H), 6.14 (dt, *J* = 15.8, 6.5 Hz, 1H), 4.93 (dd, *J* = 6.5, 1.3 Hz, 2H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 166.6, 143.8, 141.2, 133.1, 130.4, 129.8, 128.5, 124.4, 123.5, 123.0, 107.7, 65.6.
HRMS (EI): *m/z* for $C_{14}H_{12}O_3$ $[M]^+$ calcd.: 228.0786, found: 228.0789.

(*E*)-3-(thiazol-5-yl)allyl benzoate (1m)



The title compound was isolated (starting from 1.7 mmol of the corresponding allylic alcohol; 376 mg, 1.53 mmol, 90%) as a white solid.
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.67 (s, 1H), 8.12 – 8.04 (m, 2H), 7.80 (s, 1H), 7.61 – 7.55 (m, 1H), 7.50 – 7.35 (m, 2H), 6.90 (d, *J* = 15.7 Hz, 1H), 6.26 (dt, *J* = 15.7, 6.2 Hz, 1H), 4.96 (dd, *J* = 6.2, 1.5 Hz, 2H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 166.4, 152.2, 142.3, 136.4, 133.3, 130.1, 129.8, 128.6, 127.0, 123.6, 64.8.
HRMS (ESI): *m/z* for $C_{13}H_{12}NO_2S$ $[M+H]^+$ calcd.: 246.0583, found: 246.0583.

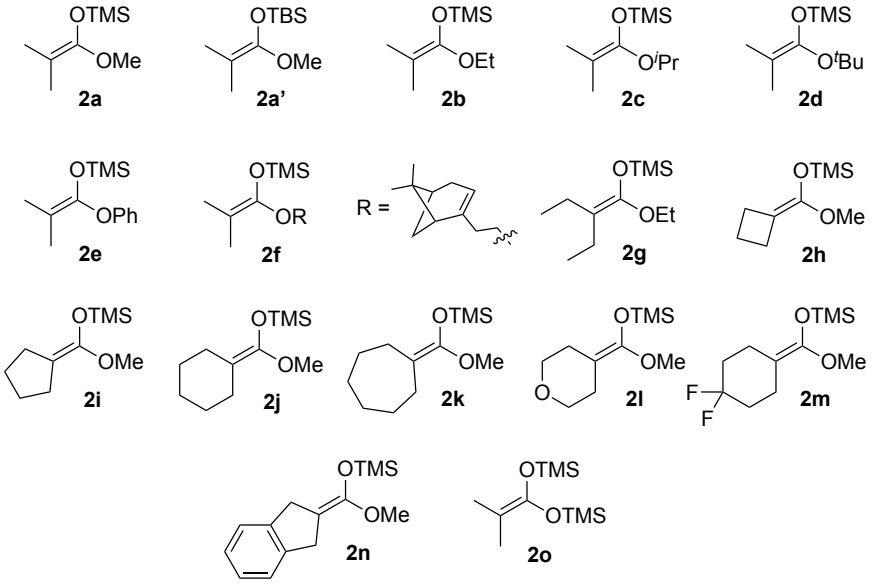
(*E*)-3-(6-methoxynaphthalen-2-yl)allyl benzoate (1o)



The title compound was isolated (starting from 5.0 mmol of the corresponding allylic alcohol; 700 mg, 2.20 mmol, 44%) as a white solid.
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 – 8.07 (m, 2H), 7.76 – 7.65 (m, 3H), 7.63 – 7.54 (m, 2H), 7.46 (t, *J* = 7.8 Hz, 2H), 7.17 – 7.09 (m, 2H), 6.88 (d, *J* = 15.8 Hz, 1H), 6.49 (dt, *J* = 15.9, 6.5 Hz, 1H), 5.03 (dd, *J* = 6.5, 1.3 Hz, 2H), 3.92 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 166.6, 158.1, 134.7, 134.6, 133.1, 131.8, 130.4, 129.8, 129.7, 129.1, 128.51, 127.3, 126.8, 124.3, 122.7, 119.2, 106.0, 65.9, 55.5.
HRMS (EI): *m/z* for $C_{21}H_{18}O_3$ $[M]^+$ calcd.: 318.1256, found: 318.1256.

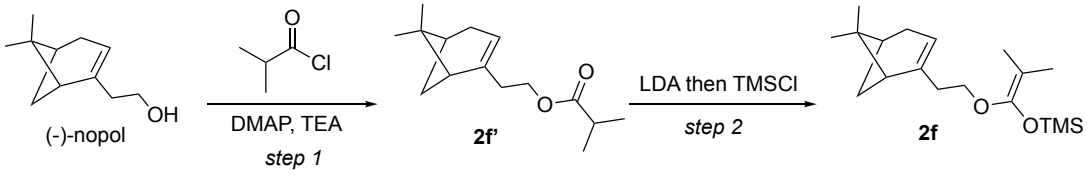
2.4.3 Synthesis of Silyl Ketene Acetals

2a was purchased from TCI America. **2a'** was synthesized following a published procedure.[21] **2b** was synthesized following a published procedure.[22] **2c** was synthesized following a published procedure.[23] **2d** was synthesized following a published procedure.[24] **2e** was synthesized following a published procedure.[25]



Scheme 2.4 Silyl ketene acetals used in this report

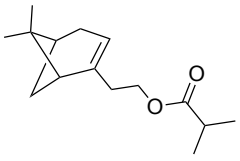
2f was synthesized by following the procedure:



Scheme 2.5 Synthesis of **2f**

Step 1: In a 250 mL round-bottom flask were added (-)-nopol (5.13 mL, 30.0 mmol, 1.00 equiv), DMAP (0.36 g, 3.0 mmol, 0.10 equiv), DCM (60 mL), and triethylamine (8.36 mL, 60.0 mmol, 2.00 equiv). Isobutyryl chloride (3.33 mL, 31.5 mmol, 1.05 equiv) was added dropwise at 0 °C. The mixture was stirred at r.t. for 3 h. After this time, the mixture was quenched by adding 50 mL of water. The organic layer was separated and washed with 50 mL of brine. After evaporation of the solvent under vacuum, the crude mixture was purified by flash column chromatography (10:1 hexanes:EtOAc, stained with CAM solution) to give (-)-nopyl isobutyrate (6.17 g, 26.1 mmol, 87%) as a colorless oil.

(-)-nopyl isobutyrate (2f')

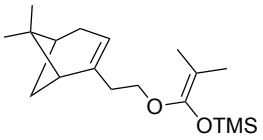


^{1}H NMR (600 MHz, $CDCl_3$) δ 5.26 (s, 1H), 4.16 – 3.99 (m, 2H), 2.49 (m, 1H), 2.37 – 2.30 (m, 1H), 2.28 – 2.14 (m, 4H), 2.08 – 2.01 (m, 2H), 1.25 (s, 3H), 1.14 – 1.10 (m, 7H), 0.80 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 177.2, 144.3, 118.8, 62.5, 45.8, 40.8, 38.1, 36.1, 34.1, 31.7, 31.4, 26.4, 21.2, 19.1, 19.1.

HRMS (EI): *m/z* for $C_{15}H_{24}O_2$ $[M]^+$ calcd.: 236.1776, found: 236.1780.

Step 2: To a suspended solution of diisopropylamine (1.83 mL, 13.0 mmol, 1.30 equiv) in THF (15 mL) was added ^{n}BuLi (4.58 mL, 2.62 M in hexanes, 12.0 mmol, 1.20 equiv) at 0 °C. The mixture was stirred for 15 min at 0 °C. A solution of (-)-nopyl isobutyrate (2.36 g, 10.0 mmol, 1.00 equiv) in THF (5 mL) was then added dropwise to the LDA solution at -78 °C. After the solution was stirred for 2 h at -78 °C, TMSCl (1.52 mL, 12.0 mmol, 1.20 equiv) was added to the mixture. The mixture was stirred for 12 h at room temperature, after which time he mixture was poured into ice water (50 mL) and hexanes (50 mL). The organic layer was washed with brine (50 mL), dried over anhydrous $MgSO_4$, and concentrated to give **2f** (2.90 g, 9.40 mmol, 94%) as a yellow oil. **2f** was used for the allylation reaction without further purification.

((1-(2-(6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)ethoxy)-2-methylprop-1-en-1-yl)oxy)trimethylsilane (2f)



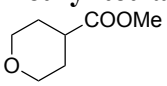
^{1}H NMR (500 MHz, C_6D_6) δ 5.34 (tq, *J* = 2.9, 1.5 Hz, 1H), 3.94 (ddd, *J* = 7.9, 7.0, 1.0 Hz, 2H), 2.49 – 2.44 (m, 2H), 2.40 (dt, *J* = 8.5, 5.6 Hz, 1H), 2.33 – 2.17 (m, 2H), 2.13 – 2.04 (m, 2H), 1.87 (s, 3H), 1.77 (s, 3H), 1.32 (d, *J* = 8.5 Hz, 1H), 1.31 (s, 3H), 0.96 (s, 3H), 0.31 (s, 9H).
^{13}C NMR (126 MHz, C_6D_6) δ 149.4, 145.5, 119.0, 91.7, 67.7, 46.8, 41.7, 38.7, 37.9, 32.5, 32.2, 27.0, 21.9, 17.9, 17.4, 0.8.
HRMS (EI): *m/z* for $C_{18}H_{32}O_2Si$ $[M]^+$ calcd.: 308.2172, found: 308.2173.

2g and **2j** was synthesized following a published procedure.[26] **2h** was synthesized following a published procedure.[27] **2i** was synthesized following a published procedure.[28] **2k** was synthesized following a published procedure.[29]

2l was synthesized by the following procedure:

To a solution of diisopropylamine (5.08 mL, 36.0 mmol, 1.20 equiv) in THF (30 mL) was added ^{n}BuLi (13.1 mL, 2.52 M in hexanes, 33.0 mmol, 1.10 equiv) at 0 °C. The mixture was stirred for 15 min at 0 °C. A solution of ester **2l'** (4.00 mL, 30.0 mmol, 1.00 equiv) in THF (10 mL) was then added dropwise to the LDA solution at -78 °C. After the solution was stirred for 2 h at -78 °C, TMSCl (4.57 mL, 36.0 mmol, 1.20 equiv) was added to the mixture. The mixture was stirred for 12 h at room temperature, after which time the mixture was poured into ice water (150 mL) and hexanes (150 mL). The organic layer was washed with brine (100 mL), dried over anhydrous $MgSO_4$, and concentrated to give a mixture of **2l** and **2l**' (6.11 g, 8:1) as a yellow oil. This mixture was used for the allylation reaction without further purification.

methyl tetrahydro-2*H*-pyran-4-carboxylate (2l')

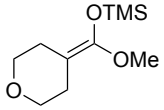


2l' was purchased from Synthonix. NMR spectra of **2l'** were acquired for comparison with those of **2l**.

^{1}H NMR (600 MHz, C_6D_6) δ 3.78 – 3.67 (m, 2H), 3.31 (s, 3H), 3.11 – 2.94 (m, 2H), 2.14 (tt, *J* = 11.2, 4.1 Hz, 1H), 1.75 – 1.63 (m, 2H), 1.55 – 1.45 (m, 2H).

^{13}C NMR (151 MHz, C_6D6) δ 174.4, 67.0, 51.2, 40.2, 29.1.

(methoxy(tetrahydro-4*H*-pyran-4-ylidene)methoxy)trimethylsilane (2l)



^{1}H NMR (300 MHz, C_6D_6) δ 3.62 (q, *J* = 5.2 Hz, 4H), 3.26 (s, 3H), 2.31 (t, *J* = 5.4 Hz, 2H), 2.21 (t, *J* = 5.4 Hz, 2H), 0.13 (s, 9H).

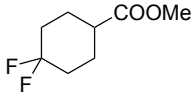
^{13}C NMR (126 MHz, C_6D_6) δ 149.0, 94.6, 69.1, 68.7, 56.7, 28.3, 27.8, 0.0.

HRMS (EI): *m/z* for $C_{10}H_{20}O_3Si$ $[M]^+$ calcd.: 216.1182, found: 216.1183.

2m was synthesized following the procedure described:

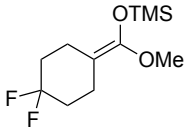
To a suspended solution of diisopropylamine (1.83 mL, 13.0 mmol, 1.30 equiv) in THF (15 mL) was added ^{n}BuLi (4.58 mL, 2.62 M in hexanes, 12.0 mmol, 1.20 equiv) at 0 °C. The mixture was stirred for 15 min at 0 °C. After this time, a solution of ester **2m'** (1.78 g, 10.0 mmol, 1.00 equiv) in THF (5 mL) was added dropwise to the LDA solution at -78 °C. After the solution was stirred for 2 h at -78 °C, TMSCl (1.52 mL, 12.0 mmol, 1.20 equiv) was added to the mixture. The mixture was stirred for 12 h at room temperature, after which time the mixture was diluted with pentane (100 mL) and filtered through anhydrous $MgSO_4$. After removal of solvent, the mixture was distilled to give **2m** (b.p. 68 – 70 °C, 0.6 torr) as a slightly yellow oil (1.76 g, 7.15 mmol, 72%).

methyl 4,4-difluorocyclohexane-1-carboxylate (2m')



2m' was purchased from PharmaBlock.

((4,4-difluorocyclohexylidene)(methoxy)methoxy)trimethylsilane (2m)



^{1}H NMR (500 MHz, C_6D_6) δ 3.21 (s, 3H), 2.36 – 2.28 (m, 2H), 2.28 – 2.15 (m, 2H), 1.91 – 1.67 (m, 4H), 0.09 (s, 9H).

^{13}C NMR (126 MHz, C_6D_6) δ 149.2, 123.2 (t, *J* = 240.5 Hz), 94.2, 56.6, 35.0 (t, *J* = 23.0 Hz), 34.7 (t, *J* = 23.2 Hz), 23.3 (t, *J* = 5.0 Hz), 22.7 (t, *J* = 5.4 Hz), -0.1.

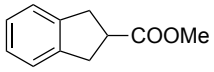
^{19}F NMR (376 MHz, C_6D_6) δ -97.0 – -97.3 (m, 2F).

HRMS (EI): *m/z* for $C_{11}H_{20}F_2O_2Si$ $[M]^+$ calcd.: 250.1201, found: 250.1202.

2n was synthesized following the procedure described:

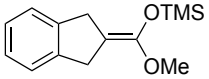
To a suspended solution of diisopropylamine (1.83 mL, 13.0 mmol, 1.30 equiv) in THF (15 mL) was added ^{n}BuLi (4.58 mL, 2.62 M in hexanes, 12.0 mmol, 1.20 equiv) at 0 °C. The mixture was stirred for 15 min at 0 °C. After this time, a solution of ester **2n'** (1.76 g, 10.0 mmol, 1.00 equiv) in THF (5 mL) was added dropwise to the LDA solution at -78 °C. After the solution was stirred for 2 h at -78 °C, TMSCl (1.52 mL, 12.0 mmol, 1.20 equiv) was added to the mixture. The mixture was stirred for 12 h at room temperature, after which time the mixture was poured into ice water (50 mL) and hexanes (50 mL). The organic layer was washed with brine (50 mL), dried over anhydrous $MgSO_4$ and concentrated to give **2n** (2.35 g, 9.46 mmol, 95%) as a brown oil. Compound **2n** was used for the allylation reaction without further purification.

methyl 2,3-dihydro-1*H*-indene-2-carboxylate (2n')



2n' is a known compound. **2n'** was synthesized by refluxing the methanol solution of the parent carboxylic acid and $SOCl_2$ (2.0 equiv) for 2 h.

((1,3-dihydro-2*H*-inden-2-ylidene)(methoxy)methoxy)trimethylsilane (2n)



^{1}H NMR (500 MHz, C_6D_6) δ 7.14 – 7.08 (m, 4H), 3.76 (s, 2H), 3.73 (d, J = 1.1 Hz, 2H), 3.35 (s, 3H), 0.19 (s, 9H).
^{13}C NMR (126 MHz, C_6D_6) δ 149.3, 143.0, 142.6, 126.7, 126.6, 125.1, 125.0, 96.2, 55.8, 35.6, 34.8, 0.3.
HRMS (EI): *m/z* for $C_{14}H_{20}O_2Si$ $[M]^+$ calcd.: 248.1233, found: 248.1234.

2o was synthesized following a published procedure.[30]

2.4.4 Synthesis of Iridium Catalysts

Iridium catalysts were prepared according to published procedures.[31] Iridium catalyst **[Ir]-1**, **[Ir]-2**, **[Ir]-3**, and **[Ir]-4** were prepared from the corresponding (R_a,*R*,*R*)-phosphoramidite ligands. Iridium catalyst *ent*-**[Ir]-1**, *ent*-**[Ir]-2**, *ent*-**[Ir]-3**, and *ent*-**[Ir]-4** were prepared from the corresponding (S_a,*S*,*S*)-phosphoramidite ligands.

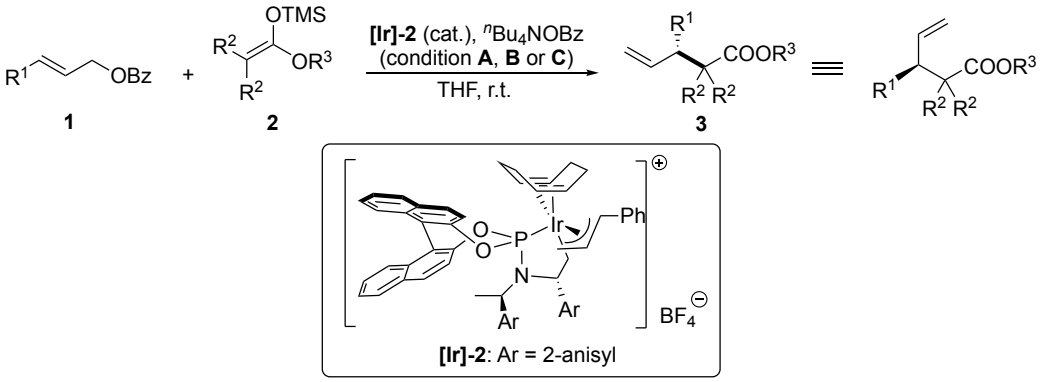
2.4.5 General Procedure for Allylations of Silyl Ketene Acetals

Condition A: in a nitrogen-filled dry-box, the allylic benzoate **1** (0.200 mmol, 1.00 equiv), **[Ir]-2** (6.9 mg, 0.006 mmol, **3 mol%**), and tetrabutylammonium benzoate ($^{n}Bu_4NOBz$, 2.2 mg, 0.006 mmol, **3 mol%**) were added to a 1-dram vial containing a magnetic stir bar. THF (**0.4 mL**) and the silyl ketene acetal **2** (0.300 mmol, 1.50 equiv) were then added sequentially by syringe. The vial was sealed with a cap containing PTFE/silicone septa and removed from the dry box. The reaction mixture was stirred at r.t. for 12 h.

Condition B: in a nitrogen-filled dry-box, the allylic benzoate **1** (0.200 mmol, 1.00 equiv), **[Ir]-2** (9.2 mg, 0.008 mmol, **4 mol%**), and $^{n}Bu_4NOBz$ (2.9 mg, 0.008 mmol, **4 mol%**) were added

to a 1-dram vial containing a magnetic stir bar. THF (**0.8 mL**) and the silyl ketene acetal **2** (0.300 mmol, 1.50 equiv) were then added sequentially by syringe. The vial was sealed with a cap containing PTFE/silicone septa and removed from the dry box. The reaction mixture was stirred at r.t. for 12 h.

Condition C: in a nitrogen-filled dry-box, the allylic benzoate **1** (0.200 mmol, 1.00 equiv), **[Ir]-2** (6.9 mg, 0.006 mmol, **3 mol%**), and $^{n}Bu_4NOBz$ (2.2 mg, 0.006 mmol, **3 mol%**) were added to a 1-dram vial containing a magnetic stir bar. THF (**0.4 mL**) and the silyl ketene acetal **2** (0.300 mmol, 1.50 equiv) were then added sequentially by syringe. The vial was sealed with a cap containing PTFE/silicone septa. The reaction mixture was stirred at r.t. for 12 h. After this time, a second portion (**0.4 mL**) of a THF solution containing **[Ir]-2** (6.9 mg, 0.006 mmol, **3 mol%**) and $^{n}Bu_4NOBz$ (2.2 mg, 0.006 mmol, **3 mol%**) was added into the reaction mixture by syringe. The vial was removed from the dry box. The reaction mixture was stirred at r.t. for another 12 h.



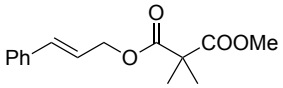
Scheme 2.6 General procedure for allylation of silyl ketene acetals

Work-up: the reaction mixture was diluted with 2 mL of hexanes, and the resulting solution was filtered through a 0.5-inch plug of silica gel (eluting with 1:1 hexanes:EtOAc, 8 mL; for polar compounds such as **3ja**, pure EtOAc was used). After evaporation of the solvent under vacuum, the crude mixture was purified by column chromatography on a Teledyne Isco Combiflash® R_f system with Redi*Sep* Gold™ columns (4-gram silica gel column). The branched/linear selectivity was determined by ^1H NMR analysis of the crude reaction mixture.

Work-up of the reaction of 1o with 2o: the reaction mixture was quenched with 5 mL of H_2O. The mixture was extracted with EtOAc (5 mL x 3). The organic layer was dried over anhydrous Na_2SO_4. After evaporation of the solvent under vacuum, the crude mixture was purified by column chromatography (100/0 to 60/40 of hexanes/EtOAc) performed on a Teledyne Isco Combiflash® R_f system with Redi*Sep* Gold™ columns (4-gram silica gel column).

2.4.6 Scope of Allylic Benzoates

1-cinnamyl 3-methyl 2,2-dimethylmalonate (sp)



The crude mixture of the reaction conducted with **[Ir]-3** and cinnamyl methyl carbonate (as

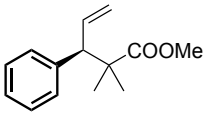
described in Table 2.1 entry 3 in the main text, following condition **A**) was purified by column chromatography (100/0 to 95/5 of hexanes/EtOAc) to give the title compound as a colorless oil (21.0 mg, 0.0802 mmol, 40%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.41 – 7.36 (m, 2H), 7.36 – 7.30 (m, 2H), 7.28 – 7.24 (m, 1H), 6.64 (d, *J* = 15.9 Hz, 1H), 6.25 (dt, *J* = 15.9, 6.3 Hz, 1H), 4.78 (dd, *J* = 6.3, 1.4 Hz, 2H), 3.72 (s, 3H), 1.47 (s, 6H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 173.4, 172.7, 136.3, 134.3, 128.8, 128.2, 126.7, 122.9, 65.9, 52.6, 50.1, 23.0.

HRMS (EI): *m/z* for $C_{15}H_{18}O_4$ $[M]^+$ calcd.: 262.1205, found: 262.1210.

methyl (*R*)-2,2-dimethyl-3-phenylpent-4-enoate (3aa)



(Condition **A**) The branched/linear selectivity was determined to be >20:1. The crude mixture was purified by column chromatography (100/0 to 95/5 of hexanes/EtOAc) to give the title compound as a colorless oil (43.9 mg, 0.201 mmol, >99%).

The **enantiomeric excess** was determined by SFC analysis to be >99% with t_R = 1.84 min (major) and t_R = 2.05 min (minor) [OJ-H, 3.0% ^{i}PrOH, 2.5 mL/min, 220 nm, 40 °C].

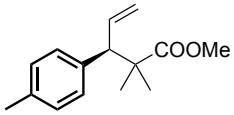
$[\alpha]_D^{25}$ = –46.5° (c 0.73, CH_2Cl_2).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.25 (m, 2H), 7.24 – 7.20 (m, 1H), 7.19 – 7.14 (m, 2H), 6.23 (dt, *J* = 16.7, 9.9 Hz, 1H), 5.16 – 5.02 (m, 2H), 3.63 – 3.56 (m, 4H), 1.18 (s, 3H), 1.12 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 177.5, 140.6, 137.2, 129.3, 128.1, 126.8, 117.6, 57.9, 51.7, 47.0, 23.4, 22.5.

HRMS (EI): *m/z* for $C_{14}H_{18}O_2$ $[M]^+$ calcd.: 218.1307, found: 218.1309.

methyl (*R*)-2,2-dimethyl-3-(*p*-tolyl)pent-4-enoate (3ba)



(Condition **A**) The branched/linear selectivity was determined to be >20:1. The crude mixture was purified by column chromatography (100/0 to 95/5 of hexanes/EtOAc) to give the title compound as a colorless oil (44.6 mg, 0.192 mmol, 96%).

The **enantiomeric excess** was determined by SFC analysis to be >99% with t_R = 1.93 min (major) and t_R = 2.19 min (minor) [OJ-H, 3.0% ^{i}PrOH, 2.5 mL/min, 220 nm, 40 °C].

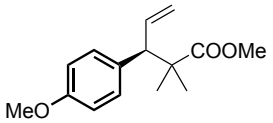
$[\alpha]_D^{25}$ = –59.6° (c 0.67, CH_2Cl_2).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.09 (d, *J* = 8.0 Hz, 2H), 7.06 (d, *J* = 8.2 Hz, 2H), 6.22 (dt, *J* = 16.8, 10.0 Hz, 1H), 5.12 – 5.05 (m, 2H), 3.62 (s, 3H), 3.57 (d, *J* = 9.6 Hz, 1H), 2.31 (s, 3H), 1.17 (s, 3H), 1.11 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 177.6, 137.4, 137.3, 136.4, 129.1, 128.9, 117.4, 57.5, 51.7, 47.0, 23.3, 22.4, 21.1.

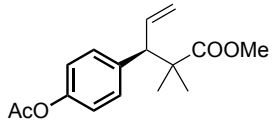
HRMS (EI): *m/z* for $C_{15}H_{20}O_2$ $[M]^+$ calcd.: 232.1463, found: 232.1465.

methyl (*R*)-3-(4-methoxyphenyl)-2,2-dimethylpent-4-enoate (3ca)



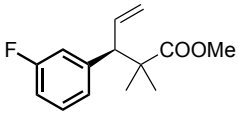
(Condition **A**) The branched/linear selectivity was determined to be >20:1. The crude mixture was purified by column chromatography (100/0 to 90/10 of hexanes/EtOAc) to give the title compound as a colorless oil (46.4 mg, 0.187 mmol, 93%).
The **enantiomeric excess** was determined by SFC analysis to be >99% with t_R = 2.15 min (major) and t_R = 2.38 min (minor) [OJ-H, 3.0% *i*PrOH, 2.5 mL/min, 220 nm, 40 °C].
[α]$_D^{25}$ = –50.7° (c 0.77, CH_2Cl_2).
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.09 (d, *J* = 8.7 Hz, 2H), 6.82 (d, *J* = 8.7 Hz, 2H), 6.19 (dt, *J* = 16.9, 9.8 Hz, 1H), 5.13 – 5.04 (m, 2H), 3.78 (s, 3H), 3.61 (s, 3H), 3.56 (d, *J* = 9.5 Hz, 1H), 1.16 (s, 3H), 1.10 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 177.6, 158.4, 137.3, 132.5, 130.2, 117.3, 113.5, 57.0, 55.3, 51.7, 47.1, 23.2, 22.4.
HRMS (EI): *m/z* for $C_{15}H_{20}O_3$ $[M]^+$ calcd.: 248.1412, found: 248.1413.

methyl (*R*)-3-(4-acetoxyphenyl)-2,2-dimethylpent-4-enoate (3da)



(Condition **B**) The branched/linear selectivity was determined to be >20:1. The crude mixture was purified by column chromatography (100/0 to 80/20 of hexanes/EtOAc) to give the title compound as a colorless oil (the reaction was conducted on a 0.100 mmol scale; 24.1 mg, 0.0872 mmol, 87%).
The **enantiomeric excess** was determined by SFC analysis to be >99% with t_R = 4.49 min (major) and t_R = 4.08 min (minor) [IC, 3.0% *i*PrOH, 2.5 mL/min, 220 nm, 40 °C].
[α]$_D^{25}$ = –34.7° (c 0.53, CH_2Cl_2).
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.21 – 7.15 (m, 2H), 7.04 – 6.95 (m, 2H), 6.18 (dt, *J* = 16.8, 9.9 Hz, 1H), 5.15 – 5.05 (m, 2H), 3.64 – 3.57 (m, 4H), 2.28 (s, 3H), 1.17 (s, 3H), 1.11 (s, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 177.4, 169.6, 149.5, 138.0, 136.8, 130.2, 121.1, 117.8, 57.2, 51.8, 47.0, 23.3, 22.3, 21.3.
HRMS (EI): *m/z* for $C_{16}H_{20}O_4$ $[M]^+$ calcd.: 276.1362, found: 276.1364.

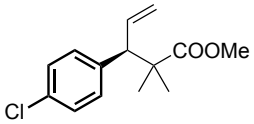
methyl (*R*)-3-(3-fluorophenyl)-2,2-dimethylpent-4-enoate (3ea)



(Condition **B**) The branched/linear selectivity was determined to be >20:1. The crude mixture was purified by column chromatography (100/0 to 95/5 of hexanes/EtOAc) to give the title compound as a colorless oil (44.8 mg, 0.190 mmol, 95%).
The **enantiomeric excess** was determined by SFC analysis to be >99% with t_R = 1.02 min (major) and t_R = 0.92 min (minor) [OJ-H, 2.0% *i*PrOH, 2.5 mL/min, 220 nm, 40 °C].
[α]$_D^{25}$ = –37.8° (c 0.75, CH_2Cl_2).
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 – 7.21 (m, 1H), 6.96 – 6.86 (m, 3H), 6.17 (dt, *J* = 16.8, 9.9

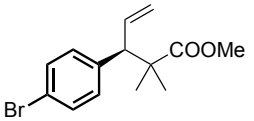
Hz, 1H), 5.19 – 5.04 (m, 2H), 3.63 – 3.58 (m, 4H), 1.18 (s, 3H), 1.12 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 177.2, 162.6 (d, J = 245.3 Hz), 143.1 (d, J = 6.7 Hz), 136.5, 129.5 (d, J = 8.3 Hz), 125.0 (d, J = 2.9 Hz), 118.1, 116.1 (d, J = 21.5 Hz), 113.7 (d, J = 21.2 Hz), 57.5, 51.8, 47.0, 23.2, 22.6.
^{19}F NMR (376 MHz, $CDCl_3$) δ -113.5 – -113.6 (m, 1F).
HRMS (EI): *m/z* for $C_{14}H_{17}FO_2$ $[M]^+$ calcd.: 236.1213, found: 236.1216.

methyl (*R*)-3-(4-chlorophenyl)-2,2-dimethylpent-4-enoate (3fa)



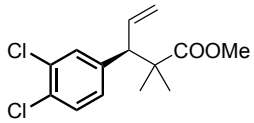
(Condition **B**) The branched/linear selectivity was determined to be >20:1. The crude mixture was purified by column chromatography (100/0 to 95/5 of hexanes/EtOAc) to give the title compound as a colorless oil (50.2 mg, 0.199 mmol, >99%).
The **enantiomeric excess** was determined by SFC analysis to be >99% with t_R = 1.50 min (major) and t_R = 1.69 min (minor) [OJ-H, 3.0% ^{i}PrOH, 2.5 mL/min, 220 nm, 40 °C].
$[\alpha]_D^{25}$ = –52.7° (c 0.84, CH_2Cl_2).
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (d, J = 8.5 Hz, 2H), 7.12 (d, J = 8.5 Hz, 2H), 6.19 (ddd, J = 16.9, 10.2, 9.5 Hz, 1H), 5.19 – 5.05 (m, 2H), 3.63 (s, 3H), 3.60 (d, J = 9.5 Hz, 1H), 1.18 (s, 3H), 1.12 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 177.3, 139.1, 136.6, 132.7, 130.6, 128.3, 118.0, 57.2, 51.8, 46.9, 23.1, 22.6.
HRMS (EI): *m/z* for $C_{14}H_{17}ClO_2$ $[M]^+$ calcd.: 252.0917, found: 252.0916.

methyl (*R*)-3-(4-bromophenyl)-2,2-dimethylpent-4-enoate (3ga)



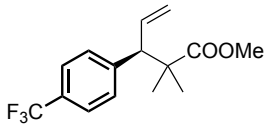
(Condition **B**) The branched/linear selectivity was determined to be >20:1. The crude mixture was purified by column chromatography (100/0 to 95/5 of hexanes/EtOAc) to give the title compound as a colorless oil (57.3 mg, 0.193 mmol, 96%).
The **enantiomeric excess** was determined by SFC analysis to be >99% with t_R = 1.74 min (major) and t_R = 1.95 min (minor) [OJ-H, 3.0% ^{i}PrOH, 2.5 mL/min, 220 nm, 40 °C].
$[\alpha]_D^{25}$ = –50.3° (c 0.91, CH_2Cl_2).
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.40 (d, J = 8.3 Hz, 2H), 7.04 (d, J = 8.3 Hz, 2H), 6.16 (dt, J = 16.9, 9.8 Hz, 1H), 5.16 – 5.07 (m, 2H), 3.61 (s, 3H), 3.57 (d, J = 9.5 Hz, 1H), 1.16 (s, 3H), 1.10 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 177.2, 139.6, 136.5, 131.2, 131.0, 120.8, 118.1, 57.2, 51.8, 46.9, 23.1, 22.6.
HRMS (EI): *m/z* for $C_{14}H_{17}BrO_2$ $[M]^+$ calcd.: 296.0412, found: 296.0414.

methyl (*R*)-3-(3,4-dichlorophenyl)-2,2-dimethylpent-4-enoate (3ha)



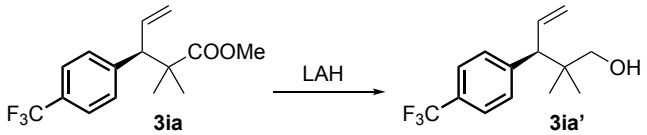
(Condition **C**) The branched/linear selectivity was determined to be >20:1. The crude mixture was purified by column chromatography (100/0 to 95/5 of hexanes/EtOAc) to give the title compound as a colorless oil (49.9 mg, 0.174 mmol, 87%).
The **enantiomeric excess** was determined by SFC analysis to be >99% with t_R = 1.20 min (major) and t_R = 1.31 min (minor) [OJ-H, 5.0% ^{i}PrOH, 2.5 mL/min, 220 nm, 40 ^{o}C].
[α]$_D^{25}$ = –56.8^o (c 0.73, CH_2Cl_2).
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.3 Hz, 1H), 7.26 (d, *J* = 2.2 Hz, 1H), 7.01 (dd, *J* = 8.3, 2.1 Hz, 1H), 6.13 (ddd, *J* = 16.9, 10.2, 9.5 Hz, 1H), 5.19 – 5.15 (m, 1H), 5.14 – 5.08 (m, 1H), 3.62 (s, 3H), 3.56 (d, *J* = 9.5 Hz, 1H), 1.17 (s, 3H), 1.11 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 177.0, 141.0, 135.9, 132.2, 131.1, 130.9, 130.0, 128.6, 118.6, 56.9, 51.9, 46.9, 22.9, 22.8.
HRMS (EI): *m/z* for $C_{14}H_{16}Cl_2O_2$ $[M]^+$ calcd.: 286.0527, found: 286.0529.

methyl (*R*)-2,2-dimethyl-3-(4-(trifluoromethyl)phenyl)pent-4-enoate (3ia)



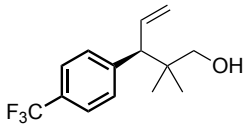
(Condition **C**) The branched/linear selectivity was determined to be >20:1. The crude mixture was purified by column chromatography (100/0 to 95/5 of hexanes/EtOAc) to give the title compound as a colorless oil (48.0 mg, 0.168 mmol, 84%).
[α]$_D^{25}$ = –39.5^o (c 0.72, CH_2Cl_2).
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.0 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 6.21 (dt, *J* = 17.0, 9.8 Hz, 1H), 5.17 (dd, *J* = 10.2, 1.7 Hz, 1H), 5.12 (dd, *J* = 17.0, 1.5 Hz, 1H), 3.67 (d, *J* = 9.6 Hz, 1H), 3.61 (s, 3H), 1.18 (s, 3H), 1.13 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 177.1, 144.8, 136.2, 129.6, 129.1 (q, *J* = 32.2 Hz), 125.1 (q, *J* = 3.7 Hz), 124.3 (q, *J* = 272.0 Hz), 118.5, 57.6, 51.8, 46.9, 23.1, 22.7.
^{19}F NMR (376 MHz, $CDCl_3$) δ -62.5 (s, 3F).
HRMS (EI): *m/z* for $C_{15}H_{17}F_3O_2$ $[M]^+$ calcd.: 286.1181, found: 286.1179.

We were unable to separate the enantiomers of compound **3ia** on our SFC system. To measure the enantiomeric excess, **3ia** was converted to **3ia'** following the procedure for the preparation of **4a**.



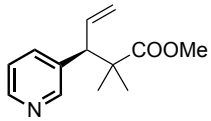
Scheme 2.7 Synthesis of **3ia'**

(*R*)-2,2-dimethyl-3-(4-(trifluoromethyl)phenyl)pent-4-en-1-ol (3ia')



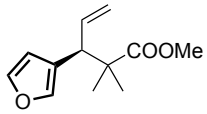
The title compound was obtained as a colorless oil (starting from 0.152 mmol of **3ia**; 31.4 mg, 0.122 mmol, 80%).
The **enantiomeric excess** was determined by SFC analysis to be >99% with t_R = 2.79 min (major) and t_R = 4.10 min (minor) [AD-H, 3.0% *i*PrOH, 2.5 mL/min, 220 nm, 40 °C].
$[\alpha]_D^{25}$ = –52.8° (c 0.50, CH_2Cl_2).
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.1 Hz, 2H), 7.33 (d, *J* = 8.1 Hz, 2H), 6.29 (dt, *J* = 16.7, 10.1 Hz, 1H), 5.21 – 5.09 (m, 2H), 3.45 (d, *J* = 9.9 Hz, 1H), 3.38 (d, *J* = 10.8 Hz, 1H), 3.24 (d, *J* = 10.8 Hz, 1H), 0.93 (s, 3H), 0.83 (s, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 146.1, 137.5, 129.5, 128.5 (q, *J* = 32.4 Hz), 124.9 (q, *J* = 3.8 Hz), 124.3 (q, *J* = 271.7 Hz), 117.5, 70.4, 56.0, 38.7, 22.1, 21.8.
^{19}F NMR (376 MHz, $CDCl_3$) δ -62.4 (s, 3F).
HRMS (EI): *m/z* for $C_{14}H_{17}F_3O$ $[M]^+$ calcd.: 258.1231, found: 258.1230.

methyl (*R*)-2,2-dimethyl-3-(pyridin-3-yl)pent-4-enoate (3ja)



(Condition **C**) The branched/linear selectivity was determined to be >20:1. The crude mixture was purified by column chromatography (100/0 to 50/50 of hexanes/EtOAc) to give the title compound as a colorless oil (38.0 mg, 0.173 mmol, 87%).
The **enantiomeric excess** was determined by SFC analysis to be >99% with t_R = 2.20 min (major) and t_R = 1.72 min (minor) [IC, 20.0% *i*PrOH, 2.5 mL/min, 260 nm, 40 °C].
$[\alpha]_D^{25}$ = –65.5° (c 0.31, CH_2Cl_2).
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.48 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.44 (d, *J* = 2.3 Hz, 1H), 7.51 (dt, *J* = 7.9, 2.0 Hz, 1H), 7.23 (ddd, *J* = 7.9, 4.8, 0.8 Hz, 1H), 6.19 (ddd, *J* = 16.9, 10.2, 9.4 Hz, 1H), 5.18 (dd, *J* = 10.1, 1.6 Hz, 1H), 5.15 – 5.09 (m, 1H), 3.66 – 3.57 (m, 4H), 1.19 (s, 3H), 1.13 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 177.0, 150.6, 148.2, 136.5, 136.2, 136.0, 123.2, 118.7, 55.3, 51.9, 46.9, 23.0, 22.6.
HRMS (EI): *m/z* for $C_{13}H_{17}NO_2$ $[M]^+$ calcd.: 219.1259, found: 219.1259.

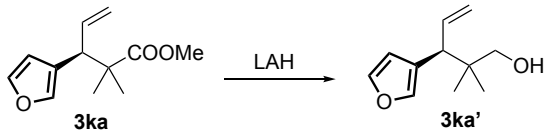
methyl (*R*)-3-(furan-3-yl)-2,2-dimethylpent-4-enoate (3ka)



(Condition **B**) The branched/linear selectivity was determined to be >20:1. The crude mixture was purified by column chromatography (100/0 to 95/5 of hexanes/EtOAc) to give the title compound as a colorless oil (35.2 mg, 0.169 mmol, 84%).
$[\alpha]_D^{25}$ = –40.4° (c 0.59, CH_2Cl_2).
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34 (s, 1H), 7.22 (s, 1H), 6.25 (s, 1H), 5.97 (dt, *J* = 16.7, 9.8 Hz, 1H), 5.19 – 5.02 (m, 2H), 3.64 (s, 3H), 3.59 (d, *J* = 9.0 Hz, 1H), 1.17 (s, 3H), 1.12 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 177.7, 142.6, 140.0, 136.5, 123.9, 117.6, 110.9, 51.8, 48.5, 46.5, 22.9, 22.5.
HRMS (EI): *m/z* for $C_{12}H_{16}O_3$ $[M]^+$ calcd.: 208.1099, found: 208.1101.

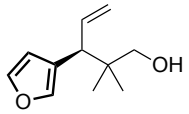
We were unable to separate enantiomers of compound **3ka** on our SFC system. To measure the enantiomeric excess, **3ka** was converted to **3ka'** following the procedure for the preparation of **4a**.



3ka **3ka'**

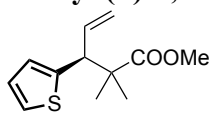
Scheme 2.8 Synthesis of **3ka'**

(*S*)-3-(furan-3-yl)-2,2-dimethylpent-4-en-1-ol (3ka')



The title compound was obtained as a colorless oil (starting from 0.178 mmol of **3ka**; 26.7 mg, 0.148 mmol, 83%).
The **enantiomeric excess** was determined by SFC analysis to be >99% with t_R = 4.00 min (major) and t_R = 4.36 min (minor) [AD-H, 3.0% ^{i}PrOH, 2.5 mL/min, 220 nm, 40 °C].
$[\alpha]_D^{25}$ = –46.0° (c 0.21, CH_2Cl_2).
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (s, 1H), 7.25 (s, 1H), 6.35 – 6.29 (m, 1H), 6.13 – 5.97 (m, 1H), 5.19 – 4.99 (m, 2H), 3.38 (d, *J* = 10.8 Hz, 1H), 3.32 (d, *J* = 10.9 Hz, 1H), 3.29 (d, *J* = 9.6 Hz, 1H), 0.92 (s, 3H), 0.86 (s, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 142.5, 139.7, 138.0, 124.8, 116.4, 111.2, 70.8, 47.1, 38.2, 22.2, 22.0.
HRMS (EI): *m/z* for $C_{11}H_{16}O_2$ $[M]^+$ calcd.: 180.1150, found: 180.1147.

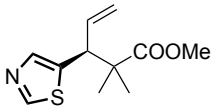
methyl (*S*)-2,2-dimethyl-3-(thiophen-2-yl)pent-4-enoate (3la)



(Condition **A**) The branched/linear selectivity was determined to be >20:1. The crude mixture was purified by column chromatography (100/0 to 95/5 of hexanes/EtOAc) to give the title compound as a colorless oil (38.7 mg, 0.173 mmol, 86%).
The **enantiomeric excess** was determined by SFC analysis to be >99% with t_R = 1.56 min (major) and t_R = 1.45 min (minor) [AD-H, 2.0% ^{i}PrOH, 2.5 mL/min, 235 nm, 40 °C].
$[\alpha]_D^{25}$ = –48.9° (c 0.57, CH_2Cl_2).
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.17 (dd, *J* = 5.2, 1.2 Hz, 1H), 6.94 (dd, *J* = 5.1, 3.6 Hz, 1H), 6.82 (dt, *J* = 3.5, 0.9 Hz, 1H), 6.07 (dt, *J* = 16.6, 9.8 Hz, 1H), 5.21 – 5.07 (m, 2H), 3.97 (d, *J* = 9.5 Hz, 1H), 3.65 (s, 3H), 1.22 (s, 3H), 1.16 (s, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 177.4, 143.0, 136.8, 126.6, 125.6, 123.9, 117.8, 53.1, 51.9, 47.2, 23.0, 22.6.

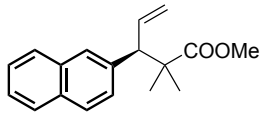
HRMS (EI): *m/z* for $C_{12}H_{16}O_2S$ $[M]^+$ calcd.: 224.0871, found: 224.0874.

methyl (*S*)-2,2-dimethyl-3-(thiazol-5-yl)pent-4-enoate (3ma)



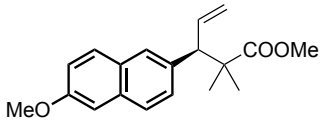
(Condition **C**) The branched/linear selectivity was determined to be >20:1. The crude mixture was purified by column chromatography (100/0 to 60/40 of hexanes/EtOAc) to give the title compound as a colorless oil (37.4 mg, 0.166 mmol, 83%).
The **enantiomeric excess** was determined by SFC analysis to be 98% with t_R = 1.78 min (major) and t_R = 1.45 min (minor) [IC, 20.0% *i*PrOH, 2.5 mL/min, 240 nm, 40 °C].
$[\alpha]_D^{25}$ = –30.8° (c 0.40, CH_2Cl_2).
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.75 (s, 1H), 7.66 (s, 1H), 6.01 (ddd, *J* = 16.8, 10.1, 9.2 Hz, 1H), 5.21 – 5.12 (m, 2H), 4.05 (d, *J* = 9.2 Hz, 1H), 3.66 (s, 3H), 1.22 (s, 3H), 1.16 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 176.9, 152.7, 141.7, 137.7, 136.1, 118.9, 52.1, 50.6, 46.9, 23.3, 22.5.
HRMS (EI): *m/z* for $C_{11}H_{15}NO_2S$ $[M]^+$ calcd.: 225.0823, found: 225.0822.

methyl (*R*)-2,2-dimethyl-3-(naphthalen-2-yl)pent-4-enoate (3na)



(Condition **A**) The branched/linear selectivity was determined to be >20:1. The crude mixture was purified
by column chromatography (100/0 to 95/5 of hexanes/EtOAc) to give the title compound as a white solid (53.7 mg, 0.200 mmol, >99%).
The **enantiomeric excess** was determined by SFC analysis to be >99% with t_R = 3.01 min (major) and t_R = 2.60 min (minor) [IC, 5.0% *i*PrOH, 2.5 mL/min, 220 nm, 40 °C].
$[\alpha]_D^{25}$ = –66.9° (c 0.90, CH_2Cl_2).
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.81 (dt, *J* = 7.8, 2.3 Hz, 2H), 7.77 (d, *J* = 8.5 Hz, 1H), 7.65 – 7.62 (m, 1H), 7.50 – 7.42 (m, 2H), 7.34 (dd, *J* = 8.5, 1.7 Hz, 1H), 6.36 (dt, *J* = 16.9, 9.8 Hz, 1H), 5.21 – 5.13 (m, 2H), 3.80 (d, *J* = 9.5 Hz, 1H), 3.63 (s, 3H), 1.25 (s, 3H), 1.18 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 177.5, 138.1, 137.1, 133.4, 132.5, 128.1, 127.9, 127.6, 127.6, 127.6, 126.06, 125.7, 117.8, 58.0, 51.8, 47.2, 23.5, 22.5.
HRMS (EI): *m/z* for $C_{18}H_{20}O_2$ $[M]^+$ calcd.: 268.1463, found: 268.1466.

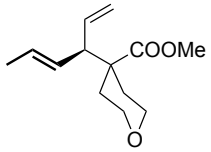
methyl (*R*)-3-(6-methoxynaphthalen-2-yl)-2,2-dimethylpent-4-enoate (3oa)



(Condition **A**) The branched/linear selectivity was determined to be >20:1. The crude mixture was purified by column chromatography (100/0 to 90/10 of hexanes/EtOAc) to give the title compound as a white solid (54.1 mg, 0.181 mmol, 91%).

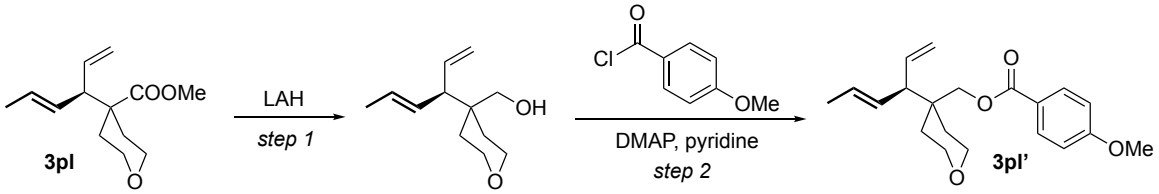
The **enantiomeric excess** was determined by SFC analysis to be >99% with t_R = 3.28 min (major) and t_R = 2.83 min (minor) [IC, 7.0% ^{i}PrOH, 2.5 mL/min, 230 nm, 40 °C].
$[\alpha]_D^{25}$ = –60.9° (c 0.23, CH_2Cl_2).
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.9 Hz, 1H), 7.66 (d, *J* = 8.5 Hz, 1H), 7.56 – 7.53 (m, 1H), 7.29 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.13 (dd, *J* = 8.9, 2.5 Hz, 1H), 7.10 (d, *J* = 2.5 Hz, 1H), 6.33 (ddd, *J* = 16.9, 10.3, 9.5 Hz, 1H), 5.24 – 5.02 (m, 2H), 3.91 (s, 3H), 3.75 (d, *J* = 9.5 Hz, 1H), 3.62 (s, 3H), 1.23 (s, 3H), 1.16 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 177.6, 157.6, 137.2, 135.7, 133.6, 129.4, 128.9, 128.1, 127.9, 126.4, 118.9, 117.6, 105.6, 57.8, 55.4, 51.7, 47.2, 23.5, 22.5.
HRMS (EI): *m/z* for $C_{19}H_{22}O_3$ $[M]^+$ calcd.: 298.1569, found: 298.1574.

methyl (*R*,*E*)-4-(hexa-1,4-dien-3-yl)tetrahydro-2*H*-pyran-4-carboxylate (3pl)



(Condition **C**) The branched/linear selectivity was determined to be >20:1. The crude mixture was purified by column chromatography (100/0 to 85/15 of hexanes/EtOAc) to give the title compound as a colorless oil (23.0 mg, 0.103 mmol, 52%).
$[\alpha]_D^{25}$ = –8.2° (c 0.13, CH_2Cl_2).
^{1}H NMR (600 MHz, $CDCl_3$) δ 5.73 (ddd, *J* = 17.0, 10.2, 8.7 Hz, 1H), 5.52 – 5.42 (m, 1H), 5.40 – 5.32 (m, 1H), 5.07 (ddd, *J* = 10.2, 1.9, 0.7 Hz, 1H), 5.01 (ddd, *J* = 17.0, 1.9, 1.0 Hz, 1H), 3.90 – 3.82 (m, 2H), 3.69 (s, 3H), 3.42 – 3.31 (m, 2H), 2.75 (t, *J* = 8.7 Hz, 1H), 2.01 – 1.93 (m, 2H), 1.70 – 1.67 (m, 3H), 1.65 – 1.57 (m, 2H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 175.3, 136.6, 128.5, 128.3, 116.9, 65.8, 65.8, 56.3, 51.7, 49.1, 32.0, 31.7, 18.2.
HRMS (EI): *m/z* for $C_{13}H_{20}O_3$ $[M]^+$ calcd.: 224.1412, found: 224.1410.

Compound **3pl** does not absorb light in the wavelength range from 220 to 280 nm. To measure the enantiomeric excess, **3pl** was converted to **3pl'** following the procedure as shown below.

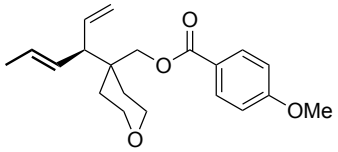


Scheme 2.9 Synthesis of **3pl'**

For step 1: following the procedure for the preparation of **4a**.
For step 2: to the DCM solution (0.40 mL) of the primary alcohol (13.8 mg, 0.0703 mmol, 1.00 equiv), DMAP (4.3 mg, 0.035 mmol, 0.50 equiv), and pyridine (11.3 μL, 0.141 mmol, 2.0 equiv) was added the acyl chloride (11.4 μL, 0.0844 mmol, 1.2 equiv) at 0 °C. The reaction was stirred at 50 °C for 12 h. The reaction was quenched with water (5 mL), and extracted with EtOAc (5 mL x 3). The organic layer was dried over anhydrous Na_2SO_4. After removal of solvent under

vacuum, the crude mixture was purified by column chromatography performed on a Teledyne Isco Combiflash® R_f system with Redi*Sep* Gold™ columns (4-gram silica gel column, 100/0 to 70/30 of hexanes/EtOAc).

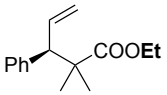
(*R*,*E*)-(4-(hexa-1,4-dien-3-yl)tetrahydro-2*H*-pyran-4-yl)methyl 4-methoxybenzoate (3pl')



The title compound was obtained as a colorless oil (21.6 mg, 0.0654 mmol, 93%).
The **enantiomeric excess** was determined by SFC analysis to be 98% with t_R = 5.94 min (major) and t_R = 6.42 min (minor) [IC, 10.0% ^{i}PrOH, 2.5 mL/min, 255 nm, 40 °C].
[α]$_D^{25}$ = –4.0° (c 0.20, CH_2Cl_2).
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.02 – 7.97 (m, 2H), 6.96 – 6.91 (m, 2H), 5.89 (ddd, *J* = 17.0, 10.2, 8.8 Hz, 1H), 5.56 – 5.43 (m, 2H), 5.13 – 5.01 (m, 2H), 4.39 – 4.28 (m, 2H), 3.87 (s, 3H), 3.81 – 3.75 (m, 2H), 3.69 – 3.62 (m, 2H), 2.93 (t, *J* = 8.3 Hz, 1H), 1.77 – 1.70 (m, 2H), 1.70 – 1.66 (m, 3H), 1.57 – 1.50 (m, 2H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 166.3, 163.6, 137.3, 131.7, 129.1, 128.0, 122.7, 116.8, 113.8, 65.5, 63.7, 63.7, 55.6, 54.0, 37.1, 30.6, 18.4.
HRMS (EI): *m/z* for $C_{20}H_{26}O_4$ $[M]^+$ calcd.: 330.1831, found: 330.1829.

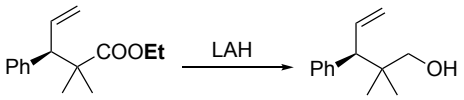
2.4.7 Scope of Silyl Ketene Acetals

ethyl (*R*)-2,2-dimethyl-3-phenylpent-4-enoate (3ab)



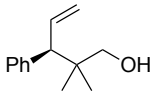
(Condition **A**) The branched/linear selectivity was determined to be >20:1. The crude mixture was purified by column chromatography (100/0 to 95/5 of hexanes/EtOAc) to give the title compound as a colorless oil (44.4 mg, 0.191 mmol, 96%).
[α]$_D^{25}$ = –44.6° (c 0.67, CH_2Cl_2).
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.26 (m, 2H), 7.23 – 7.20 (m, 1H), 7.20 – 7.16 (m, 2H), 6.23 (ddd, *J* = 16.8, 10.2, 9.6 Hz, 1H), 5.18 – 5.01 (m, 2H), 4.06 (qd, *J* = 7.2, 1.3 Hz, 2H), 3.61 (d, *J* = 9.5 Hz, 1H), 1.20 (t, *J* = 7.1 Hz, 3H), 1.18 (s, 3H), 1.12 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 177.1, 140.6, 137.2, 129.4, 128.1, 126.8, 117.6, 60.5, 57.8, 46.7, 23.4, 22.4, 14.3.
HRMS (EI): *m/z* for $C_{15}H_{20}O_2$ $[M]^+$ calcd.: 232.1463, found: 232.1465.

We were unable to separate the enantiomers of compound **3ab** on our SFC system. To measure the enantiomeric excess, **3ab** was converted to **3ab'** following the procedure for the preparation of **4a**.



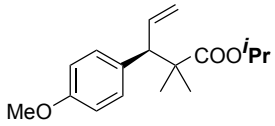
Scheme 2.10 Synthesis of **3ab'**

(*R*)-2,2-dimethyl-3-phenylpent-4-en-1-ol (3ab')



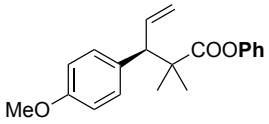
The title compound was obtained as a colorless oil (starting from 0.172 mmol of **3ab**; 27.0 mg, 0.142 mmol, 83%).
The **enantiomeric excess** was determined by SFC analysis to be >99% with t_R = 2.00 min (major) and t_R = 1.81 min (minor) [OJ-H, 10.0% ^{i}PrOH, 2.5 mL/min, 220 nm, 40 °C].
[α]$_D^{25}$ = –63.6° (c 0.45, CH_2Cl_2).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.29 (m, 2H), 7.29 – 7.20 (m, 3H), 6.43 – 6.27 (m, 1H), 5.19 – 5.12 (m, 2H), 3.47 – 3.28 (m, 3H), 0.97 (s, 3H), 0.88 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 142.0, 138.5, 129.3, 128.2, 126.4, 116.8, 71.0, 56.7, 38.8, 22.3, 22.1.
HRMS (EI): *m/z* for $C_{13}H_{18}O$ $[M]^+$ calcd.: 190.1358, found: 190.1360.

isopropyl (*R*)-3-(4-methoxyphenyl)-2,2-dimethylpent-4-enoate (3cc)



(Condition **B**) The branched/linear selectivity was determined to be >20:1. The crude mixture was purified by column chromatography (100/0 to 90/10 of hexanes/EtOAc) to give the title compound as a colorless oil (43.6 mg, 0.158 mmol, 79%).
The **enantiomeric excess** was determined by SFC analysis to be >99% with t_R = 3.40 min (major) and t_R = 3.12 min (minor) [IC, 2.0% ^{i}PrOH, 2.5 mL/min, 230 nm, 40 °C].
[α]$_D^{25}$ = –53.0° (c 0.48, CH_2Cl_2).
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17 – 7.06 (m, 2H), 6.90 – 6.73 (m, 2H), 6.18 (ddd, *J* = 16.8, 10.2, 9.4 Hz, 1H), 5.12 – 5.02 (m, 2H), 4.93 (hept, *J* = 6.3 Hz, 1H), 3.78 (s, 3H), 3.57 (d, *J* = 9.4 Hz, 1H), 1.20 (d, *J* = 6.3 Hz, 3H), 1.16 (d, *J* = 6.3 Hz, 3H), 1.14 (s, 3H), 1.08 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 176.7, 158.4, 137.5, 132.8, 130.4, 117.2, 113.5, 67.7, 56.7, 55.3, 46.6, 23.5, 22.3, 22.0, 21.9.
HRMS (EI): *m/z* for $C_{17}H_{24}O_3$ $[M]^+$ calcd.: 276.1725, found: 276.1718.

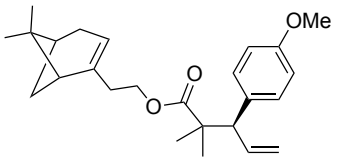
phenyl (*R*)-3-(4-methoxyphenyl)-2,2-dimethylpent-4-enoate (3ce)



(Condition **B**) The branched/linear selectivity was determined to be >20:1. The crude mixture was purified by column chromatography (100/0 to 90/10 of hexanes/EtOAc) to give the title compound

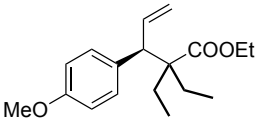
as a colorless oil (the reaction was conducted on a 0.100 mmol scale; 31.0 mg, 0.0999 mmol, >99%).
The **enantiomeric excess** was determined by SFC analysis to be >99% with t_R = 4.32 min (major) and t_R = 3.86 min (minor) [AD-H, 5.0% ^{i}PrOH, 2.5 mL/min, 230 nm, 40 °C].
[α]$_D^{25}$ = –19.2° (c 0.52, CH_2Cl_2).
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.40 – 7.33 (m, 2H), 7.25 – 7.18 (m, 3H), 7.01 – 6.94 (m, 2H), 6.90 – 6.85 (m, 2H), 6.35 – 6.24 (m, 1H), 5.24 – 5.17 (m, 2H), 3.81 (s, 3H), 3.76 (d, *J* = 9.5 Hz, 1H), 1.31 (s, 3H), 1.28 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 175.8, 158.6, 151.1, 137.1, 132.3, 130.5, 129.4, 125.8, 121.7, 117.8, 113.7, 56.8, 55.4, 47.0, 23.4, 22.4.
HRMS (EI): *m/z* for $C_{20}H_{22}O_3$ $[M]^+$ calcd.: 310.1569, found: 310.1567.

2-(6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)ethyl (3*R*)-3-(4-methoxyphenyl)-2,2-dimethylpent-4-enoate (3cf)



(Condition **B**) The branched/linear selectivity was determined to be >20:1. The crude mixture was purified by column chromatography (100/0 to 95/5 of hexanes/EtOAc) to give the title compound as a colorless oil (the reaction was conducted on a 0.100 mmol scale; 35.6 mg, 0.0931 mmol, 93%).
The **diastereomeric ratio** was determined by SFC analysis to be >20:1 with t_R = 6.25 min (major) and t_R = 5.65 min (minor) [IC, 3.0% ^{i}PrOH, 2.5 mL/min, 230 nm, 40 °C].
[α]$_D^{25}$ = –46.5° (c 0.59, CH_2Cl_2).
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.09 (d, *J* = 8.7 Hz, 2H), 6.82 (d, *J* = 8.7 Hz, 2H), 6.19 (ddd, *J* = 16.8, 10.2, 9.4 Hz, 1H), 5.29 – 5.21 (m, 1H), 5.19 – 4.98 (m, 2H), 4.13 – 3.93 (m, 2H), 3.78 (s, 3H), 3.56 (d, *J* = 9.3 Hz, 1H), 2.36 (dt, *J* = 8.5, 5.6 Hz, 1H), 2.29 – 2.16 (m, 4H), 2.10 – 2.06 (m, 1H), 2.04 (td, *J* = 5.6, 1.5 Hz, 1H), 1.27 (s, 3H), 1.16 – 1.11 (m, 4H), 1.08 (s, 3H), 0.83 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 177.2, 158.4, 144.3, 137.5, 132.7, 130.3, 118.7, 117.3, 113.5, 62.8, 56.9, 55.3, 46.9, 45.9, 40.8, 38.1, 36.1, 31.8, 31.5, 26.4, 23.4, 22.4, 21.3.
HRMS (EI): *m/z* for $C_{25}H_{34}O_3$ $[M]^+$ calcd.: 382.2508, found: 382.2510.

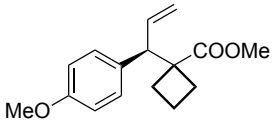
ethyl (*R*)-2,2-diethyl-3-(4-methoxyphenyl)pent-4-enoate (3cg)



(Condition **B**) The branched/linear selectivity was determined to be >20:1. The crude mixture was purified by column chromatography (100/0 to 90/10 of hexanes/EtOAc) to give the title compound as a colorless oil (55.5 mg, 0.191 mmol, 96%).
The **enantiomeric excess** was determined by SFC analysis to be >99% with t_R = 2.77 min (major) and t_R = 3.76 min (minor) [IC, 3.0% ^{i}PrOH, 2.5 mL/min, 230 nm, 40 °C].
[α]$_D^{25}$ = –83.2° (c 0.92, CH_2Cl_2).
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.01 (d, *J* = 8.7 Hz, 2H), 6.80 (d, *J* = 8.7 Hz, 2H), 6.35 (dt, *J* = 16.9,

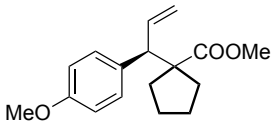
9.9 Hz, 1H), 5.14 – 4.82 (m, 2H), 4.22 – 4.02 (m, 2H), 3.77 (s, 3H), 3.37 (d, *J* = 9.7 Hz, 1H), 1.84 (dq, *J* = 14.8, 7.5 Hz, 1H), 1.62 (ddq, *J* = 21.9, 14.7, 7.4 Hz, 2H), 1.44 (dq, *J* = 14.8, 7.4 Hz, 1H), 1.22 (t, *J* = 7.2 Hz, 3H), 0.83 (q, *J* = 7.6 Hz, 6H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 175.8, 158.3, 138.7, 133.5, 129.8, 116.1, 113.6, 60.2, 55.3, 55.1, 53.1, 25.4, 23.7, 14.3, 8.5.
HRMS (EI): *m/z* for $C_{18}H_{26}O_3$ $[M]^+$ calcd.: 290.1882, found: 290.1888.

methyl (*R*)-1-(1-(4-methoxyphenyl)allyl)cyclobutane-1-carboxylate (3ch)



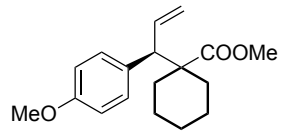
(Condition **B**) The branched/linear selectivity was determined to be >20:1. The crude mixture was purified by column chromatography (100/0 to 90/10 of hexanes/EtOAc) to give the title compound as a colorless oil (50.8 mg, 0.195 mmol, 98%).
The **enantiomeric excess** was determined by SFC analysis to be >99% with t_R = 4.64 min (major) and t_R = 4.28 min (minor) [IC, 3.0% ^{i}PrOH, 2.5 mL/min, 230 nm, 40 °C].
$[\alpha]_D^{25}$ = –82.7° (c 0.85, CH_2Cl_2).
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.08 (d, *J* = 8.7 Hz, 2H), 6.82 (d, *J* = 8.7 Hz, 2H), 6.20 (ddd, *J* = 16.9, 10.2, 8.9 Hz, 1H), 5.19 – 5.01 (m, 2H), 3.78 (s, 3H), 3.66 – 3.50 (m, 4H), 2.46 – 2.34 (m, 2H), 2.29 – 2.10 (m, 2H), 1.91 – 1.76 (m, 1H), 1.74 – 1.56 (m, 1H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 177.1, 158.4, 137.6, 132.9, 129.4, 117.2, 113.8, 55.3, 54.6, 52.0, 51.8, 28.5, 27.7, 15.7.
HRMS (EI): *m/z* for $C_{16}H_{20}O_3$ $[M]^+$ calcd.: 260.1412, found:260.1410.

methyl (*R*)-1-(1-(4-methoxyphenyl)allyl)cyclopentane-1-carboxylate (3ci)



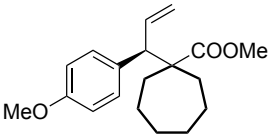
(Condition **B**) The branched/linear selectivity was determined to be >20:1. The crude mixture was purified by column chromatography (100/0 to 90/10 of hexanes/EtOAc) to give the title compound as a colorless oil (55.7 mg, 0.201 mmol, >99%).
The **enantiomeric excess** was determined by SFC analysis to be 99% with t_R = 5.85 min (major) and t_R = 5.15 min (minor) [IC, 3.0% ^{i}PrOH, 2.5 mL/min, 230 nm, 40 °C].
$[\alpha]_D^{25}$ = –74.0° (c 0.92, CH_2Cl_2).
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.08 (d, *J* = 8.7 Hz, 2H), 6.81 (d, *J* = 8.7 Hz, 2H), 6.20 (ddd, *J* = 16.9, 10.2, 9.2 Hz, 1H), 5.14 – 4.92 (m, 2H), 3.77 (s, 3H), 3.64 (d, *J* = 9.3 Hz, 1H), 3.57 (s, 3H), 2.18 – 2.02 (m, 2H), 1.71 – 1.59 (m, 2H), 1.59 – 1.45 (m, 4H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 177.3, 158.4, 138.2, 133.4, 129.8, 116.9, 113.6, 59.4, 55.5, 55.3, 51.7, 33.6, 33.1, 24.6, 24.4.
HRMS (EI): *m/z* for $C_{17}H_{22}O_3$ $[M]^+$ calcd.: 274.1569, found: 274.1573.

methyl (*R*)-1-(1-(4-methoxyphenyl)allyl)cyclohexane-1-carboxylate (3cj)



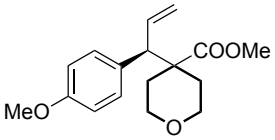
(Condition **B**) The branched/linear selectivity was determined to be >20:1. The crude mixture was purified by column chromatography (100/0 to 90/10 of hexanes/EtOAc) to give the title compound as a colorless oil (57.5 mg, 0.199 mmol, >99%).
The **enantiomeric excess** was determined by SFC analysis to be >99% with t_R = 3.86 min (major) and t_R = 5.02 min (minor) [OJ-H, 3.0% ^{i}PrOH, 2.5 mL/min, 230 nm, 40 ^{o}C].
$[\alpha]_D^{25}$ = –49.0^o (c 0.96, CH_2Cl_2).
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.01 (d, *J* = 8.7 Hz, 2H), 6.81 (d, *J* = 8.7 Hz, 2H), 6.23 (dt, *J* = 16.8, 10.0 Hz, 1H), 5.22 – 4.85 (m, 2H), 3.78 (s, 3H), 3.59 (s, 3H), 3.30 (d, *J* = 10.0 Hz, 1H), 2.21 – 2.08 (m, 1H), 2.07 – 1.99 (m, 1H), 1.71 – 1.51 (m, 3H), 1.36 – 1.12 (m, 4H), 1.08 – 1.01 (m, 1H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 175.9, 158.4, 137.3, 132.6, 130.0, 116.9, 113.4, 58.9, 55.3, 52.3, 51.3, 32.4, 31.7, 25.7, 23.8, 23.6.
HRMS (EI): *m/z* for $C_{18}H_{24}O_3$ $[M]^+$ calcd.: 288.1725, found: 288.1725.

methyl (*R*)-1-(1-(4-methoxyphenyl)allyl)cycloheptane-1-carboxylate (3ck)



(Condition **B**) The branched/linear selectivity was determined to be >20:1. The crude mixture was purified by column chromatography (100/0 to 90/10 of hexanes/EtOAc) to give the title compound as a colorless oil (59.0 mg, 0.195 mmol, 98%).
The **enantiomeric excess** was determined by SFC analysis to be >99% with t_R = 4.71 min (major) and t_R = 4.34 min (minor) [IC, 5.0% ^{i}PrOH, 2.5 mL/min, 230 nm, 40 ^{o}C].
$[\alpha]_D^{25}$ = –43.4 (c 1.0, CH_2Cl_2).
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.05 (d, *J* = 8.3 Hz, 2H), 6.81 (d, *J* = 8.3 Hz, 2H), 6.23 (dt, *J* = 16.9, 9.9 Hz, 1H), 5.23 – 4.84 (m, 2H), 3.78 (s, 3H), 3.62 (s, 3H), 3.43 (d, *J* = 9.8 Hz, 1H), 2.09 (dt, *J* = 15.0, 7.8 Hz, 2H), 1.67 – 1.24 (m, 10H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 177.1, 158.4, 137.9, 132.9, 130.1, 116.8, 113.5, 59.1, 55.3, 55.0, 51.5, 34.6, 33.7, 29.4, 29.2, 23.9, 23.8.
HRMS (EI): *m/z* for $C_{19}H_{26}O_3$ $[M]^+$ calcd.: 302.1882, found: 302.1886.

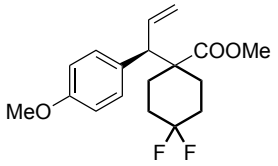
methyl (*R*)-4-(1-(4-methoxyphenyl)allyl)tetrahydro-2*H*-pyran-4-carboxylate (3cl)



(Condition **B**) The branched/linear selectivity was determined to be >20:1. The crude mixture was purified by column chromatography (100/0 to 65/35 of hexanes/EtOAc) to give the title compound as a colorless oil (53.9 mg, 0.186 mmol, 93%).
The **enantiomeric excess** was determined by SFC analysis to be >99% with t_R = 3.45 min (major) and t_R = 3.14 min (minor) [IC, 10.0% ^{i}PrOH, 2.5 mL/min, 230 nm, 40 ^{o}C].

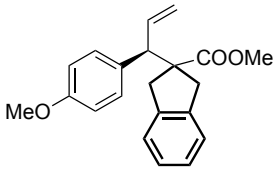
$[\alpha]_D^{25}$ = –56.2° (c 0.90, CH_2Cl_2).
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.00 (d, *J* = 8.7 Hz, 2H), 6.82 (d, *J* = 8.7 Hz, 2H), 6.21 (dt, *J* = 16.8, 10.0 Hz, 1H), 5.13 (dd, *J* = 10.1, 1.8 Hz, 1H), 5.07 (dd, *J* = 16.8, 1.0 Hz, 1H), 3.88 – 3.82 (m, 2H), 3.77 (s, 3H), 3.61 (s, 3H), 3.40 – 3.25 (m, 3H), 2.05 (dd, *J* = 13.6, 2.4 Hz, 1H), 1.93 (dd, *J* = 13.6, 2.4 Hz, 1H), 1.74 – 1.63 (m, 1H), 1.63 – 1.49 (m, 1H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 175.0, 158.6, 136.4, 131.6, 129.9, 117.7, 113.7, 65.8, 65.8, 58.6, 55.3, 51.6, 50.1, 32.3, 32.0.
HRMS (EI): *m/z* for $C_{17}H_{22}O_4$ $[M]^+$ calcd.: 290.1518, found: 290.1522.

methyl (*R*)-4,4-difluoro-1-(1-(4-methoxyphenyl)allyl)cyclohexane-1-carboxylate (3cm)



(Condition **B**) The branched/linear selectivity was determined to be >20:1. The crude mixture was purified by column chromatography (100/0 to 90/10 of hexanes/EtOAc) to give the title compound as a colorless oil (the reaction was conducted on a 0.100 mmol scale; 30.6 mg, 0.0943 mmol, 94%). The **enantiomeric excess** was determined by SFC analysis to be >99% with t_R = 1.97 min (major) and t_R = 2.19 min (minor) [OJ-H, 5.0% ^{i}PrOH, 2.5 mL/min, 230 nm, 40 °C].
$[\alpha]_D^{25}$ = –48.4° (c 0.51, CH_2Cl_2).
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.00 (d, *J* = 8.7 Hz, 2H), 6.82 (d, *J* = 8.7 Hz, 2H), 6.21 (dt, *J* = 16.8, 10.0 Hz, 1H), 5.18 – 4.99 (m, 2H), 3.78 (s, 3H), 3.62 (s, 3H), 3.36 (d, *J* = 9.9 Hz, 1H), 2.27 – 2.21 (m, 1H), 2.16 – 2.08 (m, 1H), 2.04 – 1.95 (m, 2H), 1.80 – 1.48 (m, 4H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 174.6, 158.7, 136.5, 131.8, 129.8, 117.8, 113.8, 58.0, 55.3, 51.8, 51.0, 31.5 (ddd, *J* = 25.3, 23.1, 5.2 Hz), 28.5 (d, *J* = 9.7 Hz).
^{19}F NMR (376 MHz, $CDCl_3$) δ -91.9 (d, *J* = 235.1 Hz, 1F), -102.9 (d, *J* = 234.3 Hz, 1F).
HRMS (EI): *m/z* for $C_{18}H_{22}F_2O_3$ $[M]^+$ calcd.: 324.1537, found: 324.1544.

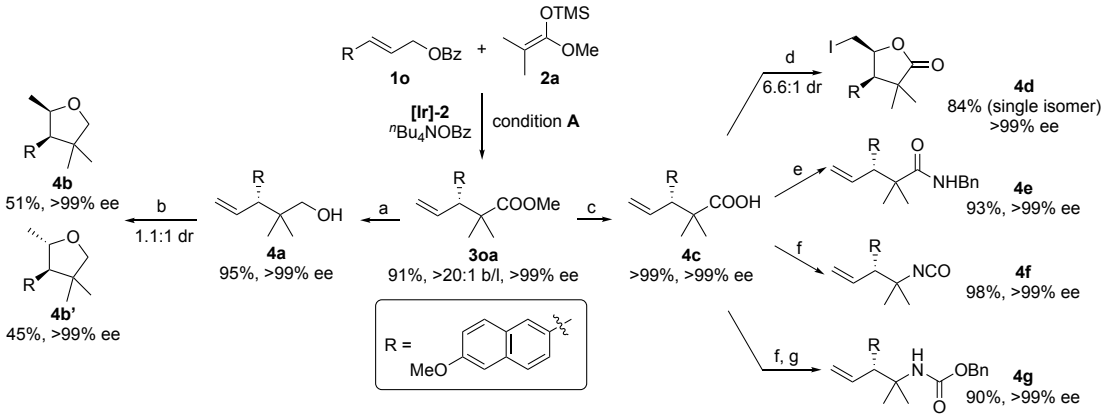
methyl (*R*)-2-(1-(4-methoxyphenyl)allyl)-2,3-dihydro-1*H*-indene-2-carboxylate (3cn)



(Condition **B**) The branched/linear selectivity was determined to be >20:1. The crude mixture was purified by column chromatography (100/0 to 90/10 of hexanes/EtOAc) to give the title compound as a colorless oil (the reaction was conducted on a 0.100 mmol scale; 31.0 mg, 0.0962 mmol, 96%). The **enantiomeric excess** was determined by SFC analysis to be >99% with t_R = 4.00 min (major) and t_R = 4.41 min (minor) [OJ-H, 7.0% ^{i}PrOH, 2.5 mL/min, 220 nm, 40 °C].
$[\alpha]_D^{25}$ = –59.2° (c 0.52, CH_2Cl_2).
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18 – 7.05 (m, 6H), 6.85 – 6.80 (m, 2H), 6.22 (ddd, *J* = 16.9, 10.1, 9.3 Hz, 1H), 5.17 – 5.01 (m, 2H), 3.78 (s, 3H), 3.69 (d, *J* = 9.3 Hz, 1H), 3.57 (s, 3H), 3.47 – 3.34 (m, 2H), 3.27 – 3.11 (m, 2H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 176.5, 158.5, 141.4, 137.7, 132.8, 129.7, 126.6, 126.6, 124.4,

124.3, 117.5, 113.8, 59.6, 55.5, 55.3, 52.1, 40.5, 39.5.
HRMS (EI): *m/z* for $C_{21}H_{22}O_3$ $[M]^+$ calcd.: 322.1569, found: 322.1571.

2.4.8 Procedures for Derivatizations of the Allylated Esters



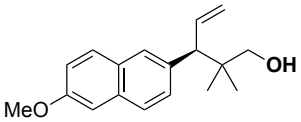
Scheme 2.11 derivatizations of allylated esters

a) Synthesis of Primary Alcohol 4a:

In a 4-dram vial equipped with a magnetic stir bar were added allylated ester **3oa** (59.7 mg, 0.200 mmol, 1.00 equiv) and anhydrous THF (4 mL). After this time, $LiAlH_4$ (11.4 mg, 0.300 mmol, 1.50 equiv) was added at 0 °C. The vial was sealed with a cap containing PTFE/silicone septa. The reaction mixture was stirred at r.t. for 2 h.

The mixture was quenched with aqueous HCl (1 M, 5 mL) at 0 °C, and was stirred at r.t. for 30 min until all the solids were dissolved. The mixture was extracted with Et_2O (3 x 5 mL). The organic layer was dried over anhydrous Na_2SO_4. After removal of solvent under vacuum, the crude mixture was purified by column chromatography performed on a Teledyne Isco Combiflash® R_f system with Redi*Sep* Gold™ columns (4-gram silica gel column, 100/0 to 60/40 of hexanes/EtOAc).

(*R*)-3-(6-methoxynaphthalen-2-yl)-2,2-dimethylpent-4-en-1-ol (4a)



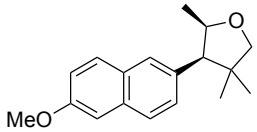
The title compound was obtained as a white solid (51.5 mg, 0.190 mmol, 95%).
The **enantiomeric excess** was determined by SFC analysis to be >99% with t_R = 4.22 min (major) and t_R = 4.53 min (minor) [AD-H, 15.0% ^{i}PrOH, 2.5 mL/min, 220 nm, 40 °C].
$[\alpha]_D^{25}$ = –99.7° (c 0.39, CH_2Cl_2).
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.74 – 7.65 (m, 2H), 7.61 – 7.55 (m, 1H), 7.35 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.20 – 6.99 (m, 2H), 6.47 – 6.35 (m, 1H), 5.22 – 4.99 (m, 2H), 3.92 (s, 3H), 3.49 (d, *J* = 9.9 Hz, 1H), 3.41 (d, *J* = 10.8 Hz, 1H), 3.32 (d, *J* = 10.9 Hz, 1H), 0.98 (s, 3H), 0.89 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 157.5, 138.6, 137.3, 133.3, 129.3, 128.9, 128.4, 127.6, 126.4, 118.8, 116.8, 105.6, 71.0, 56.5, 55.4, 39.0, 22.4, 22.2.
HRMS (EI): *m/z* for $C_{18}H_{22}O_2$ $[M]^+$ calcd.: 270.1620, found: 270.1621.

b) Synthesis of Tetrahydrofuran Derivative 4b and 4b':[32]

In a nitrogen-filled dry-box, a 1-dram vial containing a magnetic stir bar was charged with primary alcohol **4a** (29.4 mg, 0.109 mmol, 1.00 equiv), silver triflate (AgOTf, 2.8 mg, 0.011 mmol, 10 mol%), and 1,2-dichloroethane (DCE, 0.3 mL). The vial was sealed with a cap containing PTFE/silicone septa and removed from the dry box. The reaction mixture was stirred at 80 °C for 15 h.

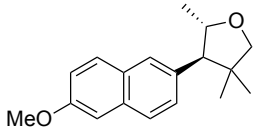
The reaction mixture was diluted with 2 mL of hexanes, and filtered through a 0.5-inch plug of silica gel (eluting with 1:1 hexanes:EtOAc, 8 mL). After evaporatoin of the solvent under vacuum, the crude mixture was purified by column chromatography on a Teledyne Isco Combiflash® R_f system with Redi*Sep* Gold™ columns (4-gram silica gel column, 100/0 to 90/10 of hexanes/EtOAc). Both diastereomers were isolated individually. The diastereomeric ratio was determined by ^{1}H NMR analysis of the crude mixture to be 1.1:1. The structures of both isomers were confirmed by NOESY analysis.

(2*R*,3*R*)-3-(6-methoxynaphthalen-2-yl)-2,4,4-trimethyltetrahydrofuran (4b)



The title compound was obtained as a white solid (15.1 mg, 0.0558 mmol, 51%).
The **enantiomeric excess** was determined by SFC analysis to be >99% with t_R = 2.68 min (major) and t_R = 4.00 min (minor) [OJ-H, 5.0% ^{i}PrOH, 2.5 mL/min, 230 nm, 40 °C].
[α]$_D^{25}$ = +67.6° (c 0.18, CH_2Cl_2).
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.74 – 7.66 (m, 2H), 7.49 (s, 1H), 7.31 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.16 – 7.10 (m, 2H), 4.63 (qd, *J* = 6.4, 5.0 Hz, 1H), 3.95 – 3.87 (m, 4H), 3.75 (d, *J* = 8.5 Hz, 1H), 2.84 (d, *J* = 5.0 Hz, 1H), 1.35 (s, 3H), 1.06 (d, *J* = 6.4 Hz, 3H), 0.73 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 157.5, 134.8, 133.3, 129.3, 129.1, 129.0, 128.7, 126.3, 118.8, 105.6, 80.1, 77.9, 61.5, 55.5, 44.4, 30.7, 24.3, 17.4.
HRMS (EI): *m/z* for $C_{18}H_{22}O_2$ $[M]^+$ calcd.: 270.1620, found: 270.1623.

(2*S*,3*R*)-3-(6-methoxynaphthalen-2-yl)-2,4,4-trimethyltetrahydrofuran (4b')



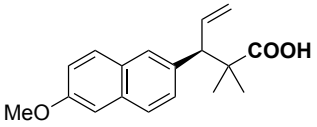
The title compound was obtained as a white solid (13.2 mg, 0.0488 mmol, 45%).
The **enantiomeric excess** was determined by SFC analysis to be >99% with t_R = 3.25 min (major) and t_R = 3.52 min (minor) [OD-H, 5.0% ^{i}PrOH, 2.5 mL/min, 230 nm, 40 °C].
[α]$_D^{25}$ = –55.3° (c 0.19, CH_2Cl_2).
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.75 – 7.67 (m, 2H), 7.53 (s, 1H), 7.28 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.17 – 7.10 (m, 2H), 4.56 (dq, *J* = 10.1, 6.0 Hz, 1H), 3.93 (s, 3H), 3.81 (d, *J* = 8.2 Hz, 1H), 3.76 (d, *J* = 8.2 Hz, 1H), 2.72 (d, *J* = 10.0 Hz, 1H), 1.27 (d, *J* = 6.0 Hz, 3H), 1.10 (s, 3H), 0.85 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 157.6, 133.7, 132.8, 129.3, 129.0, 128.0, 127.7, 126.6, 119.0, 105.6, 81.1, 78.6, 63.6, 55.5, 43.7, 26.2, 22.9, 20.4.
HRMS (EI): *m/z* for $C_{18}H_{22}O_2$ $[M]^+$ calcd.: 270.1620, found: 270.1624.

c) Synthesis of Carboxylic Acid 4c:

A 1-dram vial containing a magnetic stir bar was charged with allylated ester **3oa** (35.2 mg, 0.118 mmol, 1.00 equiv), NaOH (2 M aqueous solution, 0.24 mL, 0.48 mmol, 4.0 equiv), and MeOH (0.5 mL). The vial was sealed with a cap containing PTFE/silicone septa. The reaction mixture was stirred at 80 °C for 12 h.

The mixture was acidified with aqueous HCl solution (1 M, 5 mL) and the resulting mixture was extracted with Et_2O (3 x 5 mL). The organic layer was dried over anhydrous Na_2SO_4. After removal of solvent under vacuum, the title compound was obtained without further purification.

(*R*)-3-(6-methoxynaphthalen-2-yl)-2,2-dimethylpent-4-enoic acid (4c)



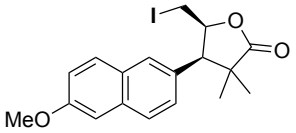
The title compound was obtained as a white solid (33.2 mg, 0.117 mmol, >99%).
The **enantiomeric excess** was determined by SFC analysis to be >99% with t_R = 3.86 min (major) and t_R = 2.81 min (minor) [AD-H, 15.0% ^{i}PrOH, 2.5 mL/min, 230 nm, 40 °C].
$[\alpha]_D^{25}$ = –70.3° (c 0.55, CH_2Cl_2).
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.9 Hz, 1H), 7.66 (d, *J* = 8.5 Hz, 1H), 7.60 (d, *J* = 1.7 Hz, 1H), 7.34 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.15 – 7.09 (m, 2H), 6.35 (dt, *J* = 17.1, 9.5 Hz, 1H), 5.18 (dd, *J* = 13.8, 2.6 Hz, 2H), 3.91 (s, 3H), 3.79 (d, *J* = 9.3 Hz, 1H), 1.24 (s, 3H), 1.18 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 183.7, 157.7, 137.0, 135.4, 133.6, 129.5, 128.9, 128.2, 128.1, 126.5, 118.9, 118.0, 105.6, 57.4, 55.4, 47.1, 23.7, 22.0.
HRMS (ESI): *m/z* for $C_{18}H_{19}O_3$ $[M–H]^-$ calcd.: 283.1340, found: 283.1341.

d) Synthesis of Lactone 4d:[33]

A 1-dram vial containing a magnetic stir bar was charged with carboxylic acid **4c** (28.4 mg, 0.100 mmol, 1.00 equiv), sodium bicarbonate ($NaHCO_3$, 11.8 mg, 0.140 mmol, 1.40 equiv), acetonitrile (1.0 mL), and water (1.0 mL). The mixture was stirred at r.t. until the carboxylic acid was completely dissolved. After this time, potassium iodide (KI, 21.6 mg, 0.130 mmol, 1.30 equiv) and iodine (I_2, 33.0 mg, 0.130 mmol, 1.30 equiv) were added into the mixture. The reaction mixture was stirred at r.t. for 2 h.

The reaction mixture was quenched with a saturated aqueous sodium thiosulfate (Na_2SO_4) solution dropwise until the yellow color disappeared. After this time, 5 mL of water was added into the mixture. The mixture was extracted with EtOAc (3 x 5 mL). The organic layer was dried over anhydrous Na_2SO_4. After removal of solvent under vacuum, the crude mixture was purified by column chromatography performed on a Teledyne Isco Combiflash® R_f system with Redi*Sep* Gold™ columns (4-gram silica gel column, 100/0 to 80/20 of hexanes/EtOAc). The diastereomeric ratio was determined by ^{1}H NMR analysis of the crude mixture to be 6.6:1. The structure of 4d was confirmed by X-ray crystallography analysis.

(4*R*,5*S*)-5-(iodomethyl)-4-(6-methoxynaphthalen-2-yl)-3,3-dimethyldihydrofuran-2(3*H*)-one (4d)



The title compound was obtained as a white solid (34.5 mg, 0.0841 mmol, 84%).
The **enantiomeric excess** was determined by SFC analysis to be >99% with t_R = 2.37 min (major) and t_R = 2.20 min (minor) [IC, 20.0% ^{i}PrOH, 2.5 mL/min, 230 nm, 40 °C].
$[\alpha]_D^{25}$ = +93.0° (c 0.32, CH_2Cl_2).
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.69 (t, *J* = 8.0 Hz, 2H), 7.50 (s, 1H), 7.19 – 7.12 (m, 3H), 5.13 (dt, *J* = 8.8, 5.7 Hz, 1H), 3.92 (s, 3H), 3.52 (d, *J* = 5.3 Hz, 1H), 3.33 (dd, *J* = 10.1, 6.1 Hz, 1H), 2.82 (dd, *J* = 10.1, 8.8 Hz, 1H), 1.52 (s, 3H), 0.96 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 181.4, 158.2, 134.1, 129.5, 129.4, 129.2, 128.8, 127.4, 127.0, 119.6, 105.7, 80.2, 57.2, 55.5, 46.0, 25.8, 21.4, 1.92.
HRMS (EI): *m/z* for $C_{18}H_{19}IO_3$ $[M]^+$ calcd.: 410.0379, found: 410.0382.

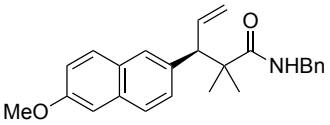
e) Synthesis of Amide 4e:

A 1-dram vial containing a magnetic stir bar was charged with carboxylic acid **4c** (14.2 mg, 0.0500 mmol, 1.00 equiv) and benzene (0.40 mL). Then, $SOCl_2$ (18.1 µL, 0.250 mmol, 5.00 equiv) was added at 0 °C. The vial was sealed with a cap containing PTFE/silicone septa. The mixture was stirred at 80 °C for 12 h. After cooling the reaction mixture to r.t., all volatile components were evaporated under vacuum.

To the same vial were added DMAP (1.2 mg, 0.010 mmol, 0.20 equiv), triethylamine (13.9 µL, 0.100 mmol, 2.00 equiv), benzylamine (10.9 µL, 0.100 mmol, 2.0 equiv), and DCE (0.4 mL). The reaction mixture was stirred at 80 °C for another 8 h.

The reaction mixture was then diluted with 2 mL of hexanes, and the resulting mixture was filtered through a 0.5-inch plug of silica gel (eluting with 1:1 hexanes:EtOAc, 8 mL). After evaporation of the solvent under vacuum, the crude mixture was purified by column chromatography on a Teledyne Isco Combiflash® R_f system with Redi*Sep* Gold™ columns (4-gram silica gel column, 100/0 to 65/35 of hexanes/EtOAc).

(R)-N-benzyl-3-(6-methoxynaphthalen-2-yl)-2,2-dimethylpent-4-enamide (4e)



The title compound was obtained as a colorless oil (17.3 mg, 0.0463 mmol, 93%).
The **enantiomeric excess** was determined by SFC analysis to be >99% with t_R = 4.70 min (major) and t_R = 4.29 min (minor) [OJ-H, 20.0% ^{i}PrOH, 2.5 mL/min, 230 nm, 40 °C].
$[\alpha]_D^{25}$ = –70.8° (c 0.29, CH_2Cl_2).
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8.9 Hz, 1H), 7.63 (d, *J* = 8.5 Hz, 1H), 7.58 (d, *J* = 1.7 Hz, 1H), 7.30 (dd, *J* = 8.5, 1.9 Hz, 1H), 7.22 – 7.16 (m, 1H), 7.16 – 7.08 (m, 4H), 6.98 – 6.91 (m, 2H), 6.44 – 6.29 (m, 1H), 5.61 (t, *J* = 5.5 Hz, 1H), 5.23 – 5.11 (m, 2H), 4.33 (dd, *J* = 14.6, 5.7 Hz, 1H), 4.27 (dd, *J* = 14.6, 5.1 Hz, 1H), 3.93 (s, 3H), 3.80 (d, *J* = 9.6 Hz, 1H), 1.25 (s, 3H), 1.19 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 176.5, 157.6, 138.2, 137.0, 136.3, 133.6, 129.5, 128.9, 128.6,

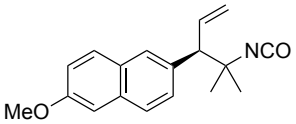
128.2, 127.9, 127.8, 127.4, 126.5, 118.9, 118.0, 105.6, 57.9, 55.5, 46.6, 43.8, 23.9, 22.9.
HRMS (ESI): *m/z* for $C_{25}H_{27}NNaO_2$ $[M+Na]^+$ calcd.: 396.1934, found: 396.1943.

f) Synthesis of Isocyanate 4f:

A 1-dram vial containing a magnetic stir bar was charged with carboxylic acid **4c** (28.4 mg, 0.100 mmol, 1.00 equiv), triethylamine (23.7 μL, 0.170 mmol, 1.70 equiv), DCE (0.40 mL), and diphenylphosphoryl azide (22.6 μL, 0.105 mmol, 1.05 equiv). The vial was sealed with a cap containing PTFE/silicone septa. The mixture was stirred at 80 °C for 12 h.

The reaction mixture was diluted with 2 mL of hexanes, and filtered through a 0.5-inch plug of silica gel (eluting with 1:1 hexanes:EtOAc, 8 mL). After removal of solvent under vacuum, the crude mixture was purified by column chromatography performed on a Teledyne Isco Combiflash® R_f system with Redi*Sep* Gold™ columns (4-gram silica gel column, 100/0 to 90/10 of hexanes/EtOAc).

(*R*)-2-(4-isocyanato-4-methylpent-1-en-3-yl)-6-methoxynaphthalene (4f)



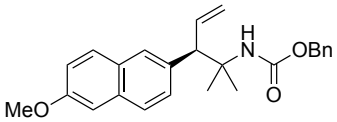
The title compound was obtained as a colorless oil (27.5 mg, 0.0977 mmol, 98%).
The **enantiomeric excess** was determined by SFC analysis to be >99% with t_R = 3.56 min (major) and t_R = 3.29 min (minor) [AD-H, 5.0% ^{i}PrOH, 2.5 mL/min, 230 nm, 40 °C].
$[\alpha]_D^{25}$ = –119.6° (c 0.46, CH_2Cl_2).
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 – 7.69 (m, 2H), 7.62 (d, *J* = 1.8 Hz, 1H), 7.39 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.19 – 7.05 (m, 2H), 6.37 (ddd, *J* = 16.9, 10.2, 9.3 Hz, 1H), 5.25 (dd, *J* = 10.2, 1.6 Hz, 1H), 5.23 – 5.11 (m, 1H), 3.92 (s, 3H), 3.35 (d, *J* = 9.3 Hz, 1H), 1.42 (s, 3H), 1.28 (s, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 157.7, 137.2, 135.8, 133.7, 129.4, 128.9, 127.8, 127.7, 126.8, 123.1, 119.1, 118.5, 105.6, 61.0, 60.7, 55.4, 29.9, 29.3.
HRMS (EI): *m/z* for $C_{18}H_{19}NO_2$ $[M]^+$ calcd.: 281.1416, found: 281.1415.

g) Synthesis of Carbamate 4g:

A 1-dram vial containing a magnetic stir bar was charged with carboxylic acid **4c** (28.4 mg, 0.100 mmol, 1.00 equiv), triethylamine (23.7 μL, 0.170 mmol, 1.70 equiv), DCE (0.40 mL), and diphenylphosphoryl azide (22.6 μL, 0.105 mmol, 1.05 equiv). The vial was sealed with a cap containing PTFE/silicone septa. The mixture was stirred at 80 °C for 100 min. After cooling the reaction mixture to r.t., benzyl alcohol (20.7 μL, 0.200 mmol, 2.00 equiv) was added. The mixture was stirred at 80 °C for 24 h. After this time, the reaction mixture was cooled to r.t.. A second batch of benzyl alcohol (20.7 μL, 0.200 mmol, 2.00 equiv) was added. The mixture was stirred at 80 °C for another 24 h to reach full conversion of the isocyanate (monitored by TLC).

The reaction mixture was diluted with 2 mL of hexanes, and the resulting mixture was filtered through a 0.5-inch plug of silica gel (eluting with 1:1 hexanes:EtOAc, 8 mL). After removal of solvent under vacuum, the crude mixture was purified by column chromatography performed on a Teledyne Isco Combiflash® R_f system with Redi*Sep* Gold™ columns (4-gram silica gel column, 100/0 to 85/15 of hexanes/EtOAc).

benzyl (*R*)-(3-(6-methoxynaphthalen-2-yl)-2-methylpent-4-en-2-yl)carbamate (4g)

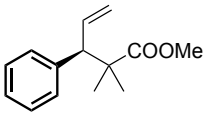


The title compound was obtained as a colorless oil (35.0 mg, 0.0899 mmol, 90%).
The **enantiomeric excess** was determined by SFC analysis to be >99% with t_R = 3.47 min (major) and t_R = 2.80 min (minor) [AD-H, 20.0% ^{i}PrOH, 2.5 mL/min, 230 nm, 40 °C].
$[\alpha]_D^{25}$ = –7.4° (c 0.58, CH_2Cl_2).
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 – 7.60 (m, 2H), 7.58 – 7.55 (m, 1H), 7.40 – 7.28 (m, 6H), 7.18 – 7.05 (m, 2H), 6.35 (dt, *J* = 17.3, 9.7 Hz, 1H), 5.25 – 4.91 (m, 4H), 4.66 (s, 1H), 4.09 (d, *J* = 9.7 Hz, 1H), 3.92 (s, 3H), 1.42 (s, 3H), 1.29 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 157.6, 137.2, 137.0, 136.1, 133.5, 129.4, 128.9, 128.6, 128.3, 128.2, 128.2, 128.0, 126.5, 118.9, 118.4, 105.6, 66.2, 57.1, 55.8, 55.4, 25.2.
HRMS (ESI): *m/z* for $C_{25}H_{27}NNaO_3$ $[M+Na]^+$ calcd.: 412.1883, found: 412.1893.

2.4.9 Determination of Absolute Configuration

The absolute configuration of **3aa** was assigned by comparing the optical rotation of this material to that reported by Tan, Cheon and Yamamoto.[34]

methyl (*R*)-2,2-dimethyl-3-phenylpent-4-enoate (3aa)



$[\alpha]_D^{25}$ = –46.6° (c 0.55, $CHCl_3$).
Lit[17]: $[\alpha]_D^{25}$ = –49.8° (c 1.1, $CHCl_3$).

The absolute configurations of all other compounds in this paper were assigned by analogy. This assigned absolute configuration is also consistent with the X-ray crystallography analysis of **4d**.

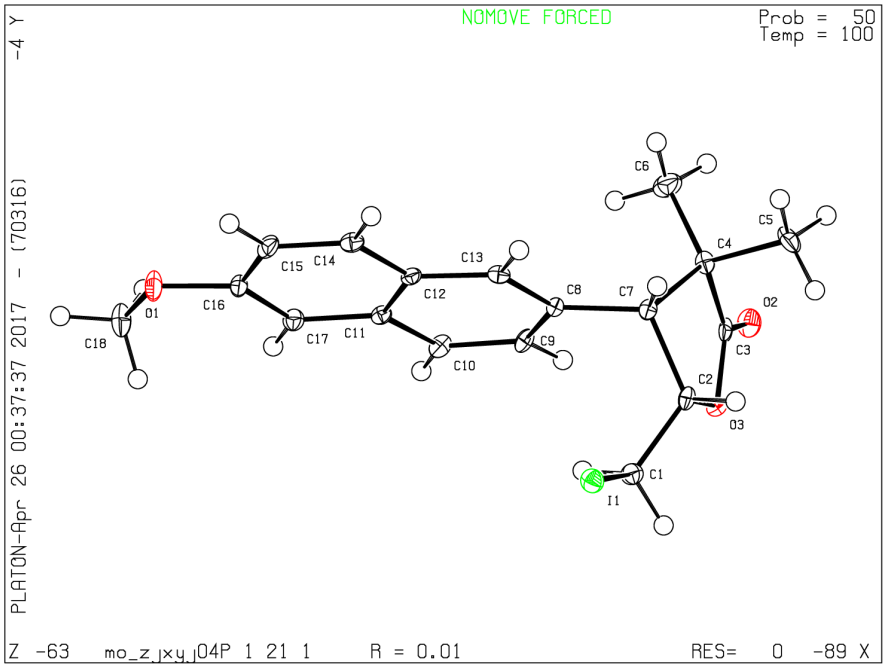
2.4.10 X-Ray Crystallography Analysis of 4d

Single crystals suitable for X-ray diffraction were obtained by slow vapor diffusion of pentane into a solution of **4d** in dichloromethane. A colorless block 0.200 x 0.140 x 0.100 mm in size was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using and scans. Crystal-to-detector distance was 40 mm and exposure time was 5 seconds per frame using a scan width of 0.5°. Data collection was 99.4% complete to 52.744° in □. A total of 12037 reflections were collected covering the indices, -10<=*h*<=10, -7<=*k*<=7, -20<=*l*<=20, with an R_{int} of 0.0147. Indexing and unit cell refinement indicated a primitive, monoclinic lattice. The space group was found to be P 21 (No. 4). The data were integrated using the Bruker SAINT software program and scaled using the SADABS software program. Solution by iterative methods (SHELXT-2014) produced a complete heavy-atom phasing model consistent

with the proposed structure. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2016). All hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2016. Absolute stereochemistry was unambiguously determined.

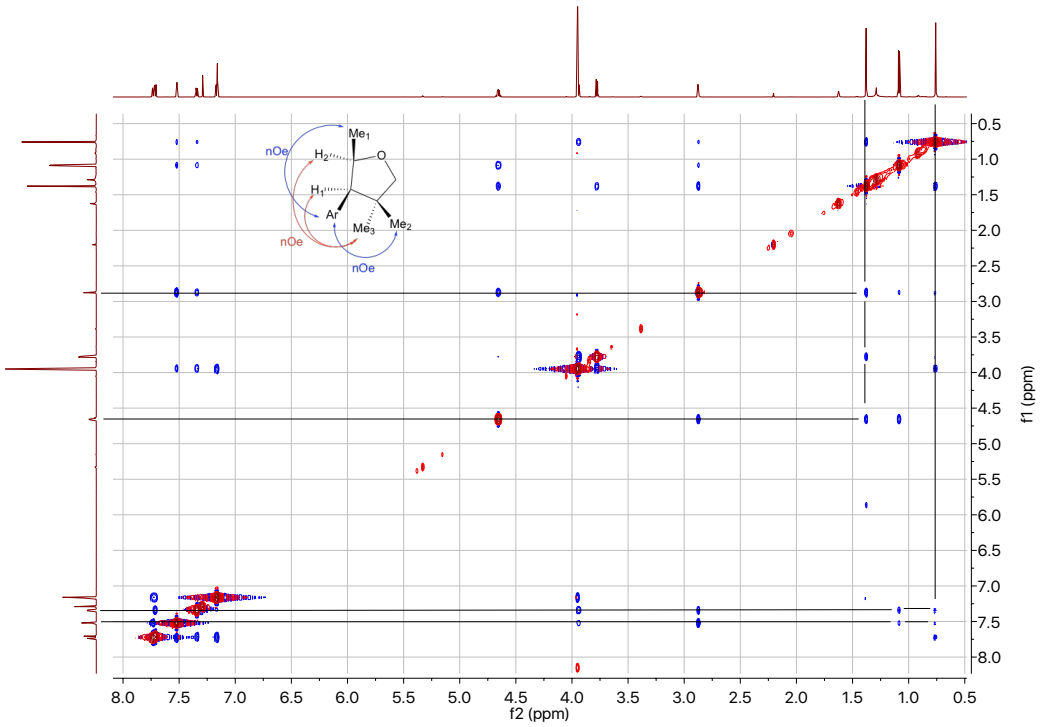
Table 2.4 Crystal data and structure refinement for **4d**

X-ray ID	**4d**	
Empirical formula	C18 H19 I O3	
Formula weight	410.23	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 21	
Unit cell dimensions	a = 8.1730(4) Å	α= 90°.
	b = 6.1366(2) Å	β= 98.6540(10)°.
	c = 16.4000(7) Å	γ = 90°.
Volume	813.17(6) $Å^3$	
Z	2	
Density (calculated)	1.675 Mg/m^3	
Absorption coefficient	1.979 mm^{-1}	
F(000)	408	
Crystal size	0.200 x 0.140 x 0.100 mm^3	
Theta range for data collection	5.953 to 52.744°.	
Index ranges	-10<=h<=10, -7<=k<=7, -20<=l<=20	
Reflections collected	12155	
Independent reflections	3313 [R(int) = 0.0147]	
Completeness to theta = 52.744°	99.4 %	
Absorption correction	Semi-empirical from equivalents	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3313 / 1 / 203	
Goodness-of-fit on F^2	1.129	
Final R indices [I>2sigma(I)]	R1 = 0.0144, wR2 = 0.0345	
R indices (all data)	R1 = 0.0147, wR2 = 0.0345	
Absolute structure parameter	0.016(7)	
Extinction coefficient	0.0139(12)	
Largest diff. peak and hole	0.434 and -0.238 $e.Å^{-3}$	

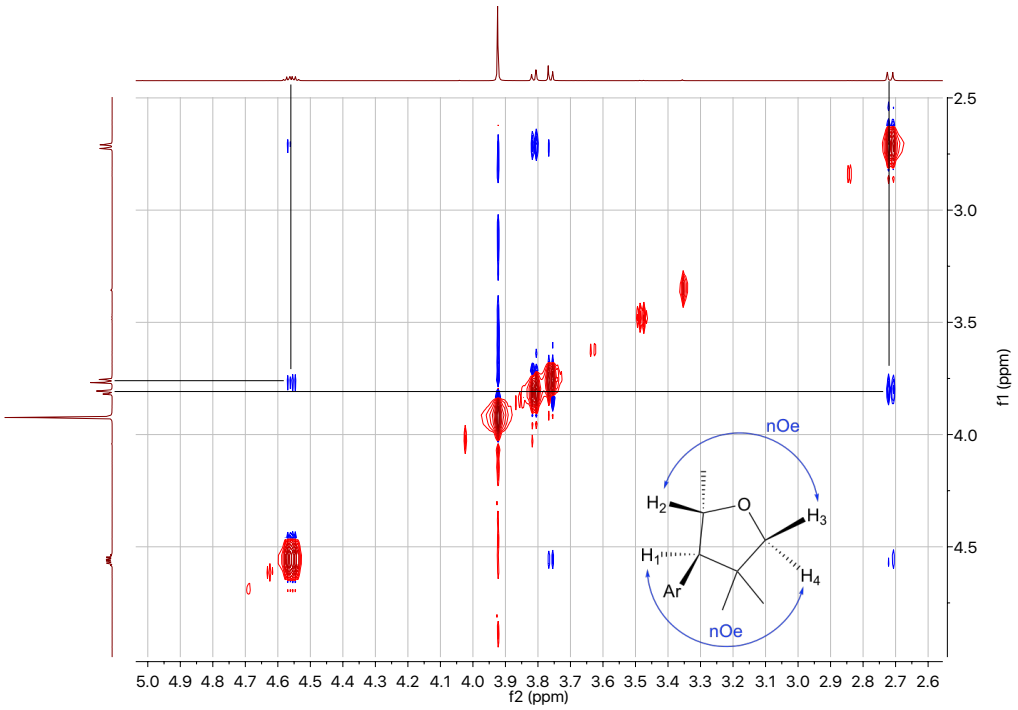


Scheme 2.12 Crystal structure of **4**

2.4.11 NOSEY Analysis of 4b and 4b'



Scheme 2.13 NOESY analysis of **4b**



Scheme 2.14 NOESY analysis of **4b**'

2.5 References

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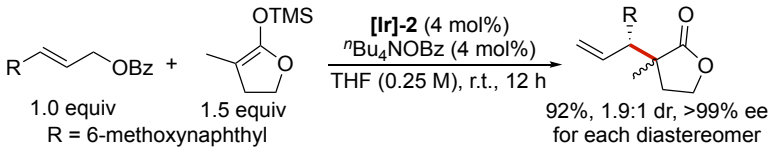
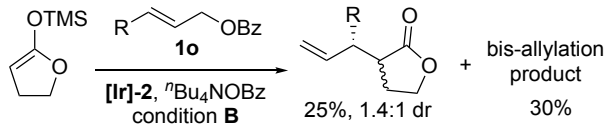
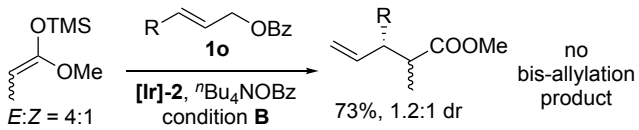
[16] Preliminary results showed excellent regio- and enantioselectivity but poor diastereoselectivity for the reaction with unsymmetrical silyl ketene acetals. For example:



[17] We also tested monosubstituted silyl ketene acetals for this allylation reaction. The reaction of **1o** with the silyl ketene acetal of γ-butyrolactone gave the product in 25% yield with 1.4:1 dr. The bis-allylation product was formed in 30% yield, which presumably resulted from the enolization of the product followed by a second allylation.



However, the reaction with the silyl ketene acetal of methyl propionate gave no bis-allylation product. This lack of reaction is presumably because acyclic esters are less acidic and less prone to enolize than lactones under the reaction condition.



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CHAPTER 3

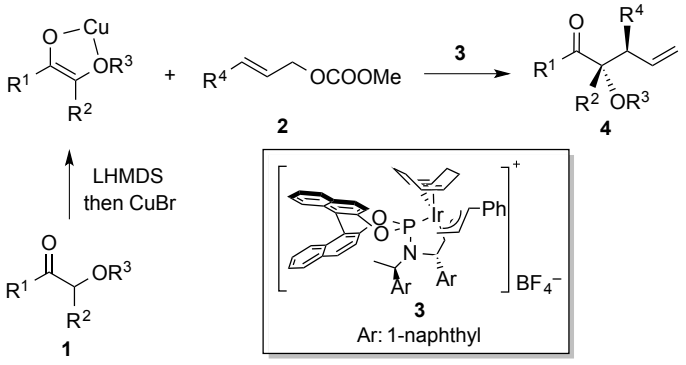
Iridium-Catalyzed Diastereoselective and Enantioselective Allylic Substitutions with Acyclic α-Alkoxy Ketones

3.1 Introduction

Transition-metal-catalyzed asymmetric allylation of enolates serves as an efficient and reliable method to construct carbon-carbon bonds with high levels of asymmetric induction.[1] The majority of these reactions form products containing a single stereocenter from a prochiral enolate as the nucleophile or a prochiral allylic compound as the electrophile. If both nucleophile and electrophile are prochiral, synthetically valuable dyads containing contiguous stereocenters could be assembled in a catalytic and stereoselective fashion.[2] However, this transformation is challenging because a new bond needs to be formed between two sterically hindered prochiral carbons with control of both absolute and relative configurations.

Metallacyclic iridium complexes catalyze allylic substitutions with a variety of carbon and heteroatom nucleophiles regio- and enantioselectively.[1b,3] Although reactions have been reported between prochiral enolates and prochiral electrophiles to afford products containing vicinal tetra-substituted and tertiary stereocenters with excellent diastereo- and enantioselectivity, reactions with unstabilized, acyclic, prochiral ketones have not been reported.[4] The main challenge facing this transformation results from the lack of control of the geometry of the unstabilized enolate of an α-branched acyclic ketone. In contrast to cyclic enolates, the backbone of the nucleophile does not dictate the geometry. Also, because α-branched, acyclic ketones do not readily form enamines, the use of amine auxiliaries has not been effective to control the geometry.[5]

In the presence of suitable metal cations, acyclic carbonyl compounds bearing α-heteroatoms form enolates with a defined geometry created by chelation. This structure has been exploited for the allylation of glycine derivatives.[6] However, these reactions occurred with low diastereoselectivity when forming products containing adjacent tetra-substituted and tertiary stereocenters.[6a] With the same strategy, Evans and co-workers achieved diastereoselective allylations of α-hydroxy, as well as α-alkoxy or α-siloxy acetophenone catalyzed by an achiral rhodium catalyst.[7] However, only products containing adjacent tertiary and tri-substituted stereocenters bearing oxygen were formed, and no enantioselective transformation was reported. We envisioned that this strategy could be followed to achieve the enantioselective allylation of unstabilized ketones with cyclometallic iridium catalysts we developed.[8]

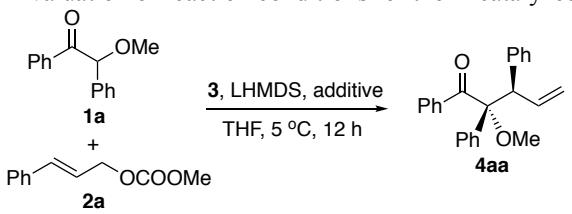


Scheme 3.1 Iridium-catalyzed diastereo- and enantioselective allylations with unstabilized copper(I) enolates of acyclic α-alkoxy ketones

Herein, we report diastereo- and enantioselective allylic alkylations with unstabilized enolates of acyclic α-alkoxy ketones catalyzed by iridium complex **3** (Scheme 3.1). The geometry of the enolates is controlled through chelation in the presence of a copper(I) cation. These reactions form, with high diastereo- and enantioselectivity, products containing vicinal oxygen-bearing tetra-substituted and tertiary stereocenters. Products containing an *O*-MOM (methoxymethyl) group on the tertiary alcohol were formed in good yield with high dr and ee, and these products can be readily converted to tertiary alcohols and tetrahydrofuran (THF) derivatives without erosion of enantiomeric purity.

3.2 Results and Discussion

Table 3.1 Evaluation of reaction conditions for the Ir-catalyzed allylation[a]



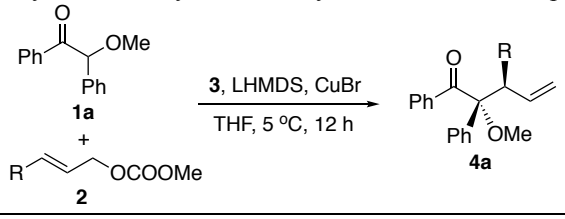
Entry	Additive	Yield/%[b]	dr[c]	ee/%[d]
1	-	95	2.0:1	n.d.
2	LiCl	>99	1:1.1	n.d.
3	$ZnCl_2$	72	16:1	n.d.
4	CuI	97	5.7:1	n.d.
5	CuCl	58	10:1	n.d.
6	CuBr	>99 (>99)	14:1	92
7	CuCN	34	2.5:1	n.d.
8	CuOAc	52	1.5:1	n.d.
9	CuSCN	94	2.3:1	n.d.
10[e]	CuBr	42	2.7:1	n.d.
11[f]	CuBr	>99	14:1	93
12[g]	CuBr	>99	12:1	95
13	$CuBr_2$	0	-	n.d.

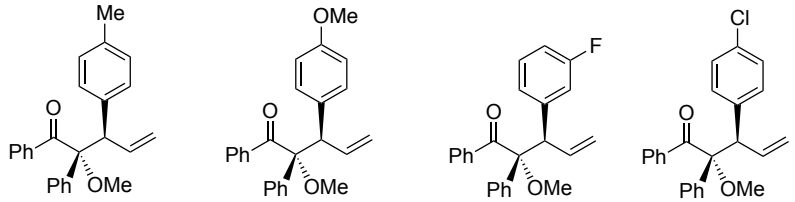
[a]The molar ratio of **1a**/**2a**/**3**/LHMDS/additive = 2/1/0.02/2/2. The absolute configuration of **4aa** was assigned by analogy. [b]Combined yield of two diastereoisomers. Determined by ^{1}H NMR analysis with mesitylene as internal standard. The yield in parentheses is an isolated yield of two diastereoisomers. [c]Determined by ^{1}H NMR analysis of crude reaction mixtures. [d]Determined by chiral SFC analysis of the major isomer. [e]KHMDS was used as the base instead of LHMDS. [f]1 equiv of CuBr was used. [g]0.5 equiv of CuBr was used. n.d. = not determined.

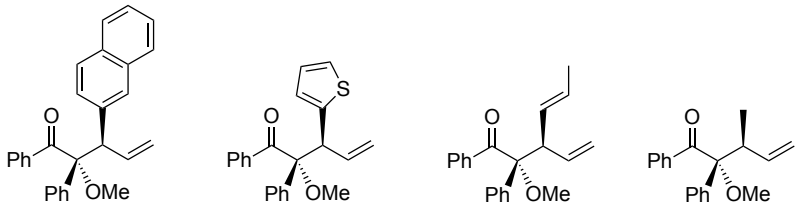
To assess the potential of developing an iridium-catalyzed allylation of an acyclic ketone enolate, we conducted the reactions between *O*-methyl benzoin (**1a**) and methyl cinnamyl carbonate (**2a**) (Table 3.1). Treatment of **1a** and **2a** with Ir complex **3** in the presence of LHMDS at 5 °C for 12 h furnished the branched product **4aa** in 95% yield (combined yield of two diastereoisomers), but with a low dr of 2.0:1 (entry 1). The reaction conducted after addition of LiCl[4o] to the lithium enolate gave the product with a lower dr of 1:1.1, slightly favoring the formation of the other diastereoisomer (entry 2). The reaction with added $ZnCl_2$[6] afforded **4aa** with excellent diastereoselectivity (16:1 dr, entry 3), albeit in a lower yield of 72%. In contrast, the reaction

conducted with added CuI occurred with a higher diastereomeric ratio to 5.7:1 while maintaining excellent conversion to yield **4aa** in 97% yield (entry 4). Similarly, Evans and coworkers observed higher diastereoselectivity with the copper(I) enolate of α-hydroxy acetophenone derivatives than with the corresponding lithium enolate.[7]

Table 3.2 Ir-catalyzed allylations of acyclic α-alkoxy ketone enolates: scope of allylic carbonates[a]





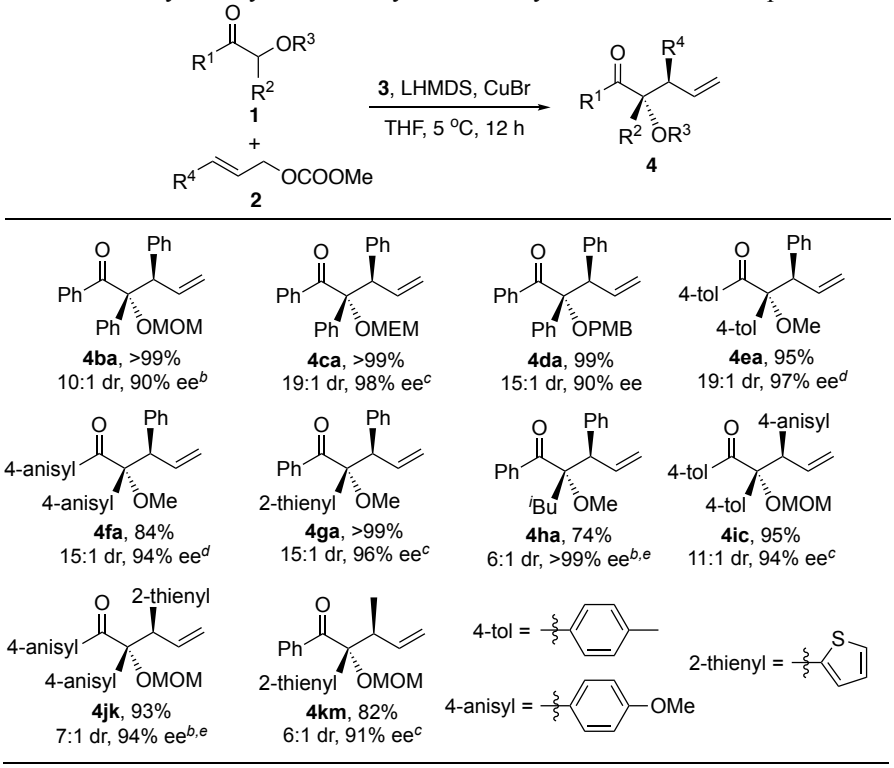


[a]The molar ratio of **1a**/**2**/**3**/LHMDS/CuBr = 2/1/0.02/2/2. The absolute configurations were assigned by analogy. The structure of **4ag** was determined by X-ray analysis. The yields were reported as the combined yields of two diastereoisomers. The diastereomeric ratios were determined by ^{1}H NMR analysis of crude reaction mixtures. The enantiomeric excesses were determined by chiral SFC analysis of major isomers. [b]0.5 equiv. of CuBr was used.

Because the anion of the copper(I) salt could influence the transmetalation, we further evaluated a series of copper(I) salts. Reactions conducted with added CuBr occurred with a higher diastereomeric ratio of 14:1 with an excellent ee of 92% (entry 6). The major diastereoisomer was isolated in 93% yield (see SI for details). Reactions with other copper(I) additives, such as CuCl, CuCN, CuOAc or CuSCN, occurred in significantly lower yield (58%, entry 5) or with lower dr (1.5–2.5:1, entries 7–9).[9]

The identity of the cation of the anionic base was crucial to obtaining high yields and diastereoselectivities. Reactions conducted with KHMDS instead of LHMDS afforded only 42% yield of **4aa** with a significantly lower dr of 2.7:1 (entry 10). Reactions conducted with one equivalent of copper in place of two equivalents led to excellent reactivity and afforded the product in identical dr and ee (entry 11), but reactions with 0.5 equiv occurred with lower dr (although slightly higher ee) as shown in entry 12.[10] In all cases, the branched product was obtained exclusively. Reactions run with $CuBr_2$ as additive gave no product, indicating the critical role of the copper(I) cation in this reaction, rather than a copper(II) cation that might be formed by disproportionation or oxidation of copper(I) salt (entry 13).

Table 3.3 Ir-catalyzed allylations of acyclic α-alkoxy ketone enolates: scope of ketones[a]



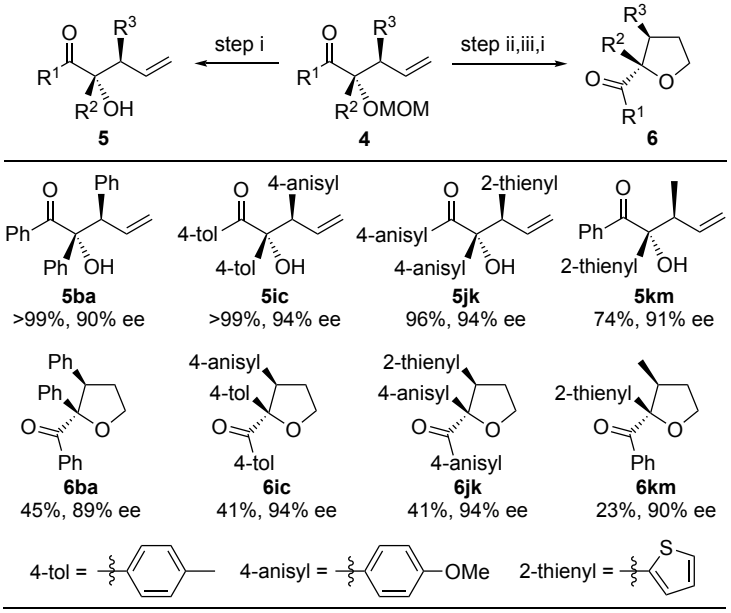
[a]The molar ratio of **1**/**2**/**3**/LHMDS/CuBr = 2/1/0.02/2/2. The absolute configurations were assigned by analogy. The yields were reported as the combined yields of two diastereoisomers. The diastereomeric ratios were determined by ^{1}H NMR analysis of crude reaction mixtures. The enantiomeric excesses were determined by chiral SFC analysis of major isomers. [b]4 mol% of **3** was used. [c]1 equiv of CuBr was used. [d]0.5 equiv of CuBr was used. [e]cinnamyl acetate was used instead of cinnamyl carbonate, and the reaction time was elongated to 36 h. The yield was reported as the isolated yield of the major diastereomer.

The scope of the allylic electrophiles that underwent the Ir-catalyzed allylic substitution with acyclic α-alkoxy ketones is summarized in Table 3.2. Various *para*-substituted cinnamyl carbonates are suitable electrophiles. Electron-neutral (**4ab**), electron-donating (**4ac**) and electron-withdrawing (**4ah**, **4ai**) functional groups on the cinnamyl aryl ring were all tolerated in this reaction, and the corresponding products were formed in excellent yield (≥94%) with high dr (≥10:1) and ee (≥90%). Cinnamyl carbonates bearing halogens at the para- or meta-position reacted cleanly,

furnishing **4ad-ag** in ≥92% yield, ≥12:1 dr and ≥91% ee. The reaction of 3,4-dichlorocinnamyl carbonate (**2g**) in the presence of 2 equivalents of CuBr gave product **4ag** in 91% yield with 15:1 dr and 89% ee (see SI for details). The same reaction with 0.5 equiv of CuBr resulted in similar yield (92%) with lower dr (12:1) and higher ee (96%).[11] The absolute stereochemistry of **4ag** was established by single crystal X-ray diffraction.

The reaction also occurred with allylic carbonates containing heteroaryl, alkenyl and alkyl substituents. The reaction of thienyl carbonate **2k** afforded **4ak** in high yield with excellent diastereo- and enantioselectivity (>99%, >20:1 dr, 92% ee). Methyl sorbyl carbonate (**2l**) reacted to form product **4al** in 75% yield with >20:1 dr and 94% ee. Even the simple crotyl carbonate (**2m**) reacted to form product **4am** in good yield, although the dr and ee (71%, 8:1 dr and 88% ee) were slightly lower than those with aryl-substituted allylic carbonates.

Table 3.4 Synthesis of enantioenriched tertiary alcohols **5** and tetrahydrofuran derivatives **6**[a]



[a]The yield for **6** is reported as the overall yield of 3 steps. The absolute structures were assigned by analogy. Steps: i) Dowex-50W-X8 (H^+ form), MeOH/H_2O, 65 °C. ii) 9-BBN then $NaBO_3 \cdot 4H_2O$. iii) TsCl, TEA.

The scope of the acyclic α-alkoxy ketones that underwent the Ir-catalyzed allylation is summarized in Table 3.3.[12,13] MOM (**1b**), MEM (methoxyethoxymethyl, **1c**), and PMB (*para*-methoxybenzyl, **1d**) protected benzoins underwent allylation in high yield with excellent diastereo- and enantioselectivity. The reaction between *O*-MOM benzoin **1b** and cinnamyl carbonate **2a** required a higher catalyst loading of 4 mol% to reach full conversion within 12 hours. Several acyclic *O*-Me benzoin derivatives bearing identical substituents at both aryl rings, such as **1e** and **1f**, as well as their *O*-MOM analogues **1i** and **1j** were suitable for this transformation (**4ea**, **4fa**, **4ic** and **4jk**, ≥84%, ≥7:1 dr, ≥94% ee).

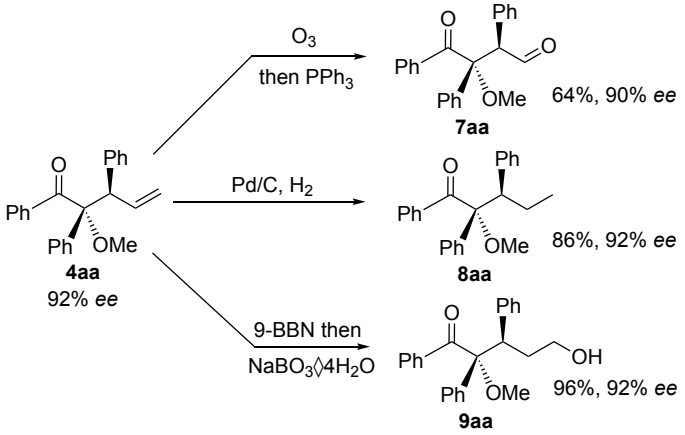
The reactions with nucleophiles derived from non-symmetrical benzoins were also examined. Benzoin **1g**, bearing a thienyl group, underwent allylation in quantitative yield with excellent dr of 15:1 and 96% ee (**4ga**). Benzoin analogue **1h**, containing an *i*-butyl group, reacted with methyl cinnamyl carbonate **2a** in low yield of 38% and low branched/linear selectivity of 4:1 (5:1 dr for

the branched product). However, the identical reaction with the less reactive cinnamyl acetate as the electrophile afforded branched product **4ha** exclusively in high yield (74%, isolated yield of the major diastereomer) with acceptable diastereoselectivity and excellent enantioselectivity (6:1 dr, >99% ee).

Allylation products containing an *O*-MOM group on the tertiary alcohol were readily transformed to enantioenriched tertiary alcohols **5** containing adjacent tertiary stereogenic centers (Table 3.2). Deprotection of **4ba** by reaction with acidic Dowex-50W-X8 resin[14] (Table 3.4, step i) afforded the corresponding alcohols **5ba** in quantitative yield without any erosion of enantiomeric purity. The synthetic value of these allylated benzoin derivatives was further demonstrated by their transformation into highly substituted THF derivatives. Hydroboration of **4ba** with 9-BBN, followed by oxidation (step ii), yielded the terminal alcohol, which was subsequently converted to the corresponding tosylate (step iii). Removal of the MOM protecting group (step i) afforded the free tertiary alcohol, which underwent a 5-*exo*-*tet* cyclization *in situ* to furnish THF derivative **6ba** in 45% yield over 3 steps.

These synthetic sequences were also applied to allylation products bearing different substituents R^1, R^2 and R^3. In all cases, substrates **4ic** ($R^1 = R^2$ = 4-tol, R^3 = 4-anisyl), **4jk** ($R^1 = R^2$ = 4-anisy, R^3 = 2-thienyl) and **4km** (R^1 = Ph, R^2 = 2-thienyl and R^3 = Me) afforded the corresponding tertiary alcohols **5ic**, **5jk** and **5km** in high yield without erosion of enantiomeric purity. Similarly, the corresponding THF derivatives **6ic**, **6jk** and **6km** were obtained in high enantiomeric purity.

The olefin moiety is a useful precursor to many functional groups. For example, ozonolysis, hydrogenation and the combination of hydroboration and oxidation of the products of allylation **4aa** afforded aldehyde **7aa**, ketone **8aa**, and primary alcohol **9aa**, respectively, in high yields without erosion of enantiomeric purity (Scheme 3.2).



Scheme 3.2 Derivatizations of **4aa**

3.3 Conclusions

In summary, we have developed Ir-catalyzed diastereo- and enantioselective allylic substitutions with unstabilized copper(I) enolates of acyclic α-alkoxy ketones. Employing metallacyclic complex **3** as the catalyst, LHMDS as the base and CuBr as the additive, allylation reactions gave the products containing vicinal tetra-substituted and tertiary stereocenters in high yield with

excellent dr and ee. The geometry of the enolates is controlled by chelation in the presence of a copper(I) cation. The synthetic utility of this method was demonstrated by the synthesis of enantioenriched THF derivatives and tertiary alcohols containing adjacent tertiary stereogenic centers. Studies to gain insight into the origin of diastereoselectivity in this reaction are ongoing in our laboratories.

3.4 Experimental

3.4.1 General Experimental Details

All air-sensitive manipulations were conducted under an inert atmosphere in a nitrogen-filled glovebox or by standard Schlenk techniques. Tetrahydrofuran was purified by passing it through a solvent column composed of activated A-1 alumina and degassed by freeze-pump-thaw method. $[Ir(cod)Cl]_2$ was obtained from Johnson-Matthey and used without further purification.

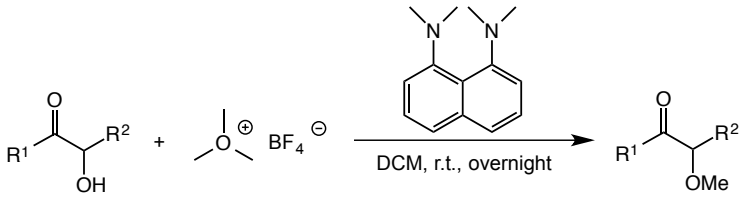
Chiral SFC analysis was conducted on a JASCO SF-2000 integrated analytical SFC system. Chiral HPLC analysis was conducted on Waters or Shimadzu chromatography system. Proton nuclear magnetic resonance (^{1}H NMR) spectra were acquired on commercial instruments (300, 400, 500 and 600 MHz) at the University of California, Berkeley NMR facility. Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were acquired at 100, 126 and 151 MHz. The proton signal for residual non-deuterated solvent (δ 7.26 for $CHCl_3$) was used as an internal reference for ^{1}H NMR spectra. For ^{13}C NMR spectra, chemical shifts are reported relative to the δ 77.16 resonance of $CHCl_3$. Coupling constant are reported in Hz. Optical rotations were measured on a Perkin Elmer 241 Automatic Polarimeter. High-resolution mass spectra were recorded on a commercial high-resolution mass spectrometer at the Micro Mass/Analytical Facility operated by the College of Chemistry, University of California, Berkeley. IR analysis was conducted on a Thermo Scientific Nicolet iS 5 FT-IR Spectrometer.

Analytical thin layer chromatography (TLC) was performed on Kieselgel 60 F_{254} glass plates pre-coated with a 0.25 mm thickness of silica gel. The TLC plates were visualized with UV light and/or by staining with Hanessian solution (ceric sulfate and ammonium molybdate in aqueous sulfuric acid) or $KMnO_4$. For the purification of substrates, column chromatography was generally performed on a Teledyne Isco Combiflash® R_f system with Redi*Sep* Gold™ columns. For the purification of the allylated ketones, column chromatography was generally performed on silica gel (Silia flash T60, 5-20 μm), typically with a 50-100:1 weight ratio of silica gel to the crude product.

3.4.2 Syntheses of Substrates and Catalyst

1) Methyl allylic carbonates **2** were prepared according to published procedures.[15]

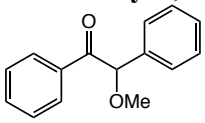
2) *α*-*O*-Methyl ketones (**1a**, **1e**–**1h**) were prepared by modification of a published procedure.[16]



Scheme 3.3 Synthesis of *α*-*O*-Methyl ketones

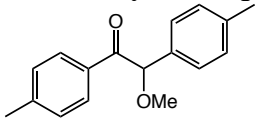
To a flame-dried 50 mL round-bottom flask was added *α*-hydroxy ketone (5.00 mmol, 1.00 equiv), trimethyloxonium tetrafluoroborate (1.18 g, 8.00 mmol, 1.60 equiv), 1,8-bis(dimethylamino)naphthalene (1.93 g, 9.00 mmol, 1.80 equiv) and 20 mL of DCM. After being stirred overnight at room temperature, the mixture was diluted with 50 mL of hexanes and 50 mL of EtOAc, and then filtered through a Celite pad to remove solid materials. The resulting solution was concentrated under reduced pressure, and the residue was purified by column chromatography (100/0 to 90/10 hexanes/EtOAc).

2-methoxy-1,2-diphenylethan-1-one (1a)



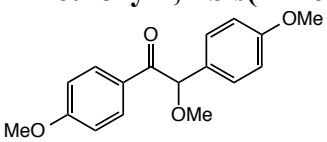
The title compound was isolated (734 mg, 3.25 mmol, 65%) as a white solid.
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.98 (d, *J* = 7.6 Hz, 2H), 7.50 (t, *J* = 7.5 Hz, 1H), 7.46 (d, *J* = 7.7 Hz, 2H), 7.40 (t, *J* = 7.7 Hz, 2H), 7.35 (t, *J* = 7.6 Hz, 2H), 7.29 (t, *J* = 7.4 Hz, 1H), 5.51 (s, 1H), 3.46 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 197.2, 136.2, 135.2, 133.4, 129.2, 129.0, 128.7, 128.6, 127.8, 86.8, 57.6.
HRMS (ESI): *m/z* for $C_{15}H_{14}O_2Na$ $[M+Na]^+$ calcd.: 249.0886, found: 249.0883.

2-methoxy-1,2-di-*p*-tolylethan-1-one (1e)



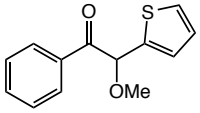
The title compound was isolated (648 mg, 2.55 mmol, 51%) as a yellow solid.
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.3 Hz, 2H), 7.33 (d, *J* = 8.1 Hz, 2H), 7.18 (d, *J* = 7.9 Hz, 2H), 7.14 (d, *J* = 7.8 Hz, 2H), 5.48 (s, 1H), 3.43 (s, 3H), 2.35 (s, 3H), 2.30 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 196.8, 144.2, 138.5, 133.4, 132.7, 129.7, 129.3, 129.3, 127.8, 86.4, 57.4, 21.8, 21.3.
HRMS (ESI): *m/z* for $C_{17}H_{18}O_2Na$ $[M+Na]^+$ calcd.: 277.1199, found: 277.1195.

2-methoxy-1,2-bis(4-methoxyphenyl)ethan-1-one (1f)



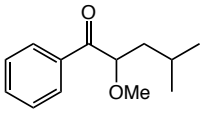
The title compound was isolated (758 mg, 2.65 mmol, 53%) as a yellow gel.
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.9 Hz, 2H), 7.36 (d, *J* = 8.8 Hz, 2H), 6.87 (d, *J* = 2.7 Hz, 2H), 6.85 (d, *J* = 2.8 Hz, 2H), 5.44 (s, 1H), 3.82 (s, 3H), 3.77 (s, 3H), 3.42 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 195.7, 163.6, 159.9, 131.5, 129.1, 128.7, 128.1, 114.4, 113.8, 86.0, 57.4, 55.6, 55.4.
HRMS (ESI): *m/z* for $C_{17}H_{18}O_4Na$ $[M+Na]^+$ calcd.: 309.1097, found: 309.1093.

2-methoxy-1-phenyl-2-(thiophen-2-yl)ethan-1-one (1g)



The title compound was isolated (434 mg, 1.87 mmol, 58% based on 2.70 mmol of *α*-hydroxy ketone employed) as a dark red gel. The corresponding *α*-hydroxy ketone was prepared according to a published procedure.[17]
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.04 (d, *J* = 6.9 Hz, 2H), 7.58 – 7.51 (m, 1H), 7.43 (t, *J* = 7.8 Hz, 2H), 7.33 (d, *J* = 5.1 Hz, 1H), 7.06 (d, *J* = 2.8 Hz, 1H), 6.96 (dd, *J* = 5.1, 3.5 Hz, 1H), 5.75 (s, 1H), 3.48 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 195.8, 138.8, 134.8, 133.6, 129.3, 128.7, 127.4, 127.2, 127.1, 81.9, 57.6.
HRMS (ESI): *m/z* for $C_{13}H_{12}O_2SNa$ $[M+Na]^+$ calcd.: 255.0450, found: 255.0447.

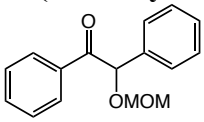
2-methoxy-4-methyl-1-phenylpentan-1-one (1h)



The title compound was isolated (657 mg, 3.19 mmol, 72% based on 4.40 mmol of *α*-hydroxy ketone employed) as a slightly yellow oil. The corresponding *α*-hydroxy ketone was prepared according to a published procedure.[17]
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (d, *J* = 7.0 Hz, 2H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.47 (t, *J* = 7.5 Hz, 2H), 4.51 (dd, *J* = 9.6, 3.8 Hz, 1H), 3.36 (s, 3H), 1.99 – 1.82 (m, 1H), 1.74 (ddd, *J* = 14.5, 9.6, 5.1 Hz, 1H), 1.60 – 1.46 (m, 1H), 0.99 (d, *J* = 6.6 Hz, 3H), 0.94 (d, *J* = 6.7 Hz, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 201.2, 135.2, 133.4, 128.8, 128.8, 83.8, 57.9, 42.4, 25.1, 23.3, 21.9.
HRMS (ESI): *m/z* for $C_{13}H_{18}O_2Na$ $[M+Na]^+$ calcd.: 229.1199, found: 229.1195.

3) *α-O*-MOM ketones (**1b**, **1i** – **1j**) were prepared according to a published procedure[18] at a 10-mmol scale.

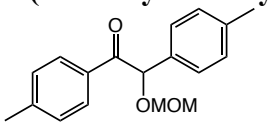
2-(methoxymethoxy)-1,2-diphenylethan-1-one (1b)



The title compound was isolated (1.92 g, 7.50 mmol, 75%) as a white solid.
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (d, *J* = 7.0 Hz, 2H), 7.52 – 7.44 (m, 3H), 7.42 – 7.32 (m, 4H), 7.32 – 7.27 (m, 1H), 5.99 (s, 1H), 4.82 – 4.72 (m, 2H), 3.35 (s, 3H).

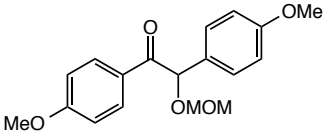
^{13}C NMR (151 MHz, $CDCl_3$) δ 196.7, 136.1, 135.3, 133.3, 129.2, 129.1, 128.8, 128.6, 128.1, 95.3, 80.4, 56.2.
HRMS (ESI): *m/z* for $C_{16}H_{16}O_3Na$ $[M+Na]^+$ calcd.: 279.0992, found: 279.0987.

2-(methoxymethoxy)-1,2-di-*p*-tolylethan-1-one (1i)



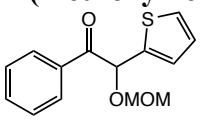
The title compound was isolated (1.87 g, 6.58 mmol, 66%) as a slightly yellow gel.
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.0 Hz, 2H), 7.34 (d, *J* = 7.8 Hz, 2H), 7.18 (d, *J* = 7.9 Hz, 2H), 7.14 (d, *J* = 7.7 Hz, 2H), 5.96 (s, 1H), 4.73 (d, *J* = 1.5 Hz, 2H), 3.36 (s, 3H), 2.35 (s, 3H), 2.30 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 196.2, 144.1, 138.6, 133.2, 132.8, 129.8, 129.3, 129.3, 128.1, 95.0, 79.8, 56.1, 21.8, 21.3.
HRMS (ESI): *m/z* for $C_{18}H_{20}O_3Na$ $[M+Na]^+$ calcd.: 307.1305, found: 307.1298.

2-(methoxymethoxy)-1,2-bis(4-methoxyphenyl)ethan-1-one (1j)



The title compound was isolated (1.80 g, 5.70 mmol, 57%) as a slightly yellow gel.
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.95 (d, *J* = 9.0 Hz, 2H), 7.38 (d, *J* = 8.7 Hz, 2H), 6.91 – 6.76 (m, 4H), 5.93 (s, 1H), 4.79 – 4.66 (m, 2H), 3.81 (s, 3H), 3.76 (s, 3H), 3.36 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 195.0, 163.6, 159.9, 131.4, 129.5, 128.4, 128.2, 114.5, 113.8, 94.9, 79.3, 56.0, 55.6, 55.4.
HRMS (ESI): *m/z* for $C_{18}H_{20}O_5Na$ $[M+Na]^+$ calcd.: 339.1203, found: 339.1195.

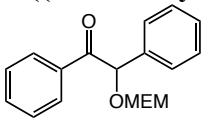
2-(methoxymethoxy)-1-phenyl-2-(thiophen-2-yl)ethan-1-one (1k)



The title compound was isolated (853 mg, 3.26 mmol, 41% based on 8.00 mmol of *α*-hydroxy ketone as the starting material) as a dark crimson gel. The corresponding *α*-hydroxy ketone was prepared according to a published procedure.[17]
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (d, *J* = 7.4 Hz, 2H), 7.54 (t, *J* = 7.4 Hz, 1H), 7.43 (t, *J* = 7.6 Hz, 2H), 7.33 (d, *J* = 5.1 Hz, 1H), 7.07 (d, *J* = 3.7 Hz, 1H), 6.96 (dd, *J* = 5.1, 3.6 Hz, 1H), 6.22 (s, 1H), 4.87 – 4.70 (m, 2H), 3.37 (s, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 195.3, 138.4, 134.8, 133.6, 129.2, 128.7, 127.7, 127.3, 127.3, 95.1, 75.2, 56.3.
HRMS (EI): *m/z* for $C_{14}H_{14}O_3S$ $[M]^+$ calcd.: 262.0664, found: 262.0668.

4) *α*-*O*-MEM ketone (**1c**) was prepared according to a published procedure[19] at a 10-mmol scale.

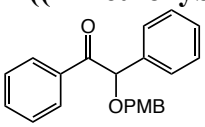
2-((2-methoxyethoxy)methoxy)-1,2-diphenylethan-1-one (1c)



The title compound was isolated (1.90 g, 6.33 mmol, 63%) as a colorless gel.
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.96 (d, *J* = 7.2 Hz, 2H), 7.53 – 7.44 (m, 3H), 7.39 (t, *J* = 7.7 Hz, 2H), 7.34 (t, *J* = 7.4 Hz, 2H), 7.29 (t, *J* = 7.3 Hz, 1H), 6.08 (s, 1H), 4.90 – 4.81 (m, 2H), 3.77 – 3.63 (m, 2H), 3.47 (t, *J* = 4.6 Hz, 2H), 3.34 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 196.6, 136.1, 135.3, 133.3, 129.2, 129.1, 128.8, 128.6, 128.2, 94.2, 80.2, 71.8, 67.6, 59.1.
HRMS (ESI): *m/z* for $C_{18}H_{20}O_4Na$ $[M+Na]^+$ calcd.: 323.1254, found: 323.1250.

5) *α-O*-PMB ketone (**1d**) was prepared according to a published procedure[20] at a 10-mmol scale.

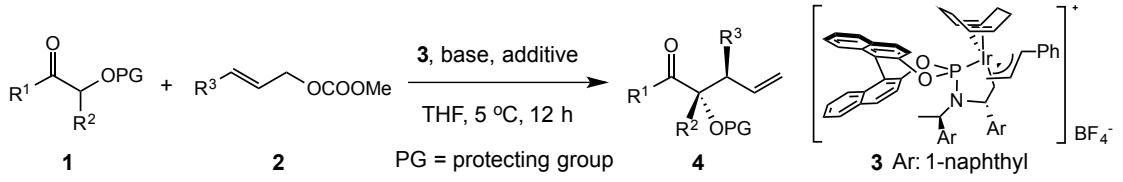
2-((4-methoxybenzyl)oxy)-1,2-diphenylethan-1-one (1d)



The title compound was isolated (1.56 g, 4.70 mmol, 47%) as a white solid.
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.95 (d, *J* = 7.5 Hz, 2H), 7.52 – 7.44 (m, 3H), 7.35 (dt, *J* = 10.8, 7.6 Hz, 4H), 7.32 – 7.21 (m, 3H), 6.91 – 6.83 (m, 2H), 5.64 (s, 1H), 4.65 – 4.52 (m, 2H), 3.81 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 197.6, 159.6, 136.5, 135.2, 133.4, 129.9, 129.5, 129.5, 129.3, 128.9, 128.5, 127.7, 114.0, 83.6, 71.2, 55.4.
HRMS (ESI): *m/z* for $C_{22}H_{20}O_3Na$ $[M+Na]^+$ calcd.: 355.1305, found: 355.1305.

6) Catalyst **3** was prepared according to a literature procedure.[21]

3.4.3 General Procedure for the Ir-Catalyzed Allylation of Acyclic α-Alkoxy Ketones



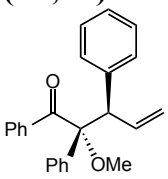
Scheme 3.4 General procedure for allylation

In a nitrogen-filled dry-box, the ketone **1** (0.250 mmol, 2.00 equiv), LHMDS (41.8 mg, 0.250 mmol, 2.00 equiv) and THF (0.20 mL) were added to a 1-dram vial. After stirring the mixture for 5 min at room temperature, CuBr (35.9 mg, 0.250 mmol, 2.00 equiv) was added, and the mixture was stirred for another 30 min at room temperature. The allyl carbonate **2** (0.125 mmol, 1.00 equiv), the catalyst **3** (2.9 mg, 0.0025 mmol, 0.020 equiv) and THF (0.20 mL) were added to another 1-dram vial. In a third 1-dram vial was added THF (approximately 0.2 mL). All the vials were sealed with caps containing PTFE/silicone septa and removed from the dry-box. After cooling all the

solutions to 5 °C, the solution of the copper enolate was transferred into the vial containing the allyl carbonate via syringe (pre-filled with N_2). THF (0.10 mL) in the third vial was used to rinse the vial of the enolate and then transferred into the vial of the allyl carbonate. After being stirred at 5 °C for 12 h, the reaction mixture was filtered through a 2-inch plug of silica gel (eluting with 1:1 hexanes:EtOAc) to remove the salts. The ratio of diastereomers was determined by ^{1}H NMR analysis of crude reaction mixture. The crude mixture was purified by flash column chromatography to give the product.

Generally, the product was obtained as a mixture of two diastereomers unless specified. For characterization, an additional preparative TLC separation was performed to remove the minor diastereomer with the same eluent system as the one used for the corresponding column chromatography.

(2*R*,3*R*)-2-methoxy-1,2,3-triphenylpent-4-en-1-one (4aa)



Prepared according to the general procedure as described above. The diastereomeric ratio was determined to be 14:1. The crude mixture was purified by flash column chromatography (hexane:toluene = 1:1) to give the title compound as a white solid (43.6 mg, 0.127 mmol, >99%; the 2 mol% of catalyst **3** contributed 0.002 mol to the amount of product). The major isomer was isolated as a white solid (39.6 mg, 0.116 mmol, 93%) with a gradient elution (hexane:toluene, 3:1 to 1:1) during column chromatography.

The **enantiomeric excess** was determined by SFC analysis to be 92% (254 nm, 40 °C), t_R = 4.47 min (major), t_R = 3.12 min (minor) [(Chiralcel® OZ-H) 1.5% ^{i}PrOH, 4.0 mL/min].

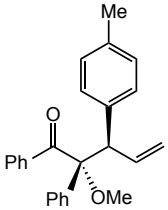
[α]$_D^{25}$ = +111° (c 0.72, CH_2Cl_2).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 – 7.82 (m, 2H), 7.42 – 7.32 (m, 1H), 7.31 – 7.19 (m, 2H), 7.19 – 7.09 (m, 3H), 7.10 – 6.96 (m, 5H), 6.92 – 6.85 (m, 2H), 6.39 (ddd, *J* = 17.0, 10.4, 8.4 Hz, 1H), 5.19 – 5.05 (m, 2H), 4.70 (d, *J* = 8.4 Hz, 1H), 3.41 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 199.3, 139.9, 139.1, 137.8, 135.8, 132.5, 131.0, 130.2, 128.1, 127.5, 127.5, 127.3, 127.1, 126.2, 116.9, 90.2, 54.7, 54.1.

HRMS (EI): *m/z* for $C_{23}H_{19}O$ [M−MeO]$^+$ calcd.: 311.1436, found: 311.1403.

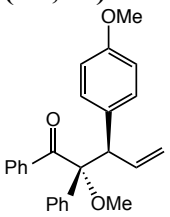
(2*R*,3*R*)-2-methoxy-1,2-diphenyl-3-(*p*-tolyl)pent-4-en-1-one (4ab)



Prepared according to the general procedure as described above. The diastereomeric ratio was determined to be 17:1. The crude mixture was purified by flash column chromatography (hexane:toluene = 1:1) to give the title compound as a colorless oil (44.1 mg, 0.124 mmol, 99%).

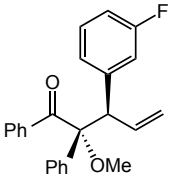
The **enantiomeric excess** was determined by SFC analysis to be 93% (254 nm, 40 °C), t_R = 2.35 min (major), t_R = 1.79 min (minor) [(Chiralcel® OZ-H) 3.0% ^{i}PrOH, 4.0 mL/min].
$[\alpha]_D^{25}$ = +82.8° (c 0.83, CH_2Cl_2).
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 – 7.84 (m, 2H), 7.43 – 7.36 (m, 1H), 7.30 – 7.22 (m, 2H), 7.22 – 7.10 (m, 3H), 7.11 – 7.00 (m, 2H), 6.90 (d, *J* = 7.9 Hz, 2H), 6.76 (d, *J* = 8.0 Hz, 2H), 6.37 (ddd, *J* = 16.7, 10.6, 8.6 Hz, 1H), 5.22 – 5.05 (m, 2H), 4.69 (d, *J* = 8.6 Hz, 1H), 3.42 (s, 3H), 2.25 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 199.2, 138.9, 137.8, 136.8, 135.8, 135.5, 132.3, 130.7, 130.1, 127.9, 127.8, 127.3, 127.3, 127.1, 116.4, 89.9, 54.0, 53.7, 20.9.
HRMS (EI): *m/z* for $C_{24}H_{21}O$ $[M-MeO]^+$ calcd.: 325.1592, found: 325.1559.

(2*R*,3*R*)-2-methoxy-3-(4-methoxyphenyl)-1,2-diphenylpent-4-en-1-one (4ac)



Prepared according to the general procedure, as described above. The diastereomeric ratio was determined to be >20:1. The crude mixture was purified by flash column chromatography (hexane:toluene, 1:1 to 1:2) to give the title compound as a slightly yellow oil (46.0 mg, 0.124 mmol, 99%).
The **enantiomeric excess** was determined by SFC analysis to be 95% (254 nm, 40 °C), t_R = 4.39 min (major), t_R = 3.55 min (minor) [(Chiralcel® OZ-H) 4.0% ^{i}PrOH, 2.5 mL/min].
$[\alpha]_D^{25}$ = +55.4° (c 0.70, CH_2Cl_2).
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 – 7.78 (m, 2H), 7.41 – 7.29 (m, 1H), 7.29 – 7.18 (m, 2H), 7.18 – 7.07 (m, 3H), 7.07 – 6.94 (m, 2H), 6.80 – 6.69 (m, 2H), 6.65 – 6.54 (m, 2H), 6.32 (ddd, *J* = 17.3, 11.1, 8.5 Hz, 1H), 5.16 – 5.04 (m, 2H), 4.64 (d, *J* = 8.3 Hz, 1H), 3.70 (d, *J* = 2.1 Hz, 3H), 3.37 (d, *J* = 2.0 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 199.4, 157.9, 139.1, 138.0, 135.9, 132.5, 132.1, 132.0, 130.3, 128.1, 127.5, 127.4, 127.2, 116.6, 112.7, 90.0, 55.2, 53.8, 53.6.
HRMS (EI): *m/z* for $C_{25}H_{24}O_3$ $[M]^+$ calcd.: 372.1725, found: 372.1725.

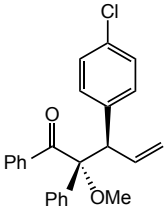
(2*R*,3*R*)-3-(3-fluorophenyl)-2-methoxy-1,2-diphenylpent-4-en-1-one (4ad)



Prepared according to the general procedure as described above. The diastereomeric ratio was determined to be >20:1. The crude mixture was purified by flash column chromatography (hexane:toluene, 3:1 to 1:1) to give the title compound as a white solid (45.4 mg, 0.125 mmol, >99%).
The **enantiomeric excess** was determined by SFC analysis to be 92% (254 nm, 40 °C), t_R = 2.17 min (major), t_R = 1.62 min (minor) [(Chiralcel® OZ-H) 2.0% ^{i}PrOH, 4.0 mL/min].
$[\alpha]_D^{25}$ = +104° (c 0.68, CH_2Cl_2).

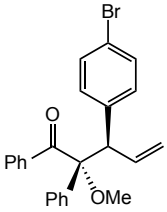
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 – 7.82 (m, 2H), 7.42 – 7.32 (m, 1H), 7.29 – 7.19 (m, 2H), 7.19 – 7.07 (m, 3H), 7.08 – 6.92 (m, 3H), 6.79 – 6.70 (m, 1H), 6.69 – 6.62 (m, 1H), 6.62 – 6.52 (m, 1H), 6.34 (ddd, *J* = 17.0, 10.3, 8.3 Hz, 1H), 5.21 – 5.05 (m, 2H), 4.69 (d, *J* = 8.3 Hz, 1H), 3.40 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 199.0, 162.1(d, *J* = 243.4 Hz), 142.5 (d, *J* = 7.3 Hz), 138.9, 137.3, 135.6, 132.7, 130.3, 128.5 (d, *J* = 8.2 Hz), 128.2, 127.7, 126.8, 126.7 (d, *J* = 2.7 Hz), 117.8 (d, *J* = 21.9 Hz), 117.3, 113.0 (d, *J* = 21.0 Hz), 90.1, 54.4, 54.2.
HRMS (EI): *m/z* for $C_{17}H_{16}FO$ $[M-PhCO]^+$ calcd.: 255.1185, found: 255.1187.

(2*R*,3*R*)-3-(4-chlorophenyl)-2-methoxy-1,2-diphenylpent-4-en-1-one (4ae)



Prepared according to the general procedure as described above. The diastereomeric ratio was determined to be 17:1. The crude mixture was purified by flash column chromatography (hexane:toluene = 1:1) to give the title compound as a white solid (45.2 mg, 0.120 mmol, 96%).
The **enantiomeric excess** was determined by SFC analysis to be 93% (254 nm, 40 °C), t_R = 4.35 min (major), t_R = 3.35 min (minor) [(Chiralcel® OZ-H) 3.0% ^{i}PrOH, 2.5 mL/min].
$[\alpha]_D^{25}$ = +62.0° (c 0.87, CH_2Cl_2).
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.91 – 7.81 (m, 2H), 7.40 – 7.33 (m, 1H), 7.27 – 7.20 (m, 2H), 7.20 – 7.09 (m, 3H), 7.05 – 6.96 (m, 4H), 6.82 – 6.71 (m, 2H), 6.34 (ddd, *J* = 17.1, 10.4, 8.3 Hz, 1H), 5.21 – 5.04 (m, 2H), 4.68 (d, *J* = 8.3 Hz, 1H), 3.40 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 199.1, 138.9, 138.6, 137.4, 135.6, 132.7, 132.4, 132.0, 130.3, 128.2, 127.7, 127.7, 127.4, 127.0, 117.2, 89.9, 54.0, 53.8.
HRMS (EI): *m/z* for $C_{17}H_{16}ClO$ $[M-PhCO]^+$ calcd.: 279.0890, found: 279.0891.

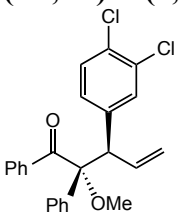
(2*R*,3*R*)-3-(4-bromophenyl)-2-methoxy-1,2-diphenylpent-4-en-1-one (4af)



Prepared according to the general procedure as described above. The diastereomeric ratio was determined to be >20:1. The crude mixture was purified by flash column chromatography (hexane:toluene = 1:1) to give the title compound as a white solid (52.6 mg, 0.125 mmol, >99%).
The **enantiomeric excess** was determined by SFC analysis to be 91% (254 nm, 40 °C), t_R = 5.50 min (major), t_R = 4.18 min (minor) [(Chiralcel® OZ-H) 3.0% ^{i}PrOH, 2.5 mL/min].
$[\alpha]_D^{25}$ = +44.2° (c 0.74, CH_2Cl_2).
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.3 Hz, 2H), 7.43 – 7.34 (m, 1H), 7.30 – 7.21 (m, 2H), 7.21 – 7.08 (m, 5H), 7.02 (d, *J* = 7.5 Hz, 2H), 6.73 (d, *J* = 8.2 Hz, 2H), 6.34 (ddd, *J* = 17.4, 10.3, 8.4 Hz, 1H), 5.20 – 5.06 (m, 2H), 4.67 (d, *J* = 8.3 Hz, 1H), 3.40 (s, 3H).

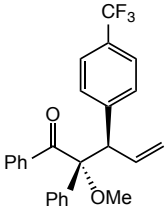
^{13}C NMR (151 MHz, $CDCl_3$) δ 199.1, 139.2, 138.8, 137.4, 135.6, 132.8, 132.7, 130.4, 130.3, 128.2, 127.7, 127.7, 127.0, 120.3, 117.2, 89.9, 53.9, 53.8.
HRMS (EI): *m/z* for $C_{17}H_{16}BrO$ $[M-PhCO]^+$ calcd.: 315.0385, found: 315.0388.

(2*R*,3*R*)-3-(3,4-dichlorophenyl)-2-methoxy-1,2-diphenylpent-4-en-1-one (4ag)



Prepared according to the general procedure as described above. The diastereomeric ratio was determined to be 15:1. The crude mixture was purified by flash column chromatography (hexane:toluene = 1:1) to give the title compound as a white solid (47.0 mg, 0.114 mmol, 91%,).
The **enantiomeric excess** was determined by SFC analysis to be 89% (254 nm, 40 °C), t_R = 4.73 min (major), t_R = 3.48 min (minor) [(Chiralcel® OZ-H) 2.0% ^{i}PrOH, 4.0 mL/min].
$[\alpha]_D^{25}$ = +58.1° (c 0.72, CH_2Cl_2).
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 – 7.75 (m, 2H), 7.45 – 7.34 (m, 1H), 7.28 – 7.13 (m, 5H), 7.11 (d, *J* = 8.4 Hz, 1H), 7.05 – 6.98 (m, 2H), 6.87 (d, *J* = 2.1 Hz, 1H), 6.70 (dd, *J* = 8.4, 2.1 Hz, 1H), 6.29 (ddd, *J* = 17.1, 10.3, 8.4 Hz, 1H), 5.24 – 5.06 (m, 2H), 4.66 (d, *J* = 8.4 Hz, 1H), 3.39 (s, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 198.9, 140.5, 138.5, 136.8, 135.3, 133.0, 132.9, 131.0, 130.6, 130.3, 130.1, 129.0, 128.2, 127.9, 127.8, 127.0, 117.7, 89.6, 53.8, 53.3.
HRMS (EI): *m/z* for $C_{17}H_{15}Cl_2O$ $[M-PhCO]^+$ calcd.: 305.0500, found: 305.0502.
If 0.50 equivalent of CuBr was employed, the title compound was isolated (47.3 mg, 0.115 mmol, 92%, 12:1 *dr*), and *ee* was determined to be 96%.

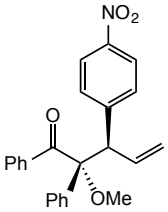
(2*R*,3*R*)-2-methoxy-1,2-diphenyl-3-(4-(trifluoromethyl)phenyl)pent-4-en-1-one (4ah)



Prepared according to the general procedure as described above. The diastereomeric ratio was determined to be 11:1. The crude mixture was purified by flash column chromatography (hexane:toluene = 1:1) to give the title compound as a colorless oil (51.5 mg, 0.125 mmol, >99%).
The **enantiomeric excess** was determined by SFC analysis to be 90% (254 nm, 40 °C), t_R = 1.86 min (major), t_R = 1.49 min (minor) [(Chiralcel® OZ-H) 3.0% ^{i}PrOH, 2.5 mL/min].
$[\alpha]_D^{25}$ = +84.3° (c 0.82, CH_2Cl_2).
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.3 Hz, 2H), 7.42 – 7.33 (m, 1H), 7.30 (d, *J* = 8.1 Hz, 2H), 7.27 – 7.20 (m, 2H), 7.20 – 7.07 (m, 3H), 7.05 – 6.89 (m, 4H), 6.36 (ddd, *J* = 17.0, 10.4, 8.5 Hz, 1H), 5.22 – 5.05 (m, 2H), 4.76 (d, *J* = 8.4 Hz, 1H), 3.41 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 199.0, 144.4, 138.7, 137.1, 135.5, 132.8, 131.4, 130.3, 128.4 (q, *J* = 32.2 Hz), 128.2, 127.8, 127.7, 127.0, 124.4 (q, *J* = 271.8 Hz), 124.1 (q, *J* = 3.8 Hz), 117.6, 90.0, 54.3, 54.0.

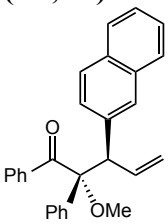
HRMS (EI): *m/z* for $C_{24}H_{18}F_3O$ $[M-MeO]^+$ calcd.: 379.1310, found: 379.1304.

(2*R*,3*R*)-2-methoxy-3-(4-nitrophenyl)-1,2-diphenylpent-4-en-1-one (4ai)



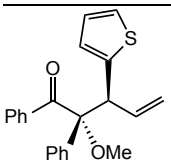
Prepared according to the general procedure as described above. The diastereomeric ratio was determined to be 10:1. The crude mixture was purified by flash column chromatography (hexane:toluene = 1:1) to give the title compound as a colorless oil (45.4 mg, 0.117 mmol, 94%).
The **enantiomeric excess** was determined by SFC analysis to be 94% (254 nm, 40 °C), t_R = 12.77 min (major), t_R = 11.95 min (minor) [(Chiralpak® AD-H) 5.0% *i*PrOH, 1.5 mL/min].
$[\alpha]_D^{25}$ = +43.4° (c 0.42, CH_2Cl_2).
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.91 – 7.84 (m, 4H), 7.41 – 7.35 (m, 1H), 7.26 – 7.20 (m, 2H), 7.20 – 7.15 (m, 1H), 7.15 – 7.10 (m, 2H), 7.03 – 6.95 (m, 4H), 6.35 (ddd, *J* = 17.1, 10.3, 8.3 Hz, 1H), 5.20 (d, *J* = 10.4 Hz, 1H), 5.11 (d, *J* = 17.1 Hz, 1H), 4.81 (d, *J* = 8.4 Hz, 1H), 3.42 (s, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 198.8, 148.2, 146.3, 138.5, 136.5, 135.1, 133.0, 131.9, 130.3, 128.3, 128.0, 127.9, 126.8, 122.4, 118.1, 89.9, 54.3, 54.1.
HRMS (EI): *m/z* for $C_{17}H_{16}NO_3$ $[M-PhCO]^+$ calcd.: 282.1130, found: 282.1130.

(2*R*,3*R*)-2-methoxy-3-(naphthalen-2-yl)-1,2-diphenylpent-4-en-1-one (4aj)



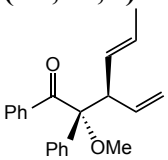
Prepared according to the general procedure as described above. The diastereomeric ratio was determined to be 13:1. The crude mixture was purified by flash column chromatography (hexane:toluene, 2:1 to 1:1) to give the title compound as a colorless oil (48.1 mg, 0.123 mmol, 98%).
The **enantiomeric excess** was determined by SFC analysis to be 93% (254 nm, 40 °C), t_R = 5.38 min (major), t_R = 4.49 min (minor) [(Chiralcel® OZ-H) 5.0% *i*PrOH, 2.5 mL/min].
$[\alpha]_D^{25}$ = +8.70° (c 0.44, CH_2Cl_2).
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.91 (d, *J* = 7.9 Hz, 2H), 7.75 – 7.68 (m, 1H), 7.65 – 7.58 (m, 1H), 7.54 (d, *J* = 8.5 Hz, 1H), 7.41 – 7.34 (m, 3H), 7.31 (s, 1H), 7.27 – 7.19 (m, 2H), 7.19 – 7.13 (m, 1H), 7.13 – 7.02 (m, 4H), 6.99 (d, *J* = 8.5 Hz, 1H), 6.48 (ddd, *J* = 18.0, 9.4, 8.5 Hz, 1H), 5.17 (m, 2H), 4.91 (d, *J* = 8.5 Hz, 1H), 3.47 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 199.1, 139.0, 137.8, 137.7, 135.8, 133.0, 132.6, 132.2, 130.3, 130.2, 129.4, 128.1, 128.0, 127.6, 127.5, 127.4, 127.3, 126.3, 125.5, 125.4, 117.0, 90.1, 54.3, 53.8.
HRMS (EI): *m/z* for $C_{28}H_{24}O_2$ $[M]^+$ calcd.: 392.1776, found: 392.1775.

(2*R*,3*S*)-2-methoxy-1,2-diphenyl-3-(thiophen-2-yl)pent-4-en-1-one (4ak)



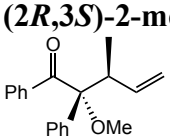
Prepared according to the general procedure as described above. The diastereomeric ratio was determined to be >20:1. The crude mixture was purified by flash column chromatography (hexane:toluene = 1:1) to give the title compound as a white solid (43.5 mg, 0.125 mmol, >99%).
The **enantiomeric excess** was determined by SFC analysis to be 92% (254 nm, 40 °C), t_R = 3.97 min (major), t_R = 3.10 min (minor) [(Chiralcel® OZ-H) 2.0% *i*PrOH, 4.0 mL/min].
[α]$_D^{25}$ = +150° (c 0.44, CH_2Cl_2).
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 – 7.85 (m, 2H), 7.38 (td, *J* = 7.4, 1.4 Hz, 1H), 7.30 – 7.18 (m, 2H), 7.16 – 7.08 (m, 5H), 7.05 (dd, *J* = 5.1, 1.2 Hz, 1H), 6.72 (dd, *J* = 5.1, 3.5 Hz, 1H), 6.44 (d, *J* = 3.5 Hz, 1H), 6.29 (ddd, *J* = 17.1, 10.3, 8.4 Hz, 1H), 5.25 – 5.12 (m, 2H), 5.01 (d, *J* = 8.4 Hz, 1H), 3.38 (s, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 199.0, 142.2, 139.1, 137.2, 135.5, 132.7, 130.3, 128.2, 127.6, 127.5, 127.2, 126.6, 125.8, 124.4, 117.2, 89.8, 54.1, 49.9.
HRMS (EI): *m/z* for $C_{22}H_{20}O_2S$ $[M]^+$ calcd.: 348.1184, found: 348.1176.

(2*R*,3*R*,*E*)-2-methoxy-1,2-diphenyl-3-vinylhex-4-en-1-one (4al)



Prepared according to the general procedure as described above. The diastereomeric ratio was determined to be >20:1. The crude mixture was purified by flash column chromatography (hexane:toluene = 1:1) and then preparative TLC (hexanes:EtOAc = 10:1) to give the title compound as a colorless oil (28.6 mg, 0.093 mmol, 75%).
The **enantiomeric excess** was determined by SFC analysis to be 94% (254 nm, 40 °C), t_R = 5.33 min (major), t_R = 3.44 min (minor) [(Chiralcel® OZ-H) 1.0% *i*PrOH, 2.5 mL/min].
[α]$_D^{25}$ = +148° (c 0.72, CH_2Cl_2).
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.89 (d, *J* = 7.2 Hz, 2H), 7.38 (t, *J* = 7.4 Hz, 1H), 7.33 – 7.17 (m, 7H), 5.86 (ddd, *J* = 16.8, 10.9, 8.1 Hz, 1H), 5.39 – 5.31 (m, 1H), 5.19 (ddq, *J* = 15.4, 7.4, 1.6 Hz, 1H), 5.15 – 5.10 (m, 2H), 4.04 (t, *J* = 7.7 Hz, 1H), 3.30 (s, 3H), 1.57 (d, *J* = 4.7 Hz, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 199.2, 138.8, 136.8, 135.7, 132.5, 130.3, 129.4, 128.1, 128.0, 127.5, 127.4, 127.2, 116.6, 88.7, 52.7, 50.0, 18.3.
HRMS (EI): *m/z* for $C_{20}H_{19}O$ $[M-MeO]^+$ calcd.: 275.1436, found: 275.1425.

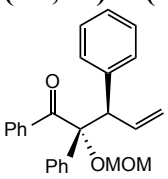
(2*R*,3*S*)-2-methoxy-3-methyl-1,2-diphenylpent-4-en-1-one (4am)



Prepared according to the general procedure as described above. The diastereomeric ratio was determined to be 8:1. The crude mixture was purified by flash column chromatography (hexane:toluene, 2:1 to 1:1) to give the title compound as a colorless oil (24.9 mg, 0.089 mmol, 71%).

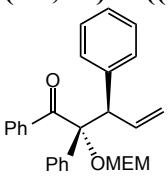
The **enantiomeric excess** was determined by SFC analysis to be 88% (254 nm, 40 °C), t_R = 3.75 min (major), t_R = 2.93 min (minor) [(Chiralcel® OD-H) 0.5% *i*PrOH, 4.0 mL/min].
$[\alpha]_D^{25}$ = +119° (c 0.27, CH_2Cl_2).
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.92 – 7.88 (m, 2H), 7.41 – 7.35 (m, 1H), 7.33 – 7.21 (m, 7H), 5.88 (ddd, *J* = 17.3, 10.4, 7.9 Hz, 1H), 5.11 – 5.01 (m, 2H), 3.51 – 3.42 (m, 1H), 3.27 (s, 3H), 0.90 (d, *J* = 6.8 Hz, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 199.7, 139.2, 138.8, 135.6, 132.6, 130.4, 128.1, 127.7, 127.5, 127.1, 115.2, 89.1, 52.6, 40.5, 17.0.
HRMS (EI): *m/z* for $C_{18}H_{17}O$ $[M-MeO]^+$ calcd.: 249.1279, found: 249.1281.

(2*R*,3*R*)-2-(methoxymethoxy)-1,2,3-triphenylpent-4-en-1-one (4ba)



Prepared according to the general procedure as described above except that 4 mol% of **3** (0.040 equiv) was used. The diastereomeric ratio was determined to be 10:1. The crude mixture was purified by flash column chromatography (hexane:toluene = 1:1) to give the title compound as a colorless oil (47.3 mg, 0.127 mmol, >99%).
The **enantiomeric excess** was determined by SFC analysis to be 90% (254 nm, 40 °C), t_R = 3.72 min (major), t_R = 2.54 min (minor) [(Chiralcel® OZ-H) 5.0% *i*PrOH, 2.5 mL/min].
$[\alpha]_D^{25}$ = +90.6° (c 0.47, CH_2Cl_2).
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.81 – 7.76 (m, 2H), 7.38 – 7.33 (m, 1H), 7.24 – 7.19 (m, 2H), 7.17 – 7.10 (m, 3H), 7.07 – 7.01 (m, 5H), 6.93 – 6.88 (m, 2H), 6.42 (ddd, *J* = 17.0, 10.3, 8.8 Hz, 1H), 5.23 – 5.15 (m, 2H), 4.91 (d, *J* = 6.2 Hz, 1H), 4.78 (d, *J* = 6.2 Hz, 1H), 4.72 (d, *J* = 8.8 Hz, 1H), 3.25 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 198.6, 139.8, 139.1, 137.6, 135.8, 132.3, 130.9, 130.6, 127.9, 127.6, 127.6, 127.4, 126.8, 126.2, 117.8, 94.4, 89.6, 57.0, 55.6.
HRMS (EI): *m/z* for $C_{24}H_{21}O_2$ $[M-MeO]^+$ calcd.: 341.1542, found: 341.1544.

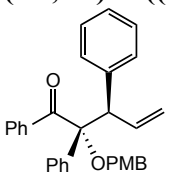
(2*R*,3*R*)-2-((2-methoxyethoxy)methoxy)-1,2,3-triphenylpent-4-en-1-one (4ca)



Prepared according to the general procedure as described above except that 1.00 equivalent of CuBr was used. The diastereomeric ratio was determined to be 19:1. The crude mixture was purified by flash column chromatography (hexane:EtOAc = 15:1 to 8:1) to give the title compound as a colorless gel (52.6 mg, 0.126 mmol, >99%).
The **enantiomeric excess** was determined by SFC analysis to be 98% (254 nm, 40 °C), t_R = 3.40 min (major), t_R = 3.01 min (minor) [(Chiralcel® OZ-H) 6.0% *i*PrOH, 2.5 mL/min].
$[\alpha]_D^{25}$ = +78.9° (c 0.53, CH_2Cl_2).

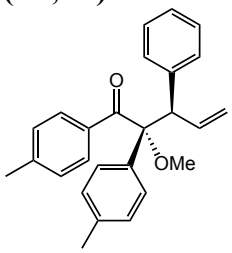
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.0 Hz, 2H), 7.34 (t, *J* = 7.4 Hz, 1H), 7.20 (t, *J* = 7.8 Hz, 2H), 7.18 – 7.08 (m, 3H), 7.07 – 7.00 (m, 5H), 6.92 – 6.87 (m, 2H), 6.41 (ddd, *J* = 17.0, 10.3, 8.9 Hz, 1H), 5.23 – 5.14 (m, 2H), 5.02 (d, *J* = 6.4 Hz, 1H), 4.89 (d, *J* = 6.5 Hz, 1H), 4.74 (d, *J* = 8.9 Hz, 1H), 3.67 (ddd, *J* = 10.4, 6.7, 3.3 Hz, 1H), 3.40 (ddd, *J* = 10.7, 5.8, 3.3 Hz, 1H), 3.29 (s, 4H), 3.22 (ddd, *J* = 10.5, 6.6, 3.3 Hz, 1H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 198.2, 139.8, 139.0, 137.5, 135.6, 132.3, 130.9, 130.6, 127.9, 127.6, 127.6, 127.3, 126.8, 126.2, 117.8, 93.2, 89.4, 71.5, 68.7, 59.2, 55.2.
HRMS (ESI): *m/z* for $C_{27}H_{28}O_4Na$ $[M+Na]^+$ calcd.: 439.1880, found: 439.1870.

(2*R*,3*R*)-2-((4-methoxybenzyl)oxy)-1,2,3-triphenylpent-4-en-1-one (4da)



Prepared according to the general procedure as described. The diastereomeric ratio was determined to be 15:1. The crude mixture was purified by flash column chromatography (hexane:toluene = 2:1 to 1:1) to give the title compound as a colorless gel (55.5 mg, 0.124 mmol, 99%).
The **enantiomeric excess** was determined by SFC analysis to be 90% (254 nm, 40 °C), t_R = 2.71 min (major), t_R = 2.18 min (minor) [(Chiralcel® OZ-H) 6.0% ^{i}PrOH, 4.0 mL/min].
$[\alpha]_D^{25}$ = +24.5° (c 0.58, CH_2Cl_2).
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (d, *J* = 7.9 Hz, 2H), 7.37 (t, *J* = 7.4 Hz, 1H), 7.23 – 7.14 (m, 3H), 7.13 – 6.99 (m, 9H), 6.93 – 6.85 (m, 2H), 6.82 (d, *J* = 8.6 Hz, 2H), 6.47 (ddd, *J* = 16.9, 10.3, 8.4 Hz, 1H), 5.25 – 5.11 (m, 2H), 4.93 (d, *J* = 9.7 Hz, 1H), 4.87 (d, *J* = 8.6 Hz, 1H), 4.22 (d, *J* = 9.7 Hz, 1H), 3.80 (s, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 199.4, 159.2, 140.2, 139.0, 137.9, 135.6, 132.6, 131.2, 130.4, 130.0, 129.7, 128.0, 127.5, 127.4, 127.3, 127.2, 126.2, 116.9, 113.7, 89.2, 66.6, 55.4, 54.2.
HRMS (ESI): *m/z* for $C_{31}H_{29}O_3$ $[M+H]^+$ calcd.: 449.2111, found: 449.2106.

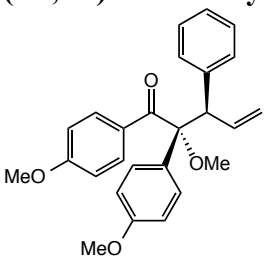
(2*R*,3*R*)-2-methoxy-3-phenyl-1,2-di-*p*-tolylpent-4-en-1-one (4ea)



Prepared according to the general procedure as described above except that 0.50 equivalent of CuBr was employed. The diastereomeric ratio was determined to be 19:1. The crude mixture was purified by flash column chromatography (hexane:ether = 10:1) to give the title compound as a colorless gel (44.3 mg, 0.120 mmol, 95%).
The **enantiomeric excess** was determined by SFC analysis to be 97% (254 nm, 40 °C), t_R = 8.23 min (major), t_R = 6.90 min (minor) [(Chiralcel® OD-H) 1.5% ^{i}PrOH, 4.0 mL/min].
$[\alpha]_D^{25}$ = +73.8° (c 0.80, CH_2Cl_2).

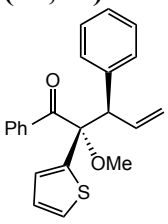
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.3 Hz, 2H), 7.10 – 7.00 (m, 5H), 6.96 – 6.82 (m, 6H), 6.37 (ddd, *J* = 17.0, 10.4, 8.4 Hz, 1H), 5.18 – 5.00 (m, 2H), 4.66 (d, *J* = 8.5 Hz, 1H), 3.38 (s, 3H), 2.29 (s, 3H), 2.26 (s, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 199.0, 143.2, 140.2, 138.1, 137.0, 136.2, 133.3, 131.1, 130.4, 128.8, 128.2, 127.2, 127.0, 126.1, 116.6, 90.0, 54.6, 53.9, 21.7, 21.2.
HRMS (EI): *m/z* for $C_{18}H_{19}O$ $[M-4\text{-Me-PhO}]^+$ calcd.: 251.1436, found: 251.1433.

(2*R*,3*R*)-2-methoxy-1,2-bis(4-methoxyphenyl)-3-phenylpent-4-en-1-one (4fa)



Prepared according to the general procedure as described above, except that 3.00 equivalents of the ketone, LHMDS and CuBr were employed. The diastereomeric ratio was determined to be >20:1. The crude mixture was purified by flash column chromatography (hexane:toluene = 1:2.5) to give the title compound as a colorless oil (43.5 mg, 0.108 mmol, 87%).
The **enantiomeric excess** was determined by SFC analysis to be 87% (254 nm, 40 °C), t_R = 2.55 min (major), t_R = 5.31 min (minor) [(Chiralpak® AD-H) 10.0% ^{i}PrOH, 4.0 mL/min].
$[\alpha]_D^{25}$ = +63.3° (c 0.78, CH_2Cl_2).
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.89 (d, *J* = 9.0 Hz, 2H), 7.09 – 7.03 (m, 3H), 6.93 (d, *J* = 8.3 Hz, 2H), 6.87 (dd, *J* = 6.6, 3.0 Hz, 2H), 6.71 (d, *J* = 9.1 Hz, 2H), 6.66 (d, *J* = 8.8 Hz, 2H), 6.36 (ddd, *J* = 17.0, 10.3, 8.5 Hz, 1H), 5.16 – 5.05 (m, 2H), 4.66 (d, *J* = 8.5 Hz, 1H), 3.77 (s, 3H), 3.74 (s, 3H), 3.38 (s, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 197.9, 162.9, 158.8, 140.3, 138.1, 132.7, 131.6, 131.1, 128.6, 128.3, 127.2, 126.1, 116.5, 113.2, 112.8, 89.6, 55.4, 55.2, 54.5, 53.7.
HRMS (EI): *m/z* for $C_{25}H_{23}O_3$ $[M-MeO]^+$ calcd.: 371.1647, found: 371.1623.
If 0.50 equivalent of CuBr, 2.00 equivalents of the ketone and LHMDS were employed, the title compound was isolated (42.2 mg, 0.105 mmol, 84%, 15:1 *dr*), and *ee* was determined to be 94%.

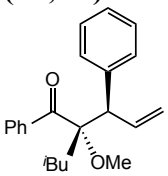
(2*S*,3*R*)-2-methoxy-1,3-diphenyl-2-(thiophen-2-yl)pent-4-en-1-one (4ga)



Prepared according to the general procedure as described above except that 1.00 equivalent of CuBr was employed. The diastereomeric ratio was determined to be 15:1. The crude mixture was purified by flash column chromatography (hexane:EtOAc = 20:1) to give the title compound as a slightly yellow solid (43.8 mg, 0.126 mmol, >99%).

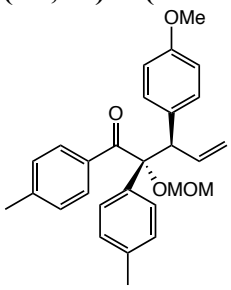
The **enantiomeric excess** was determined by SFC analysis to be 96% (254 nm, 40 °C), t_R = 5.29 min (major), t_R = 5.92 min (minor) [(Chiralpak® AD-H) 4.0% ^{i}PrOH, 2.5 mL/min].
$[\alpha]_D^{25}$ = +32.5° (c 0.26, CH_2Cl_2).
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 (d, *J* = 6.9 Hz, 2H), 7.48 (t, *J* = 7.4 Hz, 1H), 7.34 (t, *J* = 7.7 Hz, 2H), 7.24 (dd, *J* = 5.1, 1.1 Hz, 1H), 7.17 – 7.09 (m, 3H), 6.96 – 6.89 (m, 2H), 6.84 (dd, *J* = 5.0, 3.7 Hz, 1H), 6.58 (dd, *J* = 3.7, 1.1 Hz, 1H), 6.44 (ddd, *J* = 17.1, 10.3, 8.5 Hz, 1H), 5.14 (d, *J* = 10.2 Hz, 1H), 5.06 (d, *J* = 17.0 Hz, 1H), 4.47 (d, *J* = 8.5 Hz, 1H), 3.23 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 199.79, 141.11, 139.26, 137.02, 136.40, 132.76, 130.54, 130.12, 128.30, 127.71, 127.57, 126.92, 126.21, 125.80, 117.75, 91.01, 58.52, 54.78.
HRMS (EI): *m/z* for $C_{21}H_{17}OS$ $[M-MeO]^+$ calcd.: 317.1000, found: 317.0984.

(2*S*,3*R*)-2-isobutyl-2-methoxy-1,3-diphenylpent-4-en-1-one (4ha)



Prepared according to the general procedure as described above except that 4 mol% of the catalyst was employed, cinnamyl acetate was used instead of cinnamyl methyl carbonate, and the reaction time was lengthened to 36 h. The diastereomeric ratio was determined to be 6:1. The crude mixture was purified by flash column chromatography (hexane:toluene = 2:1) to give the title compound as a slightly yellow gel (as a single diastereomer, 30.0 mg, 0.093 mmol, 74%).
The **enantiomeric excess** was determined by SFC analysis to be >99% (254 nm, 40 °C), t_R = 2.75 min (major), t_R = 3.28 min (minor) [(Chiralcel® OZ-H) 1.0% ^{i}PrOH, 4.0 mL/min].
$[\alpha]_D^{25}$ = −40.7° (c 0.30, CH_2Cl_2).
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.0 Hz, 2H), 7.35 – 7.29 (m, 1H), 7.20 – 7.08 (m, 7H), 6.53 (dt, *J* = 16.8, 9.7 Hz, 1H), 5.17 – 5.03 (m, 2H), 3.88 (d, *J* = 9.4 Hz, 1H), 3.40 (s, 3H), 2.05 (dd, *J* = 15.1, 8.3 Hz, 1H), 1.85 – 1.69 (m, 2H), 0.90 (d, *J* = 6.7 Hz, 3H), 0.80 (d, *J* = 6.5 Hz, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 206.2, 140.4, 138.8, 137.7, 131.5, 130.0, 129.6, 128.3, 127.3, 126.9, 117.1, 91.4, 55.7, 51.1, 43.6, 24.6, 23.9, 23.8.
HRMS (ESI): *m/z* for $C_{22}H_{27}O_2$ $[M+H]^+$ calcd.: 323.2006, found: 323.1999.

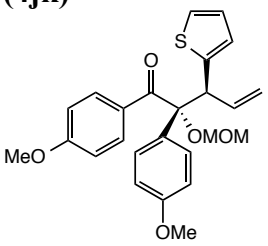
(2*R*,3*R*)-2-(methoxymethoxy)-3-(4-methoxyphenyl)-1,2-di-*p*-tolylpent-4-en-1-one (4ic)



Prepared according to the general procedure as described above except that 1.00 equiv of CuBr was used. The diastereomeric ratio was determined to be 11:1. The crude mixture was purified by column chromatography (Combiflash® system, 12-gram column, 100/0 to 85/15 hexanes/EtOAc) to give the title compound as a colorless gel (51.2 mg, 0.120 mmol, 95%).

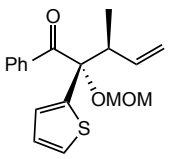
The **enantiomeric excess** was determined by SFC analysis to be 94% (254 nm, 40 °C), t_R = 5.64 min (major), t_R = 4.27 min (minor) [(Chiralcel® OZ-H) 4.0% *i*PrOH, 4.0 mL/min].
$[\alpha]_D^{25}$ = +45.7° (c 0.51, CH_2Cl_2).
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.0 Hz, 2H), 7.01 (d, *J* = 7.9 Hz, 2H), 6.96 – 6.89 (m, 4H), 6.82 (d, *J* = 8.6 Hz, 2H), 6.60 (d, *J* = 8.5 Hz, 2H), 6.41 – 6.29 (m, 1H), 5.18 – 5.07 (m, 2H), 4.88 (d, *J* = 6.1 Hz, 1H), 4.75 (d, *J* = 6.1 Hz, 1H), 4.64 (d, *J* = 8.8 Hz, 1H), 3.72 (s, 3H), 3.24 (s, 3H), 2.34 – 2.04 (m, 6H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 198.3, 157.9, 142.9, 138.0, 137.0, 136.2, 133.1, 132.2, 131.9, 130.7, 128.6, 128.3, 126.9, 117.2, 112.6, 94.1, 89.2, 57.0, 55.2, 54.4, 21.7, 21.2.
HRMS (ESI): *m/z* for $C_{28}H_{30}O_4Na$ $[M+Na]^+$ calcd.: 453.2036, found: 453.2025.

(2*R*,3*S*)-2-(methoxymethoxy)-1,2-bis(4-methoxyphenyl)-3-(thiophen-2-yl)pent-4-en-1-one (4jk)



Prepared according to the general procedure as described. The diastereomeric ratio was determined to be 7:1. The crude mixture was purified by flash column chromatography (hexane:EtOAc = 15:1 to 8:1) to give the title compound as a colorless gel (51.0 mg, 0.116 mmol, 93%).
The **enantiomeric excess** was determined by SFC analysis to be 94% (254 nm, 40 °C), t_R = 1.27 min (major), t_R = 4.60 min (minor) [(Chiralpak® AD-H) 20.0% *i*PrOH, 4.0 mL/min].
$[\alpha]_D^{25}$ = +87.8° (c 0.36, CH_2Cl_2).
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 – 7.77 (m, 2H), 7.11 – 6.92 (m, 3H), 6.78 – 6.59 (m, 5H), 6.48 (d, *J* = 3.5 Hz, 1H), 6.31 (ddd, *J* = 16.9, 10.3, 8.6 Hz, 1H), 5.27 – 5.14 (m, 2H), 4.99 (d, *J* = 8.6 Hz, 1H), 4.89 (d, *J* = 6.0 Hz, 1H), 4.75 (d, *J* = 6.0 Hz, 1H), 3.77 (s, 3H), 3.73 (s, 3H), 3.28 (s, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 196.9, 162.8, 158.8, 142.4, 137.2, 133.0, 131.6, 128.2, 127.7, 127.2, 125.8, 124.4, 117.8, 113.1, 113.0, 94.1, 88.8, 57.2, 55.4, 55.2, 51.0.
HRMS (ESI): *m/z* for $C_{25}H_{26}O_5SNa$ $[M+Na]^+$ calcd.: 461.1393, found: 461.1394.

(2*S*,3*S*)-2-(methoxymethoxy)-3-methyl-1-phenyl-2-(thiophen-2-yl)pent-4-en-1-one (4km)

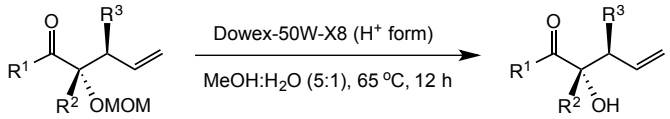


Prepared according to the general procedure as described. The diastereomeric ratio was determined to be 6:1. The crude mixture was purified by flash column chromatography (hexane:EtOAc = 15:1 to 8:1) to give the title compound as a colorless gel (32.3 mg, 0.102 mmol, 82%).
The **enantiomeric excess** was determined by SFC analysis to be 91% (254 nm, 40 °C), t_R = 2.07 min (major), t_R = 2.91 min (minor) [(Chiralpak® AD-H) 5.0% *i*PrOH, 2.5 mL/min].
$[\alpha]_D^{25}$ = +90.7° (c 0.22, CH_2Cl_2).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.97 (d, *J* = 7.8 Hz, 2H), 7.43 (t, *J* = 7.4 Hz, 1H), 7.35 – 7.30 (m, 3H), 6.96 – 6.89 (m, 1H), 6.78 (d, *J* = 3.6 Hz, 1H), 6.05 – 5.96 (m, 1H), 5.15 – 5.07 (m, 2H), 4.72 (d, *J* = 6.5 Hz, 1H), 4.67 (d, *J* = 6.5 Hz, 1H), 3.52 – 3.43 (m, 1H), 3.15 (s, 3H), 0.99 (d, *J* = 6.7 Hz, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 198.5, 141.8, 138.8, 135.8, 132.5, 130.4, 128.0, 126.5, 126.3, 125.6, 116.4, 93.5, 88.7, 56.9, 43.6, 16.2.
HRMS (EI): *m/z* for $C_{14}H_{13}O_3S$ [M−1-methylallyl]$^+$ calcd.: 261.0585, found: 261.0590.

3.4.4 Procedures for the Transformations of the Allylated Ketones

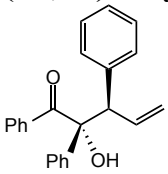
1) Tertiary alcohols (**5ba**, **5ic**, **5jk**, **5km**) were prepared based a published procedure.[22]



Scheme 3.5 Synthesis of tertiary alcohols

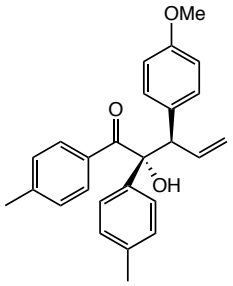
Dowex-50W-X8 resin (H^+ form, 100 mg) and the corresponding allylated ketone (0.0630 mmol) were added to a 1-dram vial containing 1.00 mL of MeOH and 0.20 ml of H_2O. The vial was sealed with a cap containing a PTFE-lined silicone-septum. The solution was heated and stirred at 65 °C for 12 h. The crude mixture was filtered through a short Celite plug to remove the solids (eluting with 1:1 hexanes:EtOAc). The resulting solution was concentrated under reduced pressure and the residue was purified by column chromatography (100/0 to 85/15 hexanes/EtOAc).

(2*R*,3*R*)-2-hydroxy-1,2,3-triphenylpent-4-en-1-one (5ba)



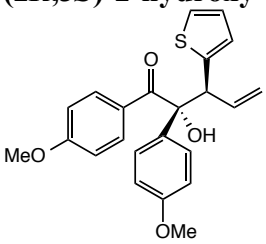
The title compound was isolated (20.7 mg, 0.0630 mmol, >99%) as a white solid.
The **enantiomeric excess** was determined by SFC analysis to be 90% (254 nm, 40 °C), t_R = 3.10 min (major), t_R = 2.46 min (minor) [(Chiralcel® OZ-H) 4.0% ^{i}PrOH, 4.0 mL/min].
$[\alpha]_D^{25}$ = +22.6° (c 0.52, CH_2Cl_2).
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.76 – 7.69 (m, 2H), 7.47 – 7.43 (m, 1H), 7.43 – 7.39 (m, 2H), 7.34 – 7.27 (m, 2H), 7.25 – 7.19 (m, 4H), 7.18 – 7.13 (m, 3H), 7.13 – 7.09 (m, 1H), 6.21 (ddd, *J* = 17.3, 10.4, 7.7 Hz, 1H), 5.19 (dt, *J* = 10.4, 1.2 Hz, 1H), 5.02 (dt, *J* = 17.3, 1.4 Hz, 1H), 4.63 (d, *J* = 7.7 Hz, 1H), 3.90 (s, 1H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 201.9, 139.8, 138.9, 137.1, 136.2, 132.4, 130.1, 129.9, 128.3, 128.2, 128.2, 127.7, 126.7, 126.4, 119.1, 85.8, 57.1.
HRMS (EI): *m/z* for $C_{23}H_{19}O$ [M−OH]$^+$ calcd.: 311.1436, found: 311.1427.

(2*R*,3*R*)-2-hydroxy-3-(4-methoxyphenyl)-1,2-di-*p*-tolylpent-4-en-1-one (5ic)



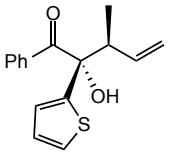
The title compound was isolated (44.1 mg, 0.114 mmol, >99% based on 0.114 mmol of the corresponding allylated ketone employed) as a white solid.
The **enantiomeric excess** was determined by SFC analysis to be 94% (254 nm, 40 °C), t_R = 2.63 min (major), t_R = 1.83 min (minor) [(Chiralcel® OZ-H) 10.0% *i*PrOH, 4.0 mL/min].
$[\alpha]_D^{25}$ = −7.6° (c 0.45, CH_2Cl_2).
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.0 Hz, 2H), 7.28 (d, *J* = 7.9 Hz, 2H), 7.20 (d, *J* = 8.7 Hz, 2H), 7.12 (d, *J* = 7.9 Hz, 2H), 7.02 (d, *J* = 7.9 Hz, 2H), 6.72 (d, *J* = 8.5 Hz, 2H), 6.13 (ddd, *J* = 17.7, 10.3, 7.8 Hz, 1H), 5.09 (d, *J* = 10.3 Hz, 1H), 4.90 (d, *J* = 17.2 Hz, 1H), 4.54 (d, *J* = 7.8 Hz, 1H), 4.12 (s, 1H), 3.73 (s, 3H), 2.34 (s, 3H), 2.25 (s, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 201.5, 158.2, 143.2, 137.6, 137.2, 137.1, 133.2, 131.3, 131.1, 130.2, 129.1, 128.8, 126.6, 118.3, 113.6, 85.3, 56.0, 55.2, 21.7, 21.2.
HRMS (ESI): *m/z* for $C_{26}H_{26}O_3Na$ $[M+Na]^+$ calcd.: 409.1774, found: 409.1768.

(2*R*,3*S*)-2-hydroxy-1,2-bis(4-methoxyphenyl)-3-(thiophen-2-yl)pent-4-en-1-one (5jk)



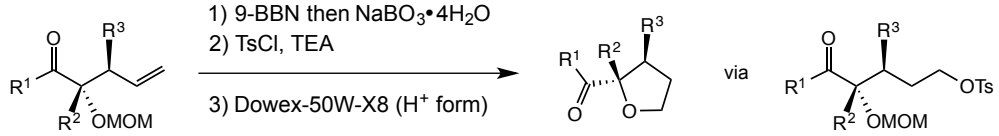
The title compound was isolated (42.2 mg, 0.107 mmol, 96% based on 0.112 mmol of the corresponding allylated ketone employed) as a white solid.
The **enantiomeric excess** was determined by SFC analysis to be 94% (254 nm, 40 °C), t_R = 4.01 min (major), t_R = 4.75 min (minor) [(Chiralcel® OD-H) 12.0% *i*PrOH, 3.5 mL/min].
$[\alpha]_D^{25}$ = −37.8° (c 0.39, CH_2Cl_2).
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.85 (d, *J* = 9.0 Hz, 2H), 7.40 (d, *J* = 8.9 Hz, 2H), 7.12 (dd, *J* = 5.1, 1.3 Hz, 1H), 6.89 (d, *J* = 3.0 Hz, 1H), 6.86 (dd, *J* = 5.1, 3.5 Hz, 1H), 6.82 – 6.76 (m, 4H), 6.08 (ddd, *J* = 17.6, 10.3, 7.8 Hz, 1H), 5.09 (d, *J* = 10.3 Hz, 1H), 4.95 (d, *J* = 17.1 Hz, 1H), 4.90 (d, *J* = 7.8 Hz, 1H), 4.29 (brs, 1H), 3.81 (s, 3H), 3.74 (s, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 199.1, 163.2, 159.0, 141.3, 136.8, 132.7, 132.1, 127.9, 127.0, 126.4, 125.2, 118.8, 113.8, 113.5, 84.4, 55.5, 55.3, 52.9, 29.8.
HRMS (ESI): *m/z* for $C_{23}H_{22}O_4Na$ $[M+Na]^+$ calcd.: 417.1131, found: 417.1126.

(2*S*,3*S*)-2-hydroxy-3-methyl-1-phenyl-2-(thiophen-2-yl)pent-4-en-1-one (5km)



The title compound was isolated (18.4 mg, 0.0676 mmol, 74% based on 0.0908 mmol of the corresponding allylated ketone employed) as a slightly yellow gel.
The **enantiomeric excess** was determined by SFC analysis to be 91% (254 nm, 40 °C), t_R = 3.19 min (major), t_R = 2.99 min (minor) [(Chiralpak® AD-H) 10.0% *i*PrOH, 2.5 mL/min].
$[\alpha]_D^{25}$ = +28° (c 0.12, CH_2Cl_2).
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (dd, *J* = 8.4, 1.3 Hz, 2H), 7.49 – 7.44 (m, 1H), 7.36 – 7.31 (m, 2H), 7.30 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.08 (dd, *J* = 3.6, 1.2 Hz, 1H), 7.00 (dd, *J* = 5.0, 3.6 Hz, 1H), 5.81 (ddd, *J* = 17.4, 10.5, 7.7 Hz, 1H), 5.06 (ddd, *J* = 10.5, 1.6, 0.8 Hz, 1H), 4.96 (dt, *J* = 17.4, 1.3 Hz, 1H), 4.37 (s, 1H), 3.53 – 3.46 (m, 1H), 1.16 (d, *J* = 6.8 Hz, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 201.4, 145.3, 138.0, 135.5, 132.7, 129.8, 128.2, 127.3, 126.0, 125.8, 117.9, 83.6, 45.4, 14.3.
HRMS (EI): *m/z* for $C_{16}H_{16}O_2S$ $[M]^+$ calcd.: 272.0871, found: 272.0872.

2) THF derivatives (**6ba**, **6ic**, **6jk**, **6km**) were prepared by methods based on published procedures.[22,23]



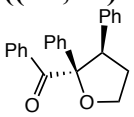
Scheme 3.6 Synthesis of THF derivatives

In dry, degassed THF (1.00 mL) was added the allylated ketone (0.163 mmol, 1.00 equiv). The solution was cooled to −78 °C. Then 9-BBN (0.65 mL as a 0.5 M solution in THF, 0.33 mmol, 2.0 equiv) was added to the reaction vessel. The reaction mixture was stirred for 1 h at −78 °C, then allowed to warm slowly to room temperature and stirred for 12 h. The resulting solution was cooled to 0 °C, at which time water (1.00 mL), and $NaBO_3 \cdot 4H_2O$ (381 mg, 2.45 mmol, 15.0 equiv) were added. The reaction mixture was allowed to warm to room temperature and was stirred for an additional 6 h. The reaction mixture was diluted with 20 mL of water, and then extracted with DCM (3 × 20 mL). The organic layer was dried over Na_2SO_4 and concentrated. The crude product was dissolved in DCM (2.00 mL), and the solution was cooled to 0 °C. At this time, triethylamine (68.2 μL, 0.489 mmol, 3.00 equiv) and TsCl (68.4 mg, 0.359 mmol, 2.20 equiv) were added. The reaction was allowed to warm to room temperature and stirred for 7 to 12 h (monitored by TLC). The resulted solution was filtered through a 2-inch plug of silica gel (eluting with EtOAc) to remove the polar residue. After removal of the solvent under vacuum, the crude mixture was purified by flash column chromatography (hexane:EtOAc = 5:1) to give the tosylate (crude). This was a mixture of the tosylate and unknown impurities.

Dowex-50W-X8 resin (H^+ form, 200 mg) and the tosylate (crude) were added into a 1-dram vial containing 2.00 mL of MeOH and 0.40 ml of H_2O. The vial was sealed with a cap containing a PTFE-lined silicone-septum. The solution was heated at 65 °C and stirred for 12 h. The ring

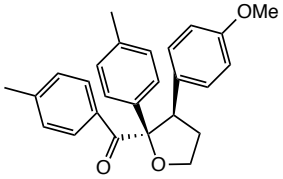
closing was achieved *in situ* after the removal of MOM group. The crude mixture was filtered through a short Celite plug to remove the solids (eluting with 1:1 hexanes:EtOAc). The crude mixture was purified by column chromatography (hexane:EtOAc = 20:1 to 10:1).

((2*R*,3*R*)-2,3-diphenyltetrahydrofuran-2-yl)(phenyl)methanone (6ba)



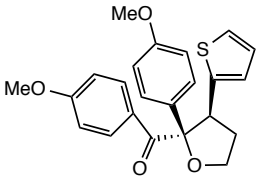
The title compound was isolated (24.1 mg, 0.0733 mmol, 45%) as a colorless gel (single isomer).
The **enantiomeric excess** was determined by SFC analysis to be 89% (254 nm, 40 °C), t_R = 3.39 min (major), t_R = 2.82 min (minor) [(Chiralcel® OZ-H) 3.0% *i*PrOH, 4.0 mL/min].
$[\alpha]_D^{25}$ = +171° (c 0.44, CH_2Cl_2).
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.04 – 7.94 (m, 2H), 7.44 – 7.37 (m, 1H), 7.29 (t, *J* = 7.8 Hz, 2H), 7.14 (d, *J* = 6.8 Hz, 2H), 7.09 – 7.00 (m, 6H), 7.00 – 6.96 (m, 2H), 4.57 (t, *J* = 7.1 Hz, 1H), 4.46 (td, *J* = 8.6, 4.4 Hz, 1H), 3.95 (q, *J* = 8.3 Hz, 1H), 2.42 (dtd, *J* = 12.3, 7.8, 4.3 Hz, 1H), 2.32 (dtd, *J* = 12.6, 8.2, 6.5 Hz, 1H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 200.2, 140.8, 138.7, 135.0, 132.6, 130.7, 129.3, 128.0, 127.9, 127.7, 127.1, 126.2, 125.8, 95.4, 68.0, 51.1, 33.1.
HRMS (EI): *m/z* for $C_{16}H_{15}O$ $[M-PhCO]^+$ calcd.: 223.1123, found: 223.1126.

((2*R*,3*R*)-3-(4-methoxyphenyl)-2-(*p*-tolyl)tetrahydrofuran-2-yl)(*p*-tolyl)methanone (6ic)



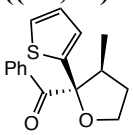
The title compound was isolated (19.7 mg, 0.0510 mmol, 41% based on 0.125 mmol of the corresponding allylated ketone employed) as a white solid (single isomer).
The **enantiomeric excess** was determined by SFC analysis to be 94% (254 nm, 40 °C), t_R = 2.91 min (major), t_R = 2.59 min (minor) [(Chiralcel® OZ-H) 10.0% *i*PrOH, 2.5 mL/min].
$[\alpha]_D^{25}$ = +93.2° (c 0.44, CH_2Cl_2).
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.1 Hz, 2H), 7.08 (d, *J* = 8.0 Hz, 2H), 6.97 (d, *J* = 7.9 Hz, 2H), 6.88 (t, *J* = 8.9 Hz, 4H), 6.60 (d, *J* = 8.0 Hz, 2H), 4.56 – 4.34 (m, 2H), 3.93 (q, *J* = 8.3 Hz, 1H), 3.70 (s, 3H), 2.39 – 2.27 (m, 4H), 2.27 – 2.13 (m, 4H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 199.8, 157.8, 143.2, 136.6, 136.0, 132.8, 132.4, 130.9, 130.3, 128.7, 128.6, 125.7, 113.0, 95.0, 67.8, 55.2, 50.2, 33.1, 21.7, 21.2.
HRMS (ESI): *m/z* for $C_{26}H_{27}O_3$ $[M+H]^+$ calcd.: 387.1955, found: 387.1953.

(4-methoxyphenyl)((2*R*,3*S*)-2-(4-methoxyphenyl)-3-(thiophen-2-yl)tetrahydrofuran-2-yl)methanone (6jk)



The title compound was isolated (18.2 mg, 0.0461 mmol, 41% based on 0.112 mmol of the corresponding allylated ketone employed) as a white solid (single isomer).
The **enantiomeric excess** was determined by SFC analysis to be 94% (254 nm, 40 °C), t_R = 4.28 min (major), t_R = 3.64 min (minor) [(Chiralcel® OZ-H) 10.0% *i*PrOH, 2.5 mL/min].
[α]$_D^{25}$ = +121° (c 0.44, CH_2Cl_2).
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (d, *J* = 9.0 Hz, 2H), 7.09 (d, *J* = 8.2 Hz, 2H), 6.97 (d, *J* = 5.2 Hz, 1H), 6.77 (d, *J* = 9.0 Hz, 2H), 6.72 (dd, *J* = 5.1, 3.4 Hz, 1H), 6.68 – 6.60 (m, 3H), 4.79 (t, *J* = 7.0 Hz, 1H), 4.44 (td, *J* = 8.4, 4.6 Hz, 1H), 3.97 (q, *J* = 8.0 Hz, 1H), 3.78 (s, 3H), 3.69 (s, 3H), 2.46 – 2.37 (m, 1H), 2.33 – 2.23 (m, 1H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 198.2, 163.1, 158.7, 143.7, 133.3, 131.1, 127.5, 126.7, 126.1, 126.0, 124.1, 113.3, 113.2, 94.4, 67.7, 55.5, 55.2, 46.6, 33.7.
HRMS (ESI): *m/z* for $C_{23}H_{23}O_4S$ $[M+H]^+$ calcd.: 395.1312, found: 395.1307.

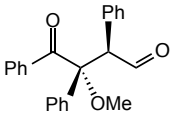
((2*S*,3*S*)-3-methyl-2-(thiophen-2-yl)tetrahydrofuran-2-yl)(phenyl)methanone (6km)



The title compound was isolated (6.6 mg, 0.024 mmol, 23% based on 0.105 mmol of the corresponding allylated ketone employed) as a colorless gel (single isomer).
The **enantiomeric excess** was determined by SFC analysis to be 90% (254 nm, 40 °C), t_R = 2.38 min (major), t_R = 3.06 min (minor) [(Chiralpak® AD-H) 5.0% *i*PrOH, 2.5 mL/min].
[α]$_D^{25}$ = +197° (c 0.16, CH_2Cl_2).
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.00 (d, *J* = 7.0 Hz, 2H), 7.44 (t, *J* = 7.4 Hz, 1H), 7.33 (t, *J* = 7.8 Hz, 2H), 7.26 – 7.24 (m, 1H), 6.94 (dd, *J* = 5.1, 3.6 Hz, 1H), 6.77 (dd, *J* = 3.6, 1.2 Hz, 1H), 4.23 (td, *J* = 8.1, 4.5 Hz, 1H), 3.81 (td, *J* = 8.2, 7.1 Hz, 1H), 3.23 – 3.12 (m, 1H), 2.12 – 2.02 (m, 1H), 1.84 – 1.73 (m, 1H), 0.88 (d, *J* = 7.0 Hz, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 200.0, 144.2, 135.2, 132.6, 130.6, 128.0, 127.4, 124.8, 124.5, 93.0, 67.9, 40.7, 33.4, 16.3.
HRMS (EI): *m/z* for $C_{16}H_{16}O_2S$ $[M]^+$ calcd.: 272.0871, found: 272.0869.

3) Ozonolysis: the allylated ketone **4aa** (34.2 mg, 0.100 mmol, 1.00 equiv) was dissolved in DCM (2.00 mL) and cooled to −78 °C. Ozone was bubbled through the solution until blue color appeared (~5 min). Then N_2 was bubbled through the solution to remove excess ozone (~10 min). PPh_3 (31.5 mg, 0.120 mmol, 1.20 equiv) was then added and the reaction mixture was warmed up to room temperature and stirred overnight at this temperature. After removal of solvent under reduced pressure, the crude mixture was purified by flash column chromatography (hexane:EtOAc = 20:1 to 10:1) to afford aldehyde **7aa** as a colorless gel (21.9 mg, 0.0637 mmol, 64%).

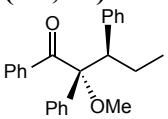
(2*R*,3*R*)-3-methoxy-4-oxo-2,3,4-triphenylbutanal (7aa)



The **enantiomeric excess** was determined by HPLC analysis to be 90% (254 nm, 25 °C), t_R = 12.0 min (major), t_R = 9.1 min (minor) [(Chiralcel® OJ-H) 6.0% ^{i}PrOH in hexane, 1.0 mL/min].
$[\alpha]_D^{25}$ = +83.1° (c 0.22, CH_2Cl_2).
^{1}H NMR (500 MHz, $CDCl_3$) δ 10.09 (d, *J* = 3.4 Hz, 1H), 7.91 (d, *J* = 6.9 Hz, 2H), 7.43 (t, *J* = 7.4 Hz, 1H), 7.30 – 7.25 (m, 2H), 7.23 – 7.09 (m, 8H), 6.85 – 6.80 (m, 2H), 4.76 (d, *J* = 3.4 Hz, 1H), 3.47 (s, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 199.3, 198.6, 138.9, 134.8, 133.2, 132.8, 131.4, 130.3, 128.4, 128.2, 128.1, 127.9, 127.4, 126.4, 90.4, 63.8, 54.9.
HRMS (EI): *m/z* for $C_{23}H_{20}O_3$ $[M]^+$ calcd.: 344.1412, found: 344.1409.

4) Hydrogenation: To the solution of the allylated keone **4aa** (34.2 mg, 0.100 mmol, 1.00 equiv) in MeOH (2.00 mL) in a 1-dram vial was added 10% Pd/C (10.0 mg, 0.0100 equiv) under N_2. Then the vial was charged with 1 atm of H_2 and the reaction mixture was stirred at room temperature for 24 h. Then the reaction mixture was filtered through a plug of silica gel. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane:EtOAc = 20:1 to 10:1) to afford ketone **8aa** as a colorless gel (29.5 mg, 0.0858 mmol, 86%).

(2*R*,3*R*)-2-methoxy-1,2,3-triphenylpentan-1-one (8aa)

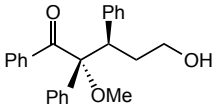


The **enantiomeric excess** was determined by HPLC analysis to be 92% (254 nm, 25 °C), t_R = 14.9 min (major), t_R = 10.5 min (minor) [(Chiralcel® OD-H) pure hexane, 1.0 mL/min].
$[\alpha]_D^{25}$ = +105° (c 0.30, CH_2Cl_2).
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.83 (d, *J* = 6.9 Hz, 2H), 7.36 (t, *J* = 7.2 Hz, 1H), 7.22 (t, *J* = 7.7 Hz, 2H), 7.18 – 7.11 (m, 3H), 7.10 – 7.00 (m, 5H), 6.81 (d, *J* = 6.2 Hz, 2H), 3.68 (dd, *J* = 12.1, 2.5 Hz, 1H), 3.38 (s, 3H), 2.17 – 2.07 (m, 1H), 1.68 – 1.59 (m, 1H), 0.71 (t, *J* = 7.3 Hz, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 199.9, 139.6, 139.4, 136.3, 132.3, 131.4, 130.2, 128.0, 127.4, 127.3, 127.0, 126.2, 90.8, 54.2, 53.4, 23.1, 12.7.
HRMS (ESI): *m/z* for $C_{24}H_{24}O_2Na$ $[M+Na]^+$ calcd.: 367.1669, found: 367.1667.

5) Hydration: Primary alcohol **10aa** was prepared according to a published procedure[23] at a 0.1-mmol scale. In dry, degassed THF (0.50 mL) was added the allylated ketone **4aa** (34.2 mg, 0.100 mmol, 1.00 equiv). The solution was cooled to −78 °C. Then 9-BBN (0.40 mL as a 0.5 M solution in THF, 0.20 mmol, 2.0 equiv) was added to the reaction vessel. The reaction mixture was stirred for 1 h at −78 °C, then allowed to warm slowly to room temperature and stirred for 12 h. The resulting solution was cooled to 0 °C, at which time water (1.00 mL), and $NaBO_3 \cdot 4H_2O$ (231 mg, 1.50 mmol, 15.0 equiv) were added. The reaction mixture was allowed to warm to room temperature and was stirred for an additional 6 h. The reaction mixture was diluted with 20 mL of water, and then extracted with DCM (3 × 20 mL). The organic layer was dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by column chromatography

(hexane:EtOAc = 20:1 to 3:1) to afford primary alcohol **9aa** as a colorless gel (34.6 mg, 0.0961 mmol, 96%).

(2*R*,3*R*)-5-hydroxy-2-methoxy-1,2,3-triphenylpentan-1-one (9aa)



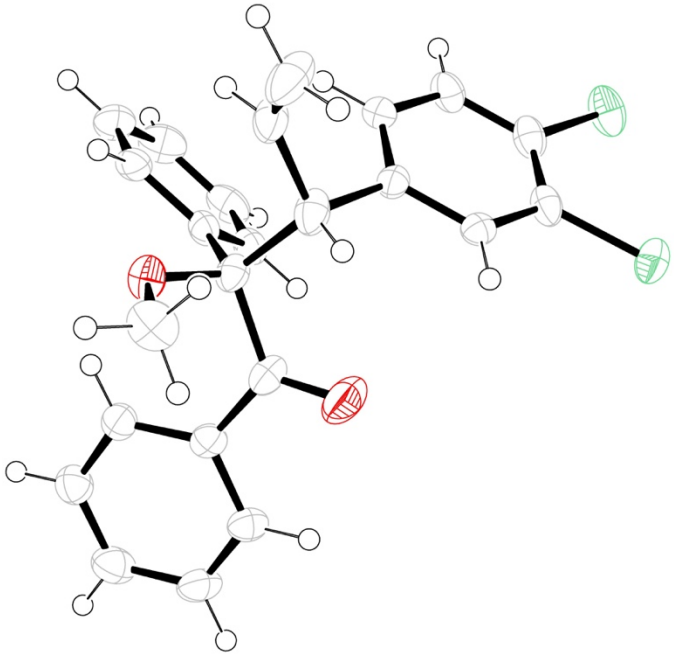
The **enantiomeric excess** was determined by HPLC analysis to be 92% (254 nm, 25 °C), t_R = 15.9 min (major), t_R = 17.9 min (minor) [(Chiralpak® AD-H) 10.0% ^{i}PrOH in hexane, 0.6 mL/min].
$[\alpha]_D^{25}$ = +86.3° (c 0.30, CH_2Cl_2).
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 – 7.81 (m, 2H), 7.40 (t, *J* = 7.4 Hz, 1H), 7.27 – 7.22 (m, 2H), 7.22 – 7.14 (m, 3H), 7.13 – 7.03 (m, 5H), 6.89 – 6.79 (m, 2H), 4.02 (dd, *J* = 12.1, 2.2 Hz, 1H), 3.52 (ddd, *J* = 11.0, 7.0, 4.1 Hz, 1H), 3.44 (s, 3H), 3.38 (ddd, *J* = 10.4, 8.8, 5.9 Hz, 1H), 2.41 (dddd, *J* = 13.6, 9.1, 7.1, 2.2 Hz, 1H), 1.99 – 1.83 (m, 1H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 199.8, 139.2, 139.2, 135.9, 132.5, 131.2, 130.3, 128.1, 127.5, 127.4, 127.3, 127.2, 126.5, 90.3, 61.4, 54.3, 47.5, 33.4.
HRMS (ESI): *m/z* for $C_{24}H_{24}O_3Na$ $[M+Na]^+$ calcd.: 383.1618, found: 383.1613.

3.4.5 X-Ray Diffraction Study of 4ag

A colorless plate 0.050 x 0.050 x 0.020 mm in size was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using phi and omega scans. Crystal-to-detector distance was 60 mm and exposure time was 10 seconds per frame using a scan width of 2.0°. Data collection was 99.9% complete to 67.000° in θ. A total of 49567 reflections were collected covering the indices, -8<=*h*<=9, -15<=*k*<=15, -22<=*l*<=22. 3699 reflections were found to be symmetry independent, with an R_{int} of 0.0600. Indexing and unit cell refinement indicated a primitive, orthorhombic lattice. The space group was found to be P 21 21 21 (No. 19). The data were integrated using the Bruker SAINT software program and scaled using the SADABS software program. Solution by iterative methods (SHELXT) produced a complete heavy-atom phasing model consistent with the proposed structure. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2014/6). All hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2014/6. Absolute stereochemistry was unambiguously determined to be *R* at C1 and C2, respectively.

Table 3.5 Crystal data and structure refinement for **4ag**

X-ray ID	**4ag**	
Empirical formula	C24 H20 Cl2 O2	
Formula weight	411.30	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	a = 8.3894(3) Å	α= 90°.
	b = 12.8310(5) Å	β= 90°.
	c = 18.7896(7) Å	γ = 90°.
Volume	2022.60(13) $Å^3$	
Z	4	
Density (calculated)	1.351 Mg/m^3	
Absorption coefficient	3.018 mm^{-1}	
F(000)	856	
Crystal size	0.050 x 0.050 x 0.020 mm^3	
Theta range for data collection	4.172 to 68.251°.	
Index ranges	-8<=h<=9, -15<=k<=15, -22<=l<=22	
Reflections collected	49567	
Independent reflections	3699 [R(int) = 0.0600]	
Completeness to theta = 67.000°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.929 and 0.756	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3699 / 0 / 263	
Goodness-of-fit on F^2	1.063	
Final R indices [I>2sigma(I)]	R1 = 0.0496, wR2 = 0.1215	
R indices (all data)	R1 = 0.0527, wR2 = 0.1246	
Absolute structure parameter	0.004(5)	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.965 and -0.467 $e.Å^{-3}$	



Scheme 3.7 Crystal structure of **4ag**

3.5 References

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"Iridium-Catalyzed Diastereoselective and Enantioselective Allylic Substitutions with Acyclic α-Alkoxy Ketones"
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[9] We also investigated the reactions with *in situ* generated catalyst, pre-formed catalysts with different ligands, and the reactions under different temperatures. The reaction catalyzed by pre-formed catalyst **3** under 5 °C or 0 °C afforded the product in excellent yield with highest dr.

[10] The solution of copper enolate was heterogeneous and was transferred into the vial containing allyl carbonate **2** and catalyst **3**. The loss of CuBr was inevitable and unable to be measured. Considering the low price of CuBr and that inadequate amount of CuBr would result in lower diastereoselectivity in this reaction (Table 3.1, entry 11 versus entry 12), we decided to use excessive CuBr (2 equiv) as the additive for further study.

[11] This result is consistent with the observations made during the determination of suitable reaction conditions (see Table 3.1, entry 6 vs. entry 12).

[12] The reaction of 2-methoxyacetophenone with cinnamyl methyl carbonate afforded the product quantitatively with dr of 1.9:1. It is likely that the corresponding product underwent epimerization under reaction condition that resulted in low dr.

[13] In several cases (**4ca**, **4ea**–**4ga**, **4ic, 4km**), viscous solutions of copper enolates were observed if 2 equiv of CuBr were added, and the consumption of limiting allylic carbonates was not completed within 12 hours. However, if less CuBr (1 or 0.5 equiv, see SI for details) was added, full conversion of the allylic carbonates was obtained within 12 hours.

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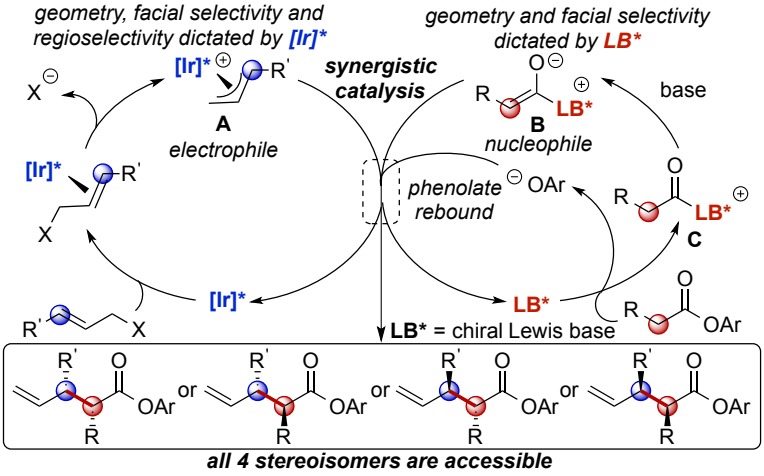
CHAPTER 4

Stereodivergent Allylic Substitutions with Aryl Acetic Acid Esters by Synergistic Iridium and Lewis Base Catalysis

4.1 Introduction

Transition metal-catalyzed allylic substitutions are useful methods for the enantioselective construction of carbon-carbon bonds.[1] If both the nucleophiles and electrophiles of the allylation reactions are prochiral, synthetically useful adducts that contain two contiguous stereocenters can be constructed in one step. However, most reported reactions of this type that afford products enantioselectively and diastereoselectively form one out of two possible relative configurations (*anti* vs. *syn*).[2] Few methods provide stereodivergent access to all four possible stereoisomers of the products with either *anti* or *syn* configuration. Recently, Carreira et al. reported the allylation of aldehydes in a stereodivergent fashion by the synergistic reactivity of iridium and amine catalysts under acidic conditions.[3] Zhang et al. reported the combination of iridium and zinc catalysts for the related allylation of α-hydroxyphenones.[4] An approach to the stereodivergent allylation of carbonyl compounds in the carboxylic acid oxidation state has not been published.[5]

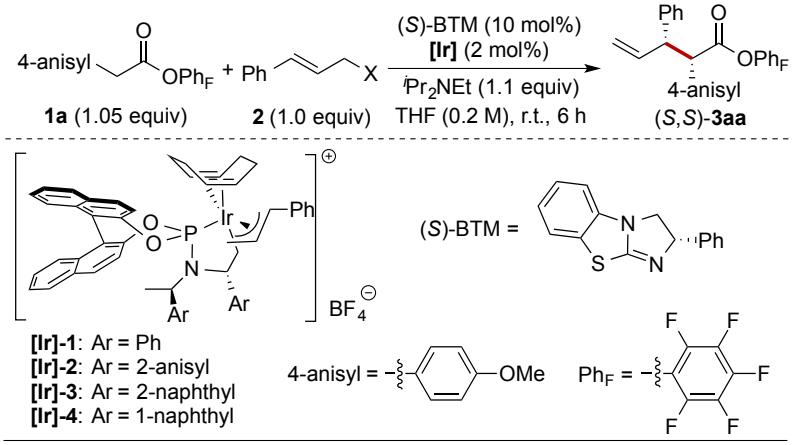


Scheme 4.1 Proposed mechanism for synergistic catalysis

Mechanistic studies[6] have revealed that metallacyclic iridium complexes[7] developed in our group govern the geometry, facial selectivity, and regioselectivity of the allyl moiety in allylation reactions (Scheme 4.1, **A**). Lewis basic chiral tertiary amines are known to react with acyl precursors to form C1-ammonium enolates that have a well-defined geometry and that react with high facial selectivity (Scheme 4.1, **B**).[8] The metalacyclic iridium catalyst for allylic substitution we discovered[7] operates under basic conditions. Thus, a system with a Lewis basic catalyst displacing an alkoxide or phenoxide anion to generate the enolate would be compatible with our iridium catalysts. We envisioned that the allylation reaction between **A** as an electrophile and **B** as a nucleophile would be highly regio-, diastereo- and enantioselective. Furthermore, the iridium complex and the Lewis base (LB) could dictate the configurations of the two stereogenic centers of the product arising from the electrophile (marked blue) and the nucleophile (marked red), respectively. Thus, our proposed allylation method could access all four possible stereoisomers of the product by simple permutations of enantiomers of the two catalysts (Ir_R+LB_R, Ir_S+LB_R, Ir_R+LB_S, Ir_S+LB_S).[9]

A critical concern that underlies our proposed transformation is the turnover of the Lewis base catalyst. Regeneration of this catalyst typically requires an intramolecular acyl transfer to a proximal nucleophile on the acyl ammonium intermediate. In this case, only lactones and lactams are accessible as the products.[8c,8d,10] Although external nucleophiles can be employed as acyl acceptors,[11] this external nucleophile can react with intermediate **C** before allylation occurs. In addition, the direct allylation of an external nucleophile can compete or override the allylation of the enolate.

Table 4.1 Evaluation of reaction conditions for the allylation of 1a[a]



Entry	[Ir]	X	b/l[b]	dr[b]	ee/%[c]	Yield/%[d]
1	**[Ir]-1**	OAc	n.d.	n.d.	n.d.	13
2	-	OBz	>99:1	>20:1	n.d.	59
3	-	OPiv	n.d.	n.d.	n.d.	8
4	-	$OPO(OEt)_2$	n.d.	6:1	n.d.	38
5	-	OCOOMe	>99:1	5:1	n.d.	43
6	-	OTroc	>99:1	9:1	n.d.	90
7	-	OBoc	>99:1	>20:1	>99	>99 (97)
8	**[Ir]-1**	OBoc	>99:1	>20:1	>99	99 (97)
9	**[Ir]-2**	-	>99:1	11:1	n.d.	71
10	**[Ir]-3**	-	>99:1	>20:1	>99	>99 (>99)
11	**[Ir]-4**	-	>99:1	>20:1	>99	99 (99)
12[e]	**[Ir]-1**	-	10:1	<1:20	>99	98 (97)
13[e]	**[Ir]-2**	-	>20:1	1:13	n.d.	57
14[e]	**[Ir]-3**	-	10:1	<1:20	>99	99 (>99)
15[e]	**[Ir]-4**	-	>20:1	1:13	>99	99 (>99)

[a]The absolute configuration of (*S*,*S*)-**3aa** was assigned by analogy. [b]Determined by ^{1}H NMR analysis of the crude reaction mixtures. [c]Determined by chiral SFC analysis of the major isomer. [d]Combined yield of two diastereomers of the branched product and the linear product. Determined by ^{1}H NMR analysis with mesitylene as an internal standard. The yield within parentheses is that of all isomers isolated. [e](*R*)-BTM was used instead of (*S*)-BTM.

We considered that a "rebound" strategy disclosed recently by Scheidt[12], Smith[13] and Snaddon[14] could be followed to regenerate the Lewis base. In this scenario, the electron-deficient

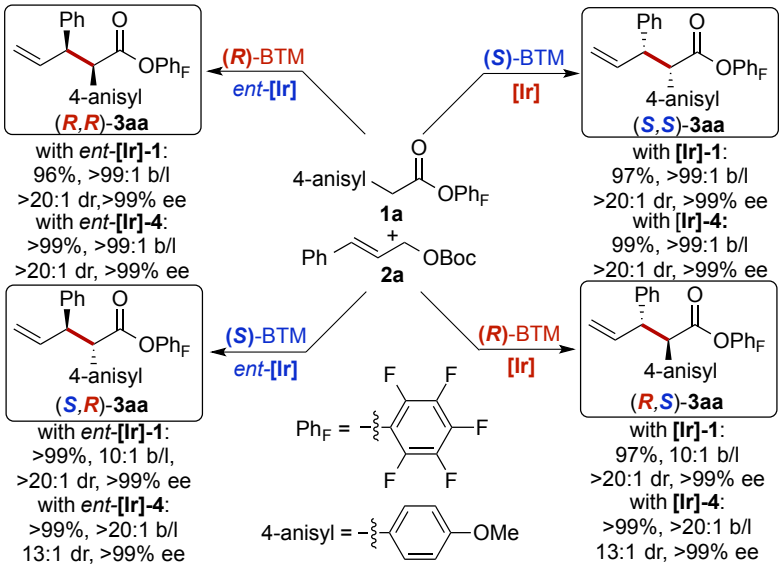
phenolate (Scheme 4.1, OAr^-) substituted by the Lewis base catalyst serves as an acyl acceptor after α-functionalization of the ester. The low concentration and low nucleophilicity of the electron-deficient phenolate would prevent the direct allylation of the phenolate.

Herein, we report stereodivergent allylic substitutions with aryl acetic acid esters catalyzed synergistically by the metallacyclic iridium complex and a chiral Lewis base. By varying the combinations of enantiomers of two catalysts, all four possible stereoisomers of the products are formed with high diastereoselectivity and enantioselectivity. The resulting chiral activated esters are readily converted to enantioenriched amides, unactivated esters, and carboxylic acids in a one-pot manner.

4.2 Results and Discussion

To develop a stereodivergent allylation of aryl acetic acid esters, we treated **1a** with **2a** in the presence of ^{i}Pr$_2$NEt as base, iridium catalyst **[Ir]-1**, and a range of Lewis base catalysts. These studies revealed that benzotetramisole (BTM)[15] was compatible with our proposed synergistic catalysis (>99% yield, >20:1 dr, see experimental for details). Reactions conducted with other Lewis bases, such as tetramisole and quinine, delivered the corresponding product in lower yields (<40%) or with lower diastereoselectivity (<4:1). The use of the pentafluorophenyl ester as the nucleophile precursor is critical; the reactions conducted with esters derived from other electron-deficient phenols, such as 4-nitrophenol and 2,4,6-tricholorophenol, gave the corresponding products with low yield and dr.

To test the effect of leaving group on the allyl moiety in this reaction, various cinnamyl alcohol derivatives were subjected to the reaction conditions (Table 4.1). The reaction conducted with *t*-butyl cinnamyl carbonate **2a** gave (*S*,*S*)-**3aa** in the highest yield (97%) with >20:1 dr and >99% ee (entry 7). Only the branched product was observed. A similar result was obtained in the absence of ^{i}Pr$_2$NEt, indicating that the *t*-butoxide generated from oxidative addition of **2a** and subsequent decarboxylation acted as a base to deprotonate the acyl-BTM adduct (entry 8).

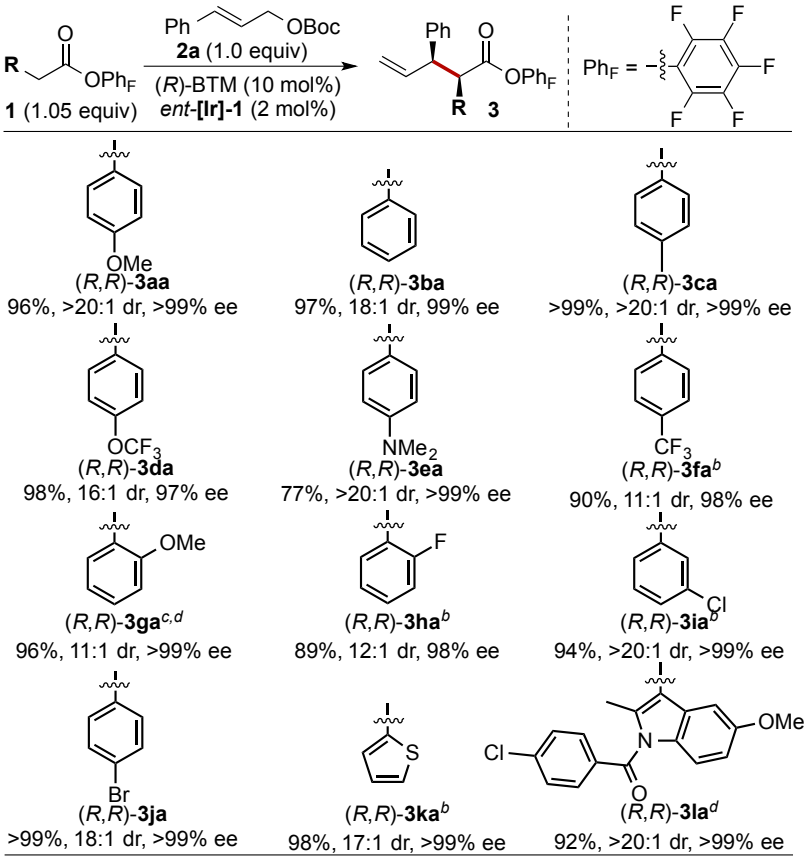


Scheme 4.1 Synthesis of all stereoisomers of **3aa**

Metallacyclic iridium catalysts with different aryl substituents on the phosphoramidite ligands were evaluated. Reactions conducted with **[Ir]-3** and **[Ir]-4** bearing naphthyl substituents on the ligands afforded (*S*,*S*)-**3aa** quantitatively with excellent diastereoselectivity and enantioselectivity (>20:1 dr, >99% ee, entry 10-11). However, the reaction conducted with **[Ir]-2** bearing 2-methoxyphenyl substituents on the ligand gave (*S*,*S*)-**3aa** in lower yield of 71% with lower dr of 11:1 (entry 9).

When the reaction was conducted with (*R*)-BTM as the Lewis base catalyst instead of (*S*)-BTM, the diastereoselectivity was completely reversed; (*R*,*S*)-**3aa** was obtained, instead of (*S*,*S*)-**3aa**, in 97% yield with >20:1 dr and >99% ee (entry 12). A small amount of linear product was observed when conducting the reaction with the catalyst combination of **[Ir]-1** and (*R*)-BTM. However, the formation of the linear product was suppressed by employing **[Ir]-4** and (*R*)-BTM as the catalysts, while maintaining high dr and ee (entry 15).

Table 4.2 Scope of esters for the allylation[a]

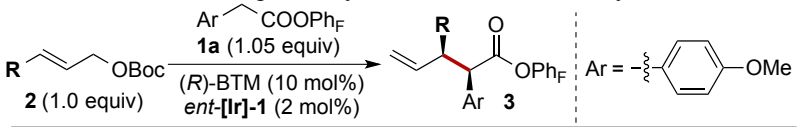


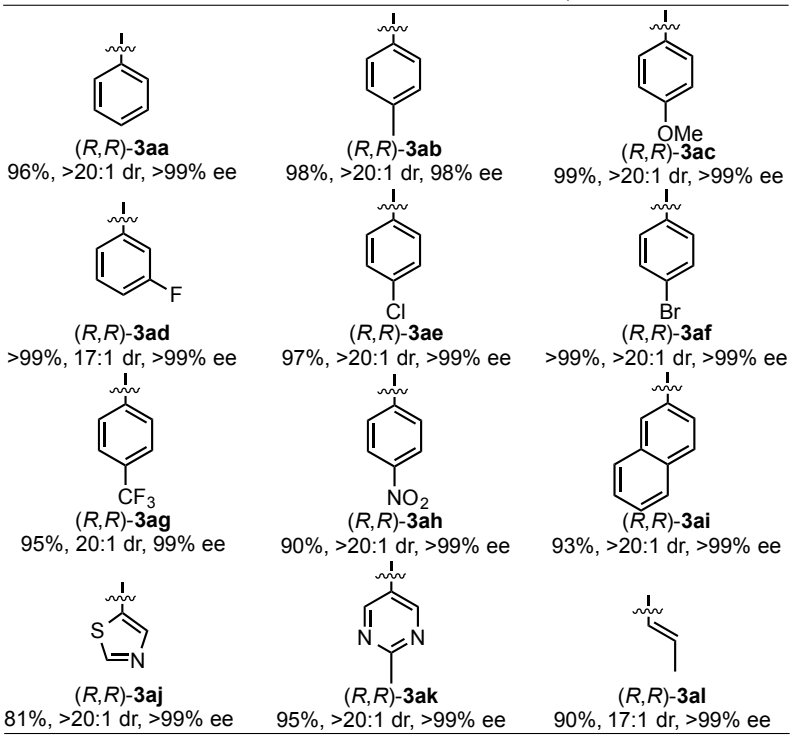
[a]The yields were reported as the combined yields of two diastereomers isolated. The branched products were obtained exclusively. [b]20 mol% of (*R*)-BTM was used. [c]Reaction time was extended to 9 h. [d]1.1 equiv of $^{i}Pr_2NEt$ was added.

To examine the stereodivergence of our allylation method, **1a** and **2a** were treated with four different combinations of the enantiomers of two catalysts under otherwise identical conditions (Scheme 4.2). As a result, all four stereoisomers of **3aa** were obtained individually in high yield with excellent diastereoselectivity and enantioselectivity, indicating nearly complete control of the

configuration at the allyl electrophile by the metallacyclic iridium complex and the enolate nucleophile by the BTM base and dominance of catalyst control of these configurations over potential substrate control. The absolute configurations of the products are consistent with the stereochemical model that is based on previous mechanistic studies on the iridium complex[6] and BTM catalyst[16] (Scheme 4.3), rendering the stereochemical outcome of our allylation method predictable.

Table 4.3 Scope of allylic carbonates for the allylation[a]



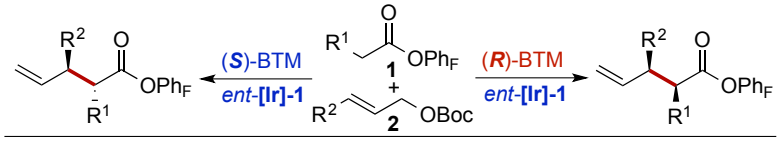


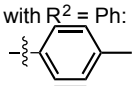
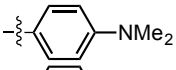
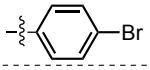
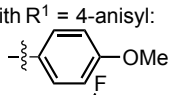
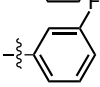
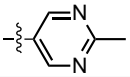
[a]The yields were reported as the combined yields of two diastereomers isolated. The branched products were obtained exclusively.

The scope of aryl acetic acid esters that underwent the stereodivergent allylic substitutions is summarized in Table 4.2. Various *para*-substituted phenyl acetic acid esters were suitable for this transformation. Electron-donating (**3aa**, **3da**, **3ea**), electron-neutral (**3ba**, **3ca**) and electron-withdrawing (**3fa**) functional groups on the phenyl ring of phenyl acetic acid esters were tolerated in this reaction, furnishing the corresponding products in high yields (≥77%), high dr (≥11:1) and excellent ee (≥97%). The reaction with 4-methylsulfonyl phenyl acetic acid ester (**1m**), a substrate bearing a readily enolizable position, due to the strong electron-withdrawing effect of the sulfonyl group, formed the product **3ma** in high yield (88%), but with modest dr (3.8:1). Further investigations showed that the low diastereoselectivity resulted from competing reaction of **1m** with **2a** occurring without participation of BTM, not from racemization of the product.

Substitutions at the *ortho* (**3ga**, **3ha**) or *meta* (**3ia**) position on the phenyl ring of phenyl acetic acid esters had little effect on the allylation reaction; the corresponding products were all obtained in ≥89% yield with ≥11:1 dr and ≥98% ee. The allylation also occurred with heteroaryl acetic acid esters. For example, **1l**, which is derived from the non-steroidal anti-inflammatory drug indomethacin, was allylated in 92% yield with >20:1 dr and >99% ee. In the cases of **3ga** and **3la**, addition of 1.1 equiv of $^{i}Pr_2NEt$ was necessary to reach full conversion of the starting allylic carbonates within 9 h, presumably by accelerating the enolization of the acyl-BTM intermediate.

Table 4.4 Examples of stereodivergence

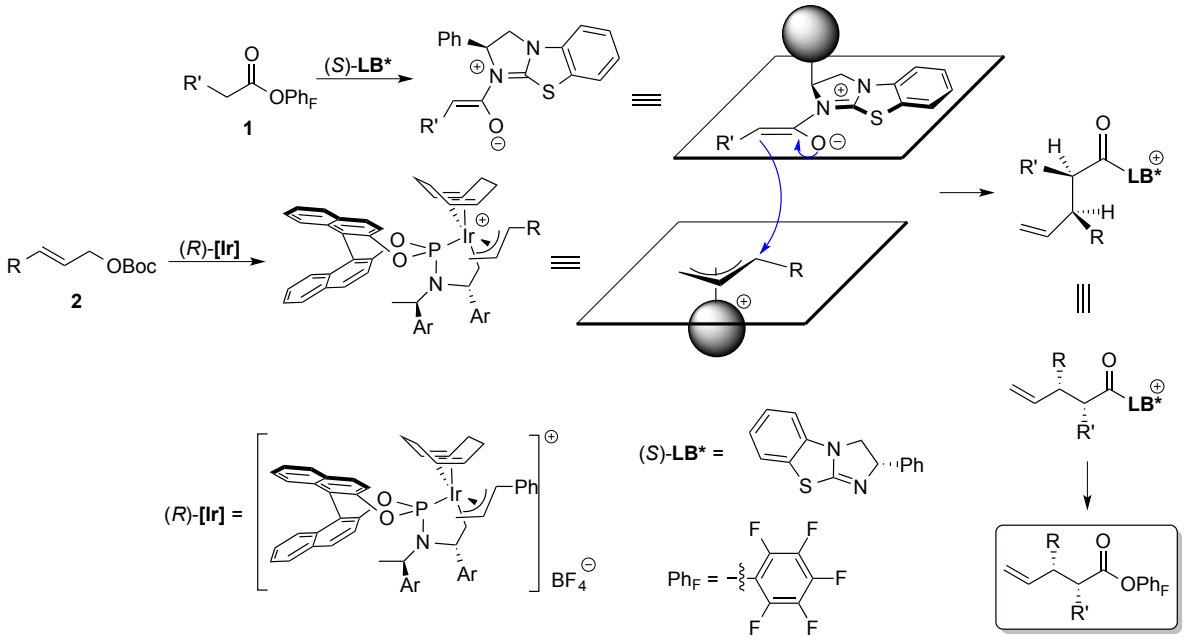


	with R^2 = Ph:	
(*S*,*R*)-**3ca**, >99% 8:1 b/l, 19:1 dr, >99% ee	R^1 = 	(*R*,*R*)-**3ca**, >99% >99:1 b/l, >20:1 dr, >99% ee
(*S*,*R*)-**3ea**, >99% 13:1 b/l, 16:1 dr, 99% ee	R^1 = 	(*R*,*R*)-**3ea**, 77% >99:1 b/l, >20:1 dr, >99% ee
(*S*,*R*)-**3ja**, >99% 8:1 b/l, 16:1 dr, >99% ee	R^1 = 	(*R*,*R*)-**3ja**, >99% >99:1 b/l, 18:1 dr, >99% ee
	with R^1 = 4-anisyl:	
(*S*,*R*)-**3ac**, 97% >20:1 b/l, >20:1 dr, 98% ee	R^2 = 	(*R*,*R*)-**3ac**, 99% >99:1 b/l, >20:1 dr, >99% ee
(*S*,*R*)-**3ad**, 99% 6:1 b/l, 12:1 dr, 95% ee	R^2 = 	(*R*,*R*)-**3ad**, >99% >99:1 b/l, 17:1 dr, >99% ee
(*S*,*R*)-**3ak**, 74% >20:1 b/l, 9:1 dr, >99% ee	R^2 = 	(*R*,*R*)-**3ak**, 95% >99:1 b/l, >20:1 dr, >99% ee

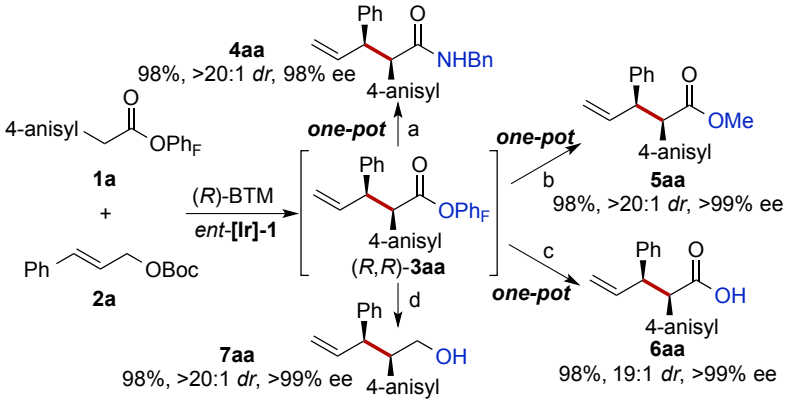
The scope of allylic carbonates that underwent the stereodivergent allylic substitutions with aryl acetic acid esters is summarized in Table 4.3.[17] Various substituents on the phenyl ring of cinnamyl carbonates were tolerated, giving the corresponding products in ≥90% yield, ≥17:1 dr, and ≥98% ee (**3aa** – **3ah**). The allylic substitutions also occurred with allylic carbonates containing heteroaryl and alkenyl substituents. Allylic carbonates bearing a thiazole ring (**2j**) and a pyrimidine ring (**2k**) reacted to form the product **3aj** and **3ak**, respectively, with high diastereoselectivity and enantioselectivity (>20:1 dr, >99% ee). The reaction with *t*-butyl sorbyl carbonate proceeded smoothly, furnishing the product **3al** in 90% yield with 17:1 dr and >99% ee.

To further demonstrate the stereodivergence of this allylation reaction, both diastereomers of **3ca**, **3ea**, **3ja**, **3ac**, **3ad**, **3ak** were prepared in high yield with high regio-, diastereo- and enantioselectivity (Table 4.4).

The pentafluorophenyl ester products generated from this allylation are readily elaborated under mild conditions. Addition of benzyl amine and $^{i}Pr_2NEt$ into the reaction mixture at the end of the allylation reaction resulted in the formation of amide **4aa** in a one-pot manner (98% yield with >20:1 dr and >99% ee). Similarly, one-pot syntheses of the methyl ester **5aa** and carboxylic acid **6aa** were realized with 4-dimethylaminopyridine (DMAP) as the catalyst for methanolysis and hydrolysis of **3aa**. Finally, the primary alcohol **7aa** was obtained through reduction of **3aa** in 98% yield with >20:1 dr and >99% ee (Scheme 4.4).



Scheme 4.3 Stereochemical model



Scheme 4.4 Derivatizations of (*R*,*R*)-**3aa**: (a) $^{i}Pr_2NEt$ (1.5 equiv), $BnNH_2$ (1.3 equiv), r.t., 12 h; (b) DMAP (0.2 equiv), Et_3N (5.0 equiv), MeOH/THF, 65 °C, 12 h; (c) DMAP (0.2 equiv), Et_3N (5.0 equiv), H_2O/THF, 65 °C, 12 h; (d) $LiAlH_4$ (1.5 equiv), THF, r.t., 12 h.

4.3 Conclusions

In summary, we show that the combination of a metallacyclic iridium complex and a chiral Lewis base catalyzes the stereodivergent allylic substitutions with aryl acetic acid esters. All four possible stereoisomers of the resulting products containing two contiguous stereocenters are accessible by simple permutations of the enantiomers of the two catalysts. The activated pentafluorophenyl esters as nucleophile precursors in this reaction allowed regeneration of the Lewis base catalyst through a "rebound" strategy, while simultaneously allowing the resulting allylation products to be converted readily to enantioenriched amides, unactivated esters and carboxylic acids.

Studies to expand the scope with respect to general aliphatic carboxylic acid derivatives are undergoing in our laboratory.

4.4 Experimental

4.4.1 General Experimental Details

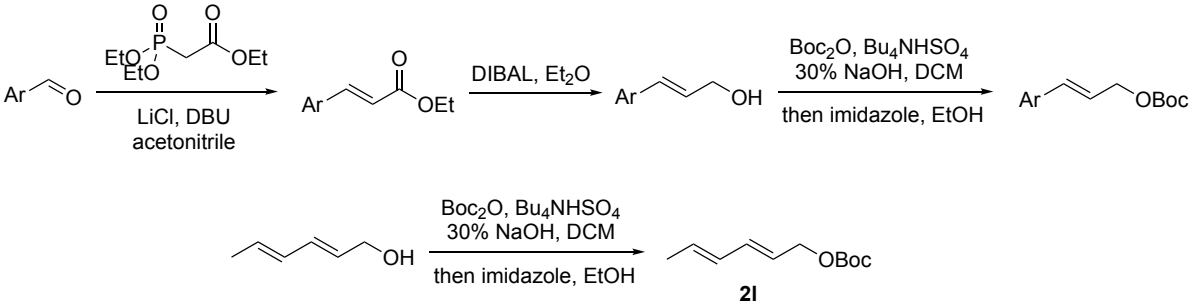
All air-sensitive manipulations were conducted under an inert atmosphere in a nitrogen-filled glovebox or by standard Schlenk techniques. Tetrahydrofuran was purified by passing it through a solvent column composed of activated A-1 alumina and degassed by freeze-pump-thaw method. $[Ir(cod)Cl]_2$ was obtained from Johnson-Matthey and used without further purification. (*R*)-BTM was obtained from Apollo Scientific. (*S*)-BTM was obtained from TCI America.

Chiral SFC analysis was conducted on a JASCO SF-2000 integrated analytical SFC system. Proton nuclear magnetic resonance (^{1}H NMR) spectra were acquired on commercial instruments (300, 400, 500 and 600 MHz) at the NMR facility of University of California, Berkeley. Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were acquired at 100, 126 and 151 MHz. Fluorine-19 nuclear magnetic resonance (^{19}F NMR) spectra were acquired at 376 MHz. The proton signal for residual non-deuterated solvent (δ 7.26 for $CHCl_3$) was used as an internal reference for ^{1}H NMR spectra. For ^{13}C NMR spectra, chemical shifts are reported relative to the δ 77.16 resonance of $CDCl_3$. For ^{19}F NMR spectra, chemical shifts are reported relative to the δ -113.15 resonance of PhF used as an external reference. Coupling constants are reported in Hz. Optical rotations were measured on a Perkin Elmer 241 Automatic Polarimeter. High-resolution mass spectra were recorded on a commercial high-resolution mass spectrometer at the Micro Mass/Analytical Facility operated by the College of Chemistry, University of California, Berkeley.

Analytical thin layer chromatography (TLC) was performed on Kieselgel 60 F_{254} glass plates pre-coated with a 0.25 mm thickness of silica gel. The TLC plates were visualized with UV light and/or by staining with $KMnO_4$. For the purification of substrates and allylation products, column chromatography was generally performed on a Teledyne Isco Combiflash® R_f system with Redi*Sep* Gold™ columns.

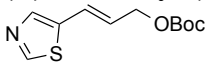
4.4.2 Syntheses of Substrates and Iridium Catalysts

1) Allylic *t*-butyl carbonates were prepared according to the procedure as shown below.[18-20]



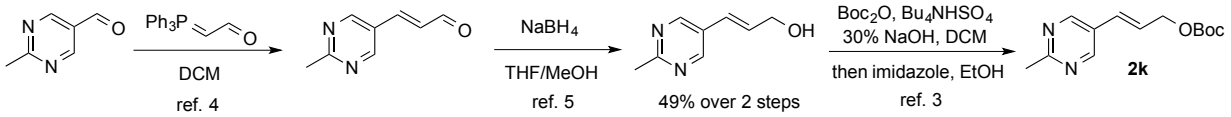
Scheme 4.5 Synthesis of allylic carbonates

(*E*)-*tert*-butyl (3-(thiazol-5-yl)allyl) carbonate (2j)



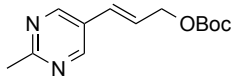
The title compound was isolated (0.33 g, 1.4 mmol, 99% starting from 1.4 mmol of the corresponding allylic alcohol) as a slightly yellow oil.
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.65 (s, 1H), 7.77 (s, 1H), 6.83 (d, J = 15.7 Hz, 1H), 6.14 (dt, J = 15.7, 6.2 Hz, 1H), 4.69 (dd, J = 6.3, 1.4 Hz, 2H), 1.50 (s, 9H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 153.3, 152.2, 142.3, 136.4, 126.6, 123.7, 82.9, 66.7, 27.9.
HRMS (ESI): *m/z* for $C_{11}H_{16}NO_3S$ $[M+H]^+$ calcd.: 242.0845, found: 242.0842.

2k was prepared according to the procedure as shown below.[20-22]



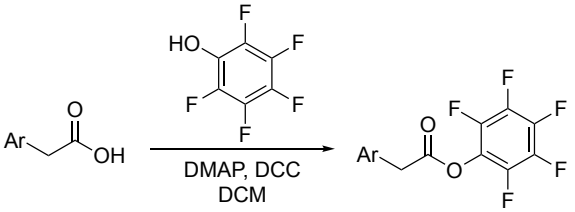
Scheme 4.6 Synthesis of **2k**

(*E*)-*tert*-butyl (3-(2-methylpyrimidin-5-yl)allyl) carbonate (2k)



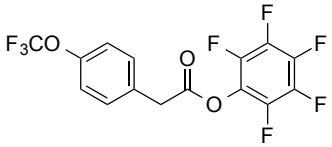
The title compound was isolated (0.26 g, 1.0 mmol, 83% starting from 1.2 mmol of the corresponding allylic alcohol) as a white solid.
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.64 (s, 2H), 6.58 (d, J = 16.1 Hz, 1H), 6.39 (dt, J = 16.1, 6.0 Hz, 1H), 4.73 (d, J = 6.0 Hz, 2H), 2.73 (s, 3H), 1.50 (s, 9H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 167.5, 154.8, 153.3, 126.9, 126.8, 126.6, 82.8, 66.8, 27.9, 25.9.
HRMS (ESI): *m/z* for $C_{13}H_{19}N_2O_3$ $[M+H]^+$ calcd.: 251.1390, found: 251.1391.

2) Aryl acetic acid esters were prepared according to the procedure as shown below.[23]



Scheme 4.7 Synthesis of aryl acetic acid esters

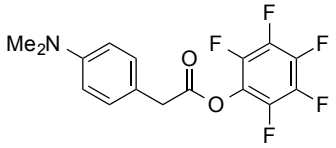
perfluorophenyl 2-(4-(trifluoromethoxy)phenyl)acetate (1d)



The title compound was isolated (1.41 g, 3.65 mmol, 73% starting from 5.00 mmol of the corresponding carboxylic acid) as a colorless oil.

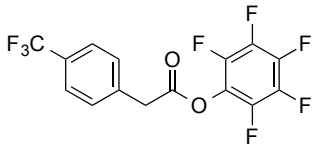
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.39 (d, *J* = 8.6 Hz, 2H), 7.24 (d, *J* = 8.8 Hz, 2H), 3.98 (s, 2H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 167.2, 149.0, 130.9, 130.8, 121.5, 120.6 (q, *J* = 257.8 Hz), 39.5.
^{19}F NMR (376 MHz, $CDCl_3$) δ -58.0 (s, 3F), -152.5 – -152.9 (m, 2F), -157.5 (t, *J* = 21.7 Hz, 1F), -162.0 – -162.3 (m, 2F).
HRMS (EI): *m/z* for $C_{15}H_6F_8O_3$ $[M]^+$ calcd.: 386.0189, found: 386.0190.

perfluorophenyl 2-(4-(dimethylamino)phenyl)acetate (1e)



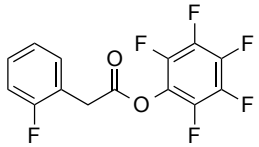
The title compound was isolated (0.78 g, 2.3 mmol, 45% yield starting from 5.00 mmol of the corresponding carboxylic acid) as a white solid.
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.21 (d, *J* = 8.6 Hz, 2H), 6.73 (d, *J* = 8.7 Hz, 2H), 3.86 (s, 2H), 2.96 (s, 6H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 168.3, 150.2, 130.0, 119.6, 112.9, 40.7, 39.4.
^{19}F NMR (376 MHz, $CDCl_3$) δ -152.4 – -152.8 (m, 2F), -158.2 (t, *J* = 21.8 Hz, 1F), -161.9 – -163.3 (m, 2F).
HRMS (ESI): *m/z* for $C_{16}H_{13}F_5NO_2$ $[M+H]^+$ calcd.: 346.0861, found: 346.0863.

perfluorophenyl 2-(4-(trifluoromethyl)phenyl)acetate (1f)



The title compound was isolated (1.15 g, 3.10 mmol, 62% starting from 5.00 mmol of the corresponding carboxylic acid) as a white solid.
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.65 (d, *J* = 8.0 Hz, 2H), 7.49 (d, *J* = 8.0 Hz, 2H), 4.04 (s, 2H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 166.9, 136.1, 130.4 (q, *J* = 33.1 Hz), 129.8, 126.0 (q, *J* = 4.0 Hz), 124.1 (q, *J* = 272.2 Hz), 40.0.
^{19}F NMR (376 MHz, $CDCl_3$) δ -62.7 (s, 3F), -152.5 – -152.8 (m, 2F), -157.4 (t, *J* = 21.7 Hz, 1F), -161.8 – -162.3 (m, 2F).
HRMS (EI): *m/z* for $C_{15}H_6F_8O_2$ $[M]^+$ calcd.: 370.0240, found: 370.0237.

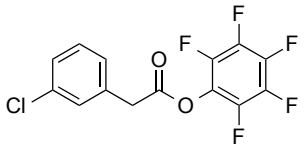
perfluorophenyl 2-(2-fluorophenyl)acetate (1h)



The title compound was isolated (1.07 g, 3.34 mmol, 67% starting from 5.00 mmol of the corresponding carboxylic acid) as a colorless oil.
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37 – 7.31 (m, 2H), 7.17 (t, *J* = 7.5 Hz, 1H), 7.12 (t, *J* = 9.0 Hz, 1H), 4.03 (s, 2H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 166.8, 161.2 (d, *J* = 247.3 Hz), 131.4 (d, *J* = 3.6 Hz), 130.0 (d, *J*

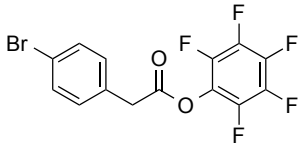
= 8.1 Hz), 124.6 (d, *J* = 3.7 Hz), 119.7 (d, *J* = 15.7 Hz), 115.8 (d, *J* = 21.4 Hz), 33.7 (d, *J* = 3.5 Hz).
^{19}F NMR (376 MHz, $CDCl_3$) δ -116.8 (s, 1F), -152.1 – -153.1 (m, 2F), -157.8 (t, *J* = 21.7 Hz, 1F), -161.5 – -163.0 (m, 2F).
HRMS (EI): *m/z* for $C_{14}H_6F_6O_2$ $[M]^+$ calcd.: 320.0272, found: 320.0274.

perfluorophenyl 2-(3-chlorophenyl)acetate (1i)



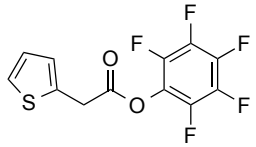
The title compound was isolated (0.71 g, 2.1 mmol, 42% starting from 5.00 mmol of the corresponding carboxylic acid) as a colorless oil.
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37 (s, 1H), 7.34 – 7.31 (m, 2H), 7.26 – 7.23 (m, 1H), 3.95 (s, 2H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 167.0, 134.9, 133.9, 130.3, 129.6, 128.3, 127.6, 39.8.
^{19}F NMR (376 MHz, $CDCl_3$) δ -152.4 – -152.9 (m, 2F), -157.6 (t, *J* = 21.8 Hz, 1F), -161.8 – -162.4 (m, 2F).
HRMS (EI): *m/z* for $C_{14}H_6ClF_5O_2$ $[M]^+$ calcd.: 335.9976, found: 335.9980.

perfluorophenyl 2-(4-bromophenyl)acetate (1j)



The title compound was isolated (1.46 g, 3.84 mmol, 77% starting from 5.00 mmol of the corresponding carboxylic acid) as a colorless oil.
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.3 Hz, 2H), 7.24 (d, *J* = 8.3 Hz, 2H), 3.93 (s, 2H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 167.1, 132.2, 131.1, 122.1, 39.7.
^{19}F NMR (376 MHz, $CDCl_3$) δ -152.5 – -153.1 (m, 2F), -157.6 (t, *J* = 21.7 Hz, 1F), -162.0 – -162.5 (m, 2F).
HRMS (EI): *m/z* for $C_{14}H_6BrF_5O_2$ $[M]^+$ calcd.: 379.9471, found: 379.9474.

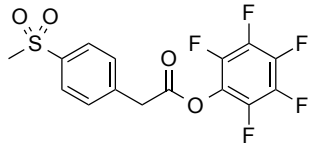
perfluorophenyl 2-(thiophen-2-yl)acetate (1k)



The title compound was isolated (0.87 g, 2.8 mmol, 56% starting from 5.00 mmol of the corresponding carboxylic acid) as a colorless oil.
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.29 (dd, *J* = 5.2, 1.2 Hz, 1H), 7.07 (dd, *J* = 3.4, 1.2 Hz, 1H), 7.02 (dd, *J* = 5.1, 3.5 Hz, 1H), 4.20 (s, 2H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 166.6, 132.7, 127.8, 127.3, 126.0, 34.5.
^{19}F NMR (376 MHz, $CDCl_3$) δ -152.2 – -152.8 (m, 2F), -157.6 (t, *J* = 21.7 Hz, 1F), -161.9 – -162.4 (m, 2F).

HRMS (EI): *m/z* for $C_{12}H_5F_5O_2S$ $[M]^+$ calcd.: 307.9930, found: 307.9931.

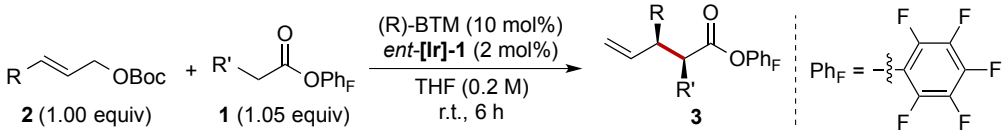
perfluorophenyl 2-(4-(methylsulfonyl)phenyl)acetate (1m)



The title compound was isolated (0.76 g, 2.0 mmol, 40% starting from 5.00 mmol of the corresponding carboxylic acid) as a white solid.
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.3 Hz, 2H), 7.58 (d, *J* = 8.1 Hz, 2H), 4.08 (s, 2H), 3.07 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 166.6, 140.4, 138.2, 130.5, 128.2, 44.6, 40.0.
^{19}F NMR (376 MHz, $CDCl_3$) δ -152.4 – -153.0 (m, 2F), -157.1 (t, *J* = 21.7 Hz, 1F), -161.7 – -162.1 (m, 2F).
HRMS (EI): *m/z* for $C_{15}H_{10}F_5O_4S$ $[M+H]^+$ calcd.: 381.0214, found: 381.0216.

3) Iridium catalysts were prepared according to published procedures.[24]

4.4.3 General Procedure for the Ir-Catalyzed Allylation of Aryl Acetic Acid Esters

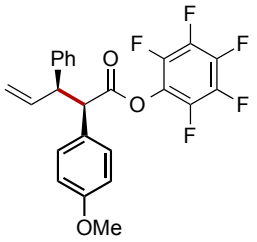


Scheme 4.8 General procedure for allylation

In a nitrogen-filled dry-box, the allyl *t*-butyl carbonate **2** (0.100 mmol, 1.00 equiv) and aryl acetic acid ester **1** (0.105 mmol, 1.05 equiv) were added to a 1-dram vial equipped with a magnetic stir bar. Thereafter, *ent*-**[Ir]-1** (8 mM in THF, 0.25 mL, 0.002 mmol, 2 mol%) and (R)-BTM (40 mM in THF, 0.25 mL, 0.010 mmol, 10 mol%) were added sequentially via syringe. The vial was sealed with a cap containing PTFE/silicone septa and removed from the dry box. The reaction mixture was stirred at r.t. for 6 h. Then the mixture was diluted with 2 mL of hexanes, and filtered through a 0.5-inch plug of silica gel (eluting with 1:1 hexanes:EtOAc, 8 mL). After removal of solvent under vacuum, the crude mixture was purified by column chromatography performed on a Teledyne Isco Combiflash® R_f system with Redi*Sep* Gold™ columns (4-gram silica gel column, 100/0 to 90/10 of hexanes/EtOAc).

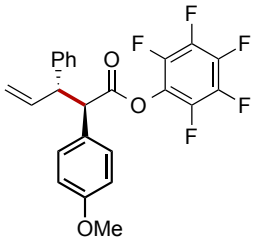
The ratio of diastereomers was determined by ^{1}H NMR analysis of crude reaction mixture. In general, the product was obtained as a mixture of two diastereomers strongly favoring one diastereomer over the other. For characterizations, an additional preparative TLC separation was performed to decrease the amount of the minor diastereomer in the product with 1:1 hexanes:toluene as eluent system. For polar substrates, 1:1 hexanes:ethyl acetate was employed instead.

perfluorophenyl (2*R*,3*R*)-2-(4-methoxyphenyl)-3-phenylpent-4-enoate ((*R*,*R*)-3aa)



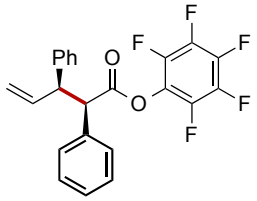
Prepared according to the general procedure as described above. The diastereomeric ratio was determined to be >20:1. The crude mixture was purified by column chromatography to give the title compound as a colorless oil (43.1 mg, 0.0962 mmol, 96%).
The **enantiomeric excess** was determined by SFC analysis to be >99% with t_R = 2.01 min (major) and t_R = 2.67 min (minor) [AD-H, 5.0% ^{i}PrOH, 2.5 mL/min, 240 nm, 40 °C].
$[\alpha]_D^{25}$ = –86.4° (c 0.29, CH_2Cl_2).
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19 – 7.08 (m, 5H), 7.06 – 7.02 (m, 2H), 6.74 – 6.69 (m, 2H), 6.18 (ddd, *J* = 17.1, 10.4, 7.8 Hz, 1H), 5.33 – 5.18 (m, 2H), 4.25 (d, *J* = 11.5 Hz, 1H), 4.09 (dd, *J* = 11.5, 7.7 Hz, 1H), 3.72 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 169.3, 159.2, 139.8, 138.6, 129.8, 128.6, 128.4, 127.0, 126.8, 116.9, 114.1, 55.8, 55.2, 53.2.
^{19}F NMR (376 MHz, $CDCl_3$) δ -151.8 – -152.1 (m, 2F), -158.1 (t, *J* = 21.8 Hz, 1F), -162.4 – -162.7 (m, 2F).
HRMS (EI): *m/z* for $C_{24}H_{17}F_5O_3$ $[M]^+$ calcd.: 448.1098, found: 448.1100.

perfluorophenyl (2*R*,3*S*)-2-(4-methoxyphenyl)-3-phenylpent-4-enoate ((*R*,*S*)-3aa)



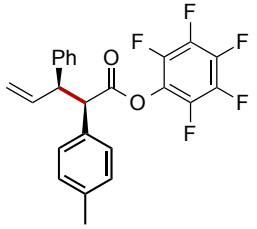
Prepared according to the general procedure as described above (**[Ir]-1** was used instead of *ent*-**[Ir]-1**). The diastereomeric ratio was determined to be >20:1. The branched/linear selectivity was determined to be 10:1. The crude mixture was purified by column chromatography to give the title compound as a white solid (43.6 mg, 0.0973 mmol, 97%).
The **enantiomeric excess** was determined by SFC analysis to be >99% with t_R = 3.76 min (major) and t_R = 3.37 min (minor) [AD-H, 5.0% ^{i}PrOH, 2.5 mL/min, 240 nm, 40 °C].
$[\alpha]_D^{25}$ = –77.1° (c 0.24, CH_2Cl_2).
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 – 7.32 (m, 6H), 7.32 – 7.26 (m, 1H), 6.96 – 6.91 (m, 2H), 5.77 (ddd, *J* = 17.0, 10.3, 7.7 Hz, 1H), 4.94 (d, *J* = 10.3 Hz, 1H), 4.82 (d, *J* = 17.0 Hz, 1H), 4.28 (d, *J* = 11.6 Hz, 1H), 4.11 (dd, *J* = 11.6, 7.7 Hz, 1H), 3.83 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 168.8, 159.6, 140.9, 138.1, 130.1, 129.0, 128.1, 127.4, 127.4, 117.5, 114.4, 55.9, 55.4, 53.0.
^{19}F NMR (376 MHz, $CDCl_3$) δ -152.1 – -152.4 (m, 2F), -158.3 (t, *J* = 21.8 Hz, 1F), -162.5 – -162.9 (m, 2F).
HRMS (EI): *m/z* for $C_{24}H_{17}F_5O_3$ $[M]^+$ calcd.: 448.1098, found: 448.1093.

perfluorophenyl (2*R*,3*R*)-2,3-diphenylpent-4-enoate (3ba)



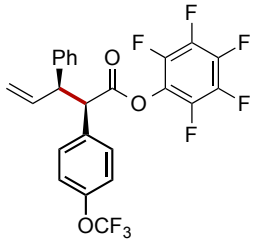
Prepared according to the general procedure as described above. The diastereomeric ratio was determined to be 18:1. The crude mixture was purified by column chromatography to give the title compound as a colorless oil (40.7 mg, 0.0974 mmol, 97%).
The **enantiomeric excess** was determined by SFC analysis to be 99% with t_R = 2.55 min (major) and t_R = 3.55 min (minor) [AD-H, 2.0% ^{i}PrOH, 2.5 mL/min, 240 nm, 40 °C].
[α]$_D^{25}$ = –70.6° (c 0.29, CH_2Cl_2).
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 – 7.13 (m, 7H), 7.11 – 7.07 (m, 1H), 7.06 – 7.03 (m, 2H), 6.20 (ddd, *J* = 17.2, 10.4, 7.7 Hz, 1H), 5.32 (d, *J* = 17.2 Hz, 1H), 5.24 (d, *J* = 10.3 Hz, 1H), 4.30 (d, *J* = 11.5 Hz, 1H), 4.14 (dd, *J* = 11.5, 7.7 Hz, 1H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 169.1, 139.6, 138.5, 135.0, 128.7, 128.7, 128.5, 128.4, 128.0, 126.9, 116.9, 56.6, 53.2.
^{19}F NMR (376 MHz, $CDCl_3$) δ -151.5 – -152.9 (m, 2F), -158.0 (t, *J* = 21.8 Hz, 1F), -162.2 – -163.3 (m, 2F).
HRMS (EI): *m/z* for $C_{23}H_{15}F_5O_2$ $[M]^+$ calcd.: 418.0992, found: 418.0996.

perfluorophenyl (2*R*,3*R*)-3-phenyl-2-(*p*-tolyl)pent-4-enoate (3ca)



Prepared according to the general procedure as described above. The diastereomeric ratio was determined to be >20:1. The crude mixture was purified by column chromatography to give the title compound as a colorless oil (43.4 mg, 0.100 mmol, >99%).
The **enantiomeric excess** was determined by SFC analysis to be >99% with t_R = 1.36 min (major) and t_R = 1.65 min (minor) [AD-H, 5.0% ^{i}PrOH, 2.5 mL/min, 240 nm, 40 °C].
[α]$_D^{25}$ = –77.4° (c 0.37, CH_2Cl_2).
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20 – 7.14 (m, 2H), 7.12 – 7.08 (m, 3H), 7.07 – 7.03 (m, 2H), 6.99 (d, *J* = 7.8 Hz, 2H), 6.18 (ddd, *J* = 17.1, 10.3, 7.8 Hz, 1H), 5.30 (d, *J* = 17.1 Hz, 1H), 5.22 (d, *J* = 10.3 Hz, 1H), 4.28 (d, *J* = 11.4 Hz, 1H), 4.12 (dd, *J* = 11.4, 7.7 Hz, 1H), 2.24 (s, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 169.3, 139.8, 138.6, 137.6, 131.9, 129.4, 128.5, 128.5, 128.4, 126.8, 116.9, 56.1, 53.1, 21.2.
^{19}F NMR (376 MHz, $CDCl_3$) δ -151.4 – -152.7 (m, 2F), -158.1 (t, *J* = 21.7 Hz, 1F), -161.9 – -162.8 (m, 2F).
HRMS (EI): *m/z* for $C_{24}H_{17}F_5O_2$ $[M]^+$ calcd.: 432.1149, found: 432.1152.

perfluorophenyl (2*R*,3*R*)-3-phenyl-2-(4-(trifluoromethoxy)phenyl)pent-4-enoate (3da)



Prepared according to the general procedure as described above. The diastereomeric ratio was determined to be 16:1. The crude mixture was purified by column chromatography to give the title compound as a colorless oil (49.3 mg, 0.0982 mmol, 98%).

The **enantiomeric excess** was determined by SFC analysis to be 97% with t_R = 1.67 min (major) and t_R = 2.21 min (minor) [AD-H, 2.0% ^{i}PrOH, 2.5 mL/min, 240 nm, 40 ^{o}C].

$[\alpha]_D^{25}$ = –69.9^o (c 0.44, CH_2Cl_2).

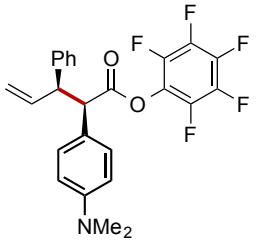
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 – 7.20 (m, 2H), 7.20 – 7.15 (m, 2H), 7.15 – 7.08 (m, 1H), 7.06 – 6.97 (m, 4H), 6.19 (ddd, *J* = 17.1, 10.4, 7.8 Hz, 1H), 5.32 (d, *J* = 17.1 Hz, 1H), 5.25 (d, *J* = 10.3 Hz, 1H), 4.30 (d, *J* = 11.4 Hz, 1H), 4.08 (dd, *J* = 11.4, 7.8 Hz, 1H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 168.8, 148.9, 139.3, 138.0, 133.8, 130.1, 128.7, 128.3, 127.2, 121.4, 120.5 (q, *J* = 257.4 Hz,), 117.3, 56.0, 53.5.

^{19}F NMR (376 MHz, $CDCl_3$) δ -58.0 (s, 3F), -150.6 – -152.1 (m, 2F), -157.6 (t, *J* = 21.7 Hz, 1F), -161.5 – -163.6 (m, 2F).

HRMS (EI): *m/z* for $C_{24}H_{14}F_8O_3$ $[M]^+$ calcd.: 502.0815, found: 502.0816.

perfluorophenyl (2*R*,3*R*)-2-(4-(dimethylamino)phenyl)-3-phenylpent-4-enoate (3ea)



Prepared according to the general procedure as described above. The diastereomeric ratio was determined to be >20:1. The crude mixture was purified by column chromatography to give the title compound as a colorless oil (35.3 mg, 0.0766 mmol, 77%).

The **enantiomeric excess** was determined by SFC analysis to be >99% with t_R = 2.78 min (major) and t_R = 4.64 min (minor) [AD-H, 5.0% ^{i}PrOH, 2.5 mL/min, 240 nm, 40 ^{o}C].

$[\alpha]_D^{25}$ = –90.9^o (c 0.21, CH_2Cl_2).

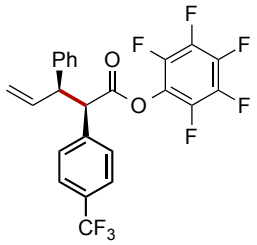
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.20 – 7.15 (m, 2H), 7.12 – 7.03 (m, 5H), 6.53 (d, *J* = 8.8 Hz, 2H), 6.17 (ddd, *J* = 17.1, 10.3, 7.8 Hz, 1H), 5.28 (d, *J* = 17.1 Hz, 1H), 5.20 (d, *J* = 10.4 Hz, 1H), 4.21 (d, *J* = 11.4 Hz, 1H), 4.10 (dd, *J* = 11.4, 7.8 Hz, 1H), 2.87 (s, 6H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 169.5, 150.0, 140.2, 139.0, 129.4, 128.5, 128.4, 126.7, 122.3, 116.7, 112.4, 55.6, 53.0, 40.5.

^{19}F NMR (376 MHz, $CDCl_3$) δ -151.5 – -152.0 (m, 2F), -158.4 (t, *J* = 21.7 Hz, 1F), -162.6 – -162.9 (m, 2F).

HRMS (EI): *m/z* for $C_{25}H_{20}F_5NO_2$ $[M]^+$ calcd.: 461.1414, found: 461.1414.

perfluorophenyl (2*R*,3*R*)-3-phenyl-2-(4-(trifluoromethyl)phenyl)pent-4-enoate (3fa)



Prepared according to the general procedure as described above (20 mol% of (R)-BTM catalyst was used instead of 10 mol%). The diastereomeric ratio was determined to be 11:1. The crude mixture was purified by column chromatography to give the title compound as a colorless oil (43.6 mg, 0.0897 mmol, 90%).

The **enantiomeric excess** was determined by SFC analysis to be 98% with t_R = 1.14 min (major) and t_R = 1.46 min (minor) [AD-H, 3.0% ^{i}PrOH, 2.5 mL/min, 240 nm, 40 °C].

$[\alpha]_D^{25}$ = –62.9° (c 0.35, CH_2Cl_2).

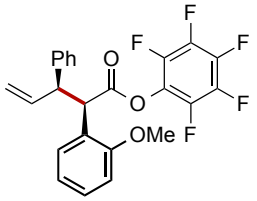
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (d, *J* = 8.2 Hz, 2H), 7.34 (d, *J* = 8.2 Hz, 2H), 7.20 – 7.15 (m, 2H), 7.15 – 7.09 (m, 1H), 7.06 – 7.01 (m, 2H), 6.19 (ddd, *J* = 17.2, 10.4, 7.8 Hz, 1H), 5.32 (d, *J* = 17.2 Hz, 1H), 5.26 (d, *J* = 10.4 Hz, 1H), 4.37 (d, *J* = 11.4 Hz, 1H), 4.12 (dd, *J* = 11.4, 7.8 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 168.5, 139.0, 137.9, 130.2 (q, *J* = 32.8 Hz), 129.0, 128.8, 128.2, 127.2, 125.6 (q, *J* = 3.9 Hz), 124.0 (q, *J* = 272.3 Hz), 117.4, 56.4, 53.4.

^{19}F NMR (376 MHz, $CDCl_3$) δ -62.8 (s, 3F), -151.6 – -152.3 (m, 2F), -157.5 (t, *J* = 21.6 Hz, 1F), -161.9 – -162.5 (m, 2F).

HRMS (EI): *m/z* for $C_{24}H_{14}F_8O_2$ $[M]^+$ calcd.: 486.0866, found: 486.0862.

perfluorophenyl (2*R*,3*R*)-2-(2-methoxyphenyl)-3-phenylpent-4-enoate (3ga)



Prepared according to the general procedure as described above (reaction time was extended to 9 h, and 1.1 equiv of diisopropylethylamine was added into reaction mixture). The diastereomeric ratio was determined to be 11:1. The crude mixture was purified by column chromatography to give the title compound as a colorless oil (42.8 mg, 0.0955 mmol, 96%).

The **enantiomeric excess** was determined by SFC analysis to be >99% with t_R = 1.31 min (major) and t_R = 2.13 min (minor) [AD-H, 5.0% ^{i}PrOH, 2.5 mL/min, 240 nm, 40 °C].

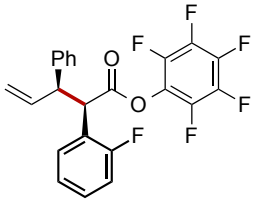
$[\alpha]_D^{25}$ = –49.5° (c 0.33, CH_2Cl_2).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.38 – 7.35 (m, 1H), 7.16 – 7.11 (m, 3H), 7.10 – 7.05 (m, 3H), 6.86 (td, *J* = 7.6, 1.1 Hz, 1H), 6.69 (dd, *J* = 8.3, 1.1 Hz, 1H), 6.21 (ddd, *J* = 17.4, 10.3, 7.8 Hz, 1H), 5.27 (d, *J* = 17.1 Hz, 1H), 5.20 (dd, *J* = 10.3, 1.0 Hz, 1H), 4.96 (d, *J* = 11.0 Hz, 1H), 4.14 (dd, *J* = 11.0, 7.8 Hz, 1H), 3.66 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 169.4, 157.0, 140.1, 139.0, 129.0, 128.9, 128.4, 128.1, 126.6,

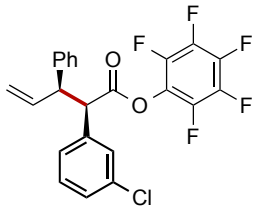
123.9, 120.8, 116.6, 110.8, 55.6, 52.4, 47.7.
^{19}F NMR (376 MHz, $CDCl_3$) δ -151.8 – -152.2 (m, 2F), -158.4 (t, *J* = 21.8 Hz, 1F), -162.4 – -163.1 (m, 2F).
HRMS (EI): *m/z* for $C_{24}H_{17}F_5O_3$ $[M]^+$ calcd.: 448.1098, found: 448.1099.

perfluorophenyl (2*R*,3*R*)-2-(2-fluorophenyl)-3-phenylpent-4-enoate (3ha)



Prepared according to the general procedure as described above (20 mol% of (R)-BTM catalyst was used instead of 10 mol%). The diastereomeric ratio was determined to be 12:1. The crude mixture was purified by column chromatography to give the title compound as a colorless oil (38.7 mg, 0.0888 mmol, 89%).
The **enantiomeric excess** was determined by SFC analysis to be 98% with t_R = 3.31 min (major) and t_R = 3.10 min (minor) [OD-H, 3.0% ^{i}PrOH, 2.0 mL/min, 240 nm, 40 °C].
$[\alpha]_D^{25}$ = –49.2° (c 0.24, CH_2Cl_2).
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 – 7.41 (m, 1H), 7.19 – 7.12 (m, 3H), 7.12 – 7.02 (m, 4H), 6.90 – 6.83 (m, 1H), 6.19 (ddd, *J* = 17.2, 10.3, 7.8 Hz, 1H), 5.30 (d, *J* = 17.2 Hz, 1H), 5.23 (d, *J* = 10.3 Hz, 1H), 4.79 (d, *J* = 11.3 Hz, 1H), 4.16 (dd, *J* = 11.3, 7.8 Hz, 1H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 168.6, 160.5 (d, *J* = 247.0 Hz), 139.4, 138.4, 129.7 (d, *J* = 8.6 Hz), 129.3 (d, *J* = 2.6 Hz), 128.5, 128.2, 127.0, 124.5 (d, *J* = 3.4 Hz), 122.5 (d, *J* = 14.3 Hz), 117.12, 115.6 (d, *J* = 22.8 Hz), 52.4, 47.7.
^{19}F NMR (376 MHz, $CDCl_3$) δ -117.2 – -117.4 (m, 1F), -151.8 – -152.6 (m, 2F), -157.8 (t, *J* = 21.7 Hz, 1F), -161.9 – -162.7 (m, 2F).
HRMS (EI): *m/z* for $C_{23}H_{14}F_6O_2$ $[M]^+$ calcd.: 436.0898, found: 436.0897.

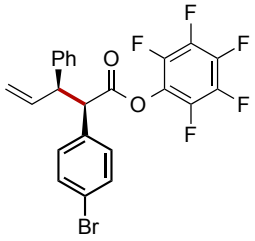
perfluorophenyl (2*R*,3*R*)-2-(3-chlorophenyl)-3-phenylpent-4-enoate (3ia)



Prepared according to the general procedure as described above (20 mol% of (R)-BTM catalyst was used instead of 10 mol%). The diastereomeric ratio was determined to be >20:1. The crude mixture was purified by column chromatography to give the title compound as a colorless oil (42.8 mg, 0.0945 mmol, 94%).
The **enantiomeric excess** was determined by SFC analysis to be >99% with t_R = 1.50 min (major) and t_R = 1.88 min (minor) [AD-H, 5.0% ^{i}PrOH, 2.5 mL/min, 240 nm, 40 °C].
$[\alpha]_D^{25}$ = –74.5° (c 0.24, CH_2Cl_2).
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (t, *J* = 1.9 Hz, 1H), 7.21 – 7.06 (m, 6H), 7.06 – 7.02 (m, 2H), 6.18 (ddd, *J* = 17.1, 10.3, 7.8 Hz, 1H), 5.31 (d, *J* = 17.2 Hz, 1H), 5.24 (d, *J* = 10.3 Hz, 1H), 4.26

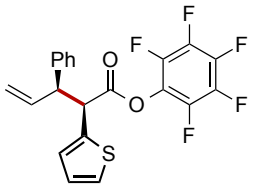
(d, J = 11.5 Hz, 1H), 4.09 (dd, J = 11.4, 7.8 Hz, 1H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 168.6, 139.2, 138.1, 137.0, 134.5, 129.9, 128.8, 128.7, 128.3, 127.2, 127.0, 117.3, 56.3, 53.3.
^{19}F NMR (376 MHz, $CDCl_3$) δ -151.7 – -152.2 (m, 2F), -157.6 (t, J = 21.6 Hz, 1F), -162.1 – -162.2 (m, 2F).
HRMS (EI): *m/z* for $C_{23}H_{14}ClF_5O_2$ $[M]^+$ calcd.: 452.0602, found: 452.0603.

perfluorophenyl (2*R*,3*R*)-2-(4-bromophenyl)-3-phenylpent-4-enoate (3ja)



Prepared according to the general procedure as described above. The diastereomeric ratio was determined to be 18:1. The crude mixture was purified by column chromatography to give the title compound as a colorless oil (49.9 mg, 0.100 mmol, >99%).
The **enantiomeric excess** was determined by SFC analysis to be >99% with t_R = 4.27 min (major) and t_R = 6.19 min (minor) [AD-H, 3.0% ^{i}PrOH, 2.5 mL/min, 240 nm, 40 °C].
$[\alpha]_D^{25}$ = –82.7° (c 0.22, CH_2Cl_2).
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.28 (m, 2H), 7.21 – 7.16 (m, 2H), 7.15 – 7.07 (m, 3H), 7.05 – 6.99 (m, 2H), 6.17 (ddd, J = 17.1, 10.4, 7.8 Hz, 1H), 5.30 (d, J = 17.2 Hz, 1H), 5.24 (d, J = 10.3 Hz, 1H), 4.26 (d, J = 11.4 Hz, 1H), 4.07 (dd, J = 11.5, 7.8 Hz, 1H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 168.7, 139.3, 138.2, 134.2, 131.9, 130.3, 128.7, 128.3, 127.2, 122.2, 117.2, 56.1, 53.2.
^{19}F NMR (376 MHz, $CDCl_3$) δ -151.8 – -152.1 (m, 2F), -157.6 (t, J = 21.7 Hz, 1F), -162.1 – -162.4 (m, 2F).
HRMS (EI): *m/z* for $C_{23}H_{14}BrF_5O_2$ $[M]^+$ calcd.: 496.0097, found: 496.0098.

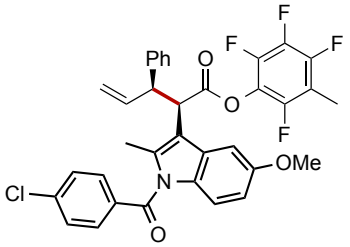
perfluorophenyl (2*S*,3*R*)-3-phenyl-2-(thiophen-2-yl)pent-4-enoate (3ka)



Prepared according to the general procedure as described above (20 mol% of (R)-BTM catalyst was used instead of 10 mol%). The diastereomeric ratio was determined to be 17:1. The crude mixture was purified by column chromatography to give the title compound as a colorless oil (41.5 mg, 0.0979 mmol, 98%).
The **enantiomeric excess** was determined by SFC analysis to be >99% with t_R = 1.42 min (major) and t_R = 1.61 min (minor) [AD-H, 5.0% ^{i}PrOH, 2.5 mL/min, 240 nm, 40 °C].
$[\alpha]_D^{25}$ = –37.4° (c 0.35, CH_2Cl_2).
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.24 – 7.21 (m, 2H), 7.19 – 7.14 (m, 1H), 7.14 – 7.10 (m, 3H), 6.85

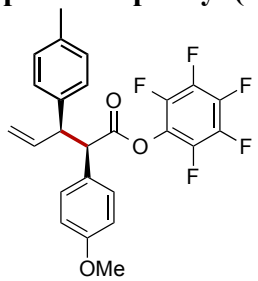
(dd, *J* = 3.7, 1.2 Hz, 1H), 6.81 (dd, *J* = 5.1, 3.5 Hz, 1H), 6.18 (ddd, *J* = 17.1, 10.3, 8.1 Hz, 1H), 5.32 (d, *J* = 17.1 Hz, 1H), 5.24 (d, *J* = 10.4 Hz, 1H), 4.58 (d, *J* = 11.3 Hz, 1H), 4.08 (dd, *J* = 11.3, 8.1 Hz, 1H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 168.2, 139.6, 137.9, 136.8, 128.7, 128.2, 127.3, 127.2, 126.8, 125.8, 117.6, 54.7, 52.2.
^{19}F NMR (376 MHz, $CDCl_3$) δ -151.4 – -151.8 (m, 2F), -157.8 (t, *J* = 21.7 Hz, 1F), -162.1 – -162.7 (m, 2F).
HRMS (EI): *m/z* for $C_{21}H_{13}F_5O_2S$ $[M]^+$ calcd.: 424.0556, found: 424.0555.

2,3,4,6-tetrafluoro-5-methylphenyl (2*R*,3*R*)-2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl)-3-phenylpent-4-enoate (3la)



Prepared according to the general procedure as described above (1.1 equiv of diisopropylethylamine was added into reaction mixture). The diastereomeric ratio was determined to be >20:1. The crude mixture was purified by column chromatography to give the title compound as a yellow oil (58.8 mg, 0.0918 mmol, 92%).
The **enantiomeric excess** was determined by SFC analysis to be >99% with t_R = 6.54 min (major) and t_R = 3.90 min (minor) [AD-H, 8.0% ^{i}PrOH, 2.5 mL/min, 240 nm, 40 °C].
$[\alpha]_D^{25}$ = –129.6° (c 0.56, CH_2Cl_2).
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.42 – 7.34 (m, 4H), 7.18 – 7.11 (m, 4H), 7.07 (d, *J* = 9.0 Hz, 1H), 7.04 – 6.99 (m, 2H), 6.73 (dd, *J* = 9.0, 2.5 Hz, 1H), 6.27 (ddd, *J* = 17.3, 10.4, 6.9 Hz, 1H), 5.40 (d, *J* = 17.3 Hz, 1H), 5.33 (d, *J* = 10.4 Hz, 1H), 4.56 – 4.42 (m, 2H), 3.88 (s, 3H), 2.02 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 168.3, 168.1, 156.0, 140.1, 139.6, 138.3, 135.9, 133.7, 131.3, 131.2, 129.2, 128.4, 128.1, 127.0, 117.2, 114.7, 112.9, 111.9, 103.0, 55.9, 49.9, 47.9, 13.5.
^{19}F NMR (376 MHz, $CDCl_3$) δ -151.6 – -152.1 (m, 2F), -157.8 (t, *J* = 21.7 Hz, 1F), -162.0 – -162.6 (m, 2F).
HRMS (EI): *m/z* for $C_{34}H_{23}ClF_5NO_4$ $[M]^+$ calcd.: 639.1236, found: 639.1230.

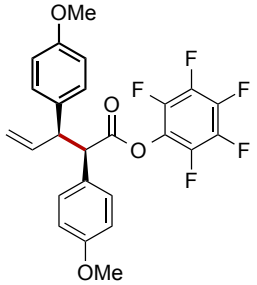
perfluorophenyl (2*R*,3*R*)-2-(4-methoxyphenyl)-3-(*p*-tolyl)pent-4-enoate (3ab)



Prepared according to the general procedure as described above. The diastereomeric ratio was determined to be >20:1. The crude mixture was purified by column chromatography to give the

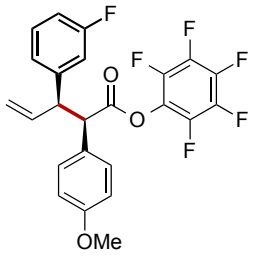
title compound as a colorless oil (45.1 mg, 0.0976 mmol, 98%).
The **enantiomeric excess** was determined by SFC analysis to be 98% with t_R = 2.10 min (major) and t_R = 2.60 min (minor) [AD-H, 5.0% *i*PrOH, 2.5 mL/min, 240 nm, 40 °C].
$[\alpha]_D^{25}$ = –76.4° (c 0.28, CH_2Cl_2).
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.14 (d, *J* = 8.7 Hz, 2H), 6.98 (d, *J* = 7.9 Hz, 2H), 6.93 (d, *J* = 8.1 Hz, 2H), 6.73 (d, *J* = 8.7 Hz, 2H), 6.16 (ddd, *J* = 17.1, 10.3, 7.8 Hz, 1H), 5.27 (d, *J* = 17.2 Hz, 1H), 5.19 (d, *J* = 10.4 Hz, 1H), 4.24 (d, *J* = 11.4 Hz, 1H), 4.07 (dd, *J* = 11.4, 7.8 Hz, 1H), 3.73 (s, 3H), 2.23 (s, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 169.4, 159.1, 138.9, 136.7, 136.4, 129.8, 129.3, 128.1, 127.1, 116.6, 114.0, 55.7, 55.2, 52.7, 21.1.
^{19}F NMR (376 MHz, $CDCl_3$) δ -151.8 – -152.0 (m, 2F), -158.1 (t, *J* = 21.8 Hz, 1F), -162.4 – -162.8 (m, 2F).
HRMS (EI): *m/z* for $C_{25}H_{19}F_5O_3$ $[M]^+$ calcd.: 462.1254, found: 462.1257.

perfluorophenyl (2*R*,3*R*)-2,3-bis(4-methoxyphenyl)pent-4-enoate (3ac)



Prepared according to the general procedure as described above. The diastereomeric ratio was determined to be >20:1. The crude mixture was purified by column chromatography to give the title compound as a colorless oil (47.4 mg, 0.0991 mmol, 99%).
The **enantiomeric excess** was determined by SFC analysis to be >99% with t_R = 3.93 min (major) and t_R = 5.89 min (minor) [AD-H, 4.0% *i*PrOH, 2.5 mL/min, 240 nm, 40 °C].
$[\alpha]_D^{25}$ = –88.5° (c 0.30, CH_2Cl_2).
^{1}H NMR (600 MHz, $CDCl_3$)) δ 7.12 (d, *J* = 8.6 Hz, 2H), 6.94 (d, *J* = 8.6 Hz, 2H), 6.77 – 6.65 (m, 4H), 6.15 (ddd, *J* = 17.6, 10.3, 7.7 Hz, 1H), 5.27 (d, *J* = 17.1 Hz, 1H), 5.20 (d, *J* = 10.1 Hz, 1H), 4.19 (d, *J* = 11.4 Hz, 1H), 4.05 (dd, *J* = 11.4, 7.7 Hz, 1H), 3.73 (s, 3H), 3.72 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 169.4, 159.2, 158.4, 138.9, 131.8, 129.8, 129.3, 127.2, 116.5, 114.1, 114.0, 55.9, 55.3, 52.3.
^{19}F NMR (376 MHz, $CDCl_3$)) δ -151.6 – -152.5 (m, 2F), -158.1 (t, *J* = 21.5 Hz, 1F), -162.2 – -163.1 (m, 2F).
HRMS (EI): *m/z* for $C_{25}H_{19}F_5O_4$ $[M]^+$ calcd.: 478.1204, found: 478.1206.

perfluorophenyl (2*R*,3*R*)-3-(3-fluorophenyl)-2-(4-methoxyphenyl)pent-4-enoate (3ad)



Prepared according to the general procedure as described above. The diastereomeric ratio was determined to be 17:1. The crude mixture was purified by column chromatography to give the title compound as a colorless oil (46.7 mg, 0.100 mmol, >99%).

The **enantiomeric excess** was determined by SFC analysis to be >99% with t_R = 1.86 min (major) and t_R = 2.92 min (minor) [AD-H, 5.0% ^{i}PrOH, 2.5 mL/min, 240 nm, 40 ^{o}C].

$[\alpha]_D^{25}$ = –85.3^o (c 0.36, CH_2Cl_2).

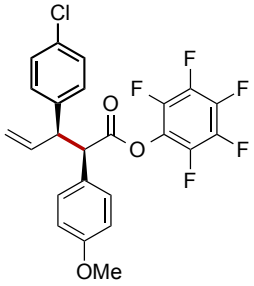
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.16 – 7.08 (m, 3H), 6.84 – 6.71 (m, 5H), 6.13 (ddd, *J* = 17.1, 10.4, 7.7 Hz, 1H), 5.30 (d, *J* = 17.1 Hz, 1H), 5.27 – 5.21 (m, 1H), 4.21 (d, *J* = 11.4 Hz, 1H), 4.10 (dd, *J* = 11.5, 7.7 Hz, 1H), 3.74 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 169.1, 162.9 (d, *J* = 246.0 Hz), 159.3, 142.4 (d, *J* = 7.0 Hz), 138.0, 130.0 (d, *J* = 8.4 Hz), 129.7, 126.6, 124.2 (d, *J* = 2.7 Hz), 117.4, 115.2 (d, *J* = 21.7 Hz), 114.2, 113.8 (d, *J* = 21.1 Hz), 55.6, 55.3, 52.8.

^{19}F NMR (376 MHz, $CDCl_3$) δ -110.7 – -115.5 (m, 1F), -151.9 – -152.1 (m, 2F), -157.9 (t, *J* = 21.8 Hz, 1F), -161.8 – -163.0 (m, 2F).

HRMS (EI): *m/z* for $C_{24}H_{16}F_6O_3$ $[M]^+$ calcd.: 466.1004, found: 466.1009.

perfluorophenyl (2*R*,3*R*)-3-(4-chlorophenyl)-2-(4-methoxyphenyl)pent-4-enoate (3ae)



Prepared according to the general procedure as described above. The diastereomeric ratio was determined to be >20:1. The crude mixture was purified by column chromatography to give the title compound as a colorless oil (46.8 mg, 0.0969 mmol, 97%).

The **enantiomeric excess** was determined by SFC analysis to be >99% with t_R = 3.04 min (major) and t_R = 4.15 min (minor) [AD-H, 5.0% ^{i}PrOH, 2.5 mL/min, 240 nm, 40 ^{o}C].

$[\alpha]_D^{25}$ = –90.9^o (c 0.54, CH_2Cl_2).

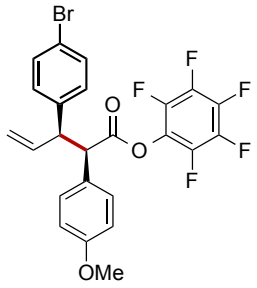
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18 – 7.09 (m, 4H), 7.00 – 6.94 (m, 2H), 6.77 – 6.70 (m, 2H), 6.13 (ddd, *J* = 17.6, 10.3, 7.5 Hz, 1H), 5.36 – 5.20 (m, 2H), 4.19 (d, *J* = 11.5 Hz, 1H), 4.09 (dd, *J* = 11.5, 7.6 Hz, 1H), 3.74 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 169.1, 159.4, 138.4, 138.2, 132.6, 129.7, 128.7, 126.7, 117.3, 114.2, 55.6, 55.3, 52.5.

^{19}F NMR (376 MHz, $CDCl_3$) δ -151.8 – -152.3 (m, 2F), -157.9 (t, *J* = 21.7 Hz, 1F), -162.4 (td, *J*

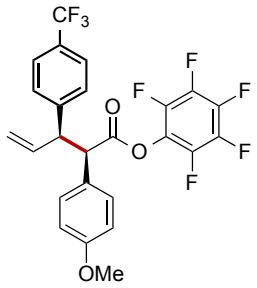
= 22.6, 5.2 Hz, 2F).
HRMS (EI): *m/z* for $C_{24}H_{16}ClF_5O_3$ $[M]^+$ calcd.: 482.0708, found: 482.0711.

perfluorophenyl (2*R*,3*R*)-3-(4-bromophenyl)-2-(4-methoxyphenyl)pent-4-enoate (3af)



Prepared according to the general procedure as described above. The diastereomeric ratio was determined to be >20:1. The crude mixture was purified by column chromatography to give the title compound as a colorless oil (52.4 mg, 0.0994 mmol, >99%).
The **enantiomeric excess** was determined by SFC analysis to be >99% with t_R = 4.12 min (major) and t_R = 5.90 min (minor) [AD-H, 5.0% *i*PrOH, 2.5 mL/min, 240 nm, 40 °C].
$[\alpha]_D^{25}$ = –77.2° (c 0.59, CH_2Cl_2).
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.4 Hz, 2H), 7.11 (d, *J* = 8.7 Hz, 2H), 6.91 (d, *J* = 8.4 Hz, 2H), 6.74 (d, *J* = 8.7 Hz, 2H), 6.12 (ddd, *J* = 17.1, 10.3, 7.6 Hz, 1H), 5.34 – 5.20 (m, 2H), 4.19 (d, *J* = 11.5 Hz, 1H), 4.07 (dd, *J* = 11.5, 7.6 Hz, 1H), 3.74 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 169.1, 159.4, 138.9, 138.1, 131.7, 130.1, 129.7, 126.6, 120.8, 117.3, 114.3, 55.6, 55.3, 52.5.
^{19}F NMR (376 MHz, $CDCl_3$) δ -151.8 – -152.2 (m, 2F), -157.9 (t, *J* = 21.7 Hz, 1F), -162.1 – -162.5 (m, 2F).
HRMS (EI): *m/z* for $C_{24}H_{16}BrF_5O_3$ $[M]^+$ calcd.: 526.0203, found: 526.0197.

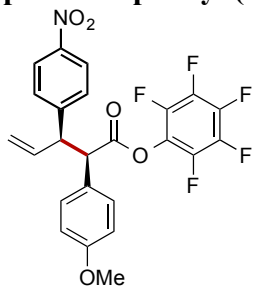
perfluorophenyl (2*R*,3*R*)-2-(4-methoxyphenyl)-3-(4-(trifluoromethyl)phenyl)pent-4-enoate (3ag)



Prepared according to the general procedure as described above. The diastereomeric ratio was determined to be 20:1. The crude mixture was purified by column chromatography to give the title compound as a colorless oil (49.0 mg, 0.0 949mmol, 95%).
The **enantiomeric excess** was determined by SFC analysis to be 99% with t_R = 2.26 min (major) and t_R = 3.17 min (minor) [AD-H, 3.0% *i*PrOH, 2.5 mL/min, 240 nm, 40 °C].
$[\alpha]_D^{25}$ = –82.2° (c 0.33, CH_2Cl_2).
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.1 Hz, 2H), 7.16 (d, *J* = 8.1 Hz, 2H), 7.12 (d, *J* = 8.7

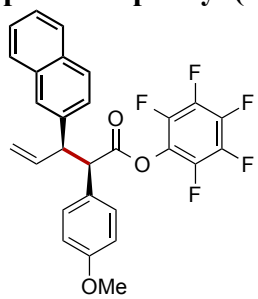
Hz, 2H), 6.73 (d, *J* = 8.7 Hz, 2H), 6.14 (ddd, *J* = 17.0, 10.3, 7.5 Hz, 1H), 5.31 (d, *J* = 17.1 Hz, 1H), 5.27 (d, *J* = 10.4 Hz, 1H), 4.25 (d, *J* = 11.5 Hz, 1H), 4.18 (dd, *J* = 11.5, 7.6 Hz, 1H), 3.73 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 169.0, 159.4, 144.0, 137.8, 129.7, 129.2 (q, *J* = 32.4 Hz), 128.8, 126.4, 125.5 (q, *J* = 3.7 Hz), 124.2 (q, *J* = 272.0 Hz), 117.8, 114.3, 55.5, 55.3, 52.9.
^{19}F NMR (376 MHz, $CDCl_3$) δ -62.6 (s, 3F), -150.6 – -154.0 (m, 2F), -157.8 (t, *J* = 21.7 Hz, 1F), -161.7 – -165.6 (m, 2F).
HRMS (EI): *m/z* for $C_{25}H_{16}F_8O_3$ $[M]^+$ calcd.: 516.0972, found: 516.0974.

perfluorophenyl (2*R*,3*R*)-2-(4-methoxyphenyl)-3-(4-nitrophenyl)pent-4-enoate (3ah)



Prepared according to the general procedure as described above. The diastereomeric ratio was determined to be >20:1. The crude mixture was purified by column chromatography to give the title compound as a colorless oil (44.6 mg, 0.0904 mmol, 90%).
The **enantiomeric excess** was determined by SFC analysis to be >99% with t_R = 4.05 min (major) and t_R = 3.82 min (minor) [AD-H, 7.0% ^{i}PrOH, 2.5 mL/min, 240 nm, 40 °C].
$[\alpha]_D^{25}$ = –99.6° (c 0.35, CH_2Cl_2).
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.7 Hz, 2H), 7.21 (d, *J* = 8.8 Hz, 2H), 7.11 (d, *J* = 8.7 Hz, 2H), 6.73 (d, *J* = 8.7 Hz, 2H), 6.13 (dddd, *J* = 17.4, 10.3, 4.5, 2.8 Hz, 1H), 5.39 – 5.27 (m, 2H), 4.26 – 4.22 (m, 2H), 3.73 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 168.7, 159.5, 147.6, 146.9, 137.1, 129.6, 129.3, 126.0, 123.8, 118.4, 114.4, 55.4, 55.3, 52.9.
^{19}F NMR (376 MHz, $CDCl_3$) δ -151.9 – -152.3 (m, 2F), -157.6 (t, *J* = 21.7 Hz, 1F), -162.0 – -162.5 (m, 2F).
HRMS (EI): *m/z* for $C_{24}H_{16}F_5NO_5$ $[M]^+$ calcd.: 493.0949, found: 493.0945.

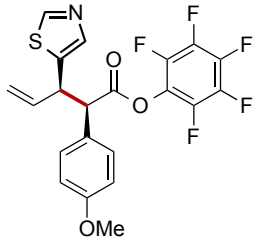
perfluorophenyl (2*R*,3*R*)-2-(4-methoxyphenyl)-3-(naphthalen-2-yl)pent-4-enoate (3ai)



Prepared according to the general procedure as described above. The diastereomeric ratio was determined to be >20:1. The crude mixture was purified by column chromatography to give the title compound as a colorless oil (46.5 mg, 0.0934 mmol, 93%).

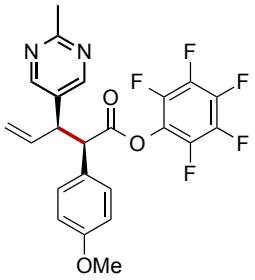
The **enantiomeric excess** was determined by SFC analysis to be >99% with t_R = 3.90 min (major) and t_R = 5.42 min (minor) [AD-H, 6.0% ^{i}PrOH, 3.0 mL/min, 240 nm, 40 °C].
$[\alpha]_D^{25}$ = –85.6° (c 0.30, CH_2Cl_2).
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.75 – 7.72 (m, 1H), 7.71 – 7.69 (m, 1H), 7.67 (d, *J* = 8.5 Hz, 1H), 7.51 (s, 1H), 7.44 – 7.38 (m, 2H), 7.21 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.18 (d, *J* = 8.8 Hz, 2H), 6.68 (d, *J* = 8.8 Hz, 2H), 6.25 (ddd, *J* = 17.2, 10.3, 7.6 Hz, 1H), 5.34 (d, *J* = 17.1 Hz, 1H), 5.25 (d, *J* = 10.4 Hz, 1H), 4.39 (d, *J* = 11.5 Hz, 1H), 4.30 (dd, *J* = 11.5, 7.6 Hz, 1H), 3.67 (s, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 169.4, 159.1, 138.6, 137.3, 133.5, 132.4, 129.7, 128.2, 127.8, 127.7, 127.40, 126.8, 126.2, 126.1, 125.8, 117.1, 114.1, 55.5, 55.2, 53.1.
^{19}F NMR (376 MHz, $CDCl_3$) δ -151.7 – -152.3 (m, 2F), -158.0 (t, *J* = 21.8 Hz, 1F), -162.2 – -162.9 (m, 2F).
HRMS (EI): *m/z* for $C_{28}H_{19}F_5O_3$ $[M]^+$ calcd.: 498.1254, found: 498.1255.

perfluorophenyl (2*R*,3*R*)-2-(4-methoxyphenyl)-3-(thiazol-5-yl)pent-4-enoate (3aj)



Prepared according to the general procedure as described above. The diastereomeric ratio was determined to be >20:1. The crude mixture was purified by column chromatography (100/0 to 70/30 of hexanes/ethyl acetate) to give the title compound as a white solid (36.7 mg, 0.0807 mmol, 81%).
The **enantiomeric excess** was determined by SFC analysis to be >99% with t_R = 2.93 min (major) and t_R = 2.59 min (minor) [AD-H, 8.0% ^{i}PrOH, 2.5 mL/min, 240 nm, 40 °C].
$[\alpha]_D^{25}$ = –87.8° (c 0.59, CH_2Cl_2).
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.58 (s, 1H), 7.41 (s, 1H), 7.18 (d, *J* = 8.7 Hz, 2H), 6.80 (d, *J* = 8.8 Hz, 2H), 6.15 (ddd, *J* = 17.1, 10.3, 7.8 Hz, 1H), 5.43 – 5.30 (m, 2H), 4.47 (dd, *J* = 11.0, 7.8 Hz, 1H), 4.13 (d, *J* = 11.0 Hz, 1H), 3.77 (s, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 168.6, 159.7, 152.6, 141.6, 137.7, 137.1, 129.8, 126.1, 118.5, 114.4, 56.6, 55.3, 45.7.
^{19}F NMR (376 MHz, $CDCl_3$) δ -151.9 – -152.2 (m, 2F), -157.7 (t, *J* = 21.5 Hz, 1F), -162.1 – -162.4 (m, 2F).
HRMS (EI): *m/z* for $C_{21}H_{14}F_5NO_3S$ $[M]^+$ calcd.: 455.0615, found: 455.0622.

perfluorophenyl (2*R*,3*R*)-2-(4-methoxyphenyl)-3-(2-methylpyrimidin-5-yl)pent-4-enoate (3ak)



Prepared according to the general procedure as described above. The diastereomeric ratio was determined to be >20:1. The crude mixture was purified by column chromatography (100/0 to 40/60 of hexanes/ethyl acetate) to give the title compound as a white solid (43.9 mg, 0.0946 mmol, 95%).

The **enantiomeric excess** was determined by SFC analysis to be >99% with t_R = 3.13 min (major) and t_R = 2.80 min (minor) [AD-H, 7.0% ^{i}PrOH, 2.5 mL/min, 240 nm, 40 ^{o}C].

$[\alpha]_D^{25}$ = –98.5^o (c 0.20, CH_2Cl_2).

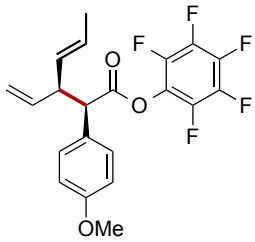
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.28 (s, 2H), 7.12 (d, *J* = 8.7 Hz, 2H), 6.76 (d, *J* = 8.7 Hz, 2H), 6.12 (ddd, *J* = 17.1, 10.4, 7.4 Hz, 1H), 5.41 – 5.28 (m, 2H), 4.21 (d, *J* = 11.4 Hz, 1H), 4.11 (dd, *J* = 11.3, 7.4 Hz, 1H), 3.74 (s, 3H), 2.62 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 168.7, 166.8, 159.7, 156.9, 136.7, 129.8, 129.7, 125.8, 118.7, 114.7, 55.3, 55.1, 48.1, 25.7.

^{19}F NMR (376 MHz, $CDCl_3$) δ -151.9 – -152.4 (m, 2F), -157.5 (t, *J* = 21.7 Hz, 1F), -161.9 – -162.4 (m, 2F).

HRMS (EI): *m/z* for $C_{23}H_{17}F_5N_2O_3$ $[M]^+$ calcd.: 464.1159, found: 464.1165.

perfluorophenyl (2*R*,3*S*,*E*)-2-(4-methoxyphenyl)-3-vinylhex-4-enoate (3al)



Prepared according to the general procedure as described above. The diastereomeric ratio was determined to be 17:1. The crude mixture was purified by column chromatography to give the title compound as a white solid (37.1 mg, 0.0900 mmol, 90%).

The **enantiomeric excess** was determined by SFC analysis to be >99% with t_R = 1.95 min (major) and t_R = 2.60 min (minor) [AD-H, 2.0% ^{i}PrOH, 2.5 mL/min, 240 nm, 40 ^{o}C].

$[\alpha]_D^{25}$ = –62.9^o (c 0.20, CH_2Cl_2).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 – 7.25 (m, 2H), 6.91 – 6.86 (m, 2H), 5.88 (ddd, *J* = 17.2, 10.3, 7.9 Hz, 1H), 5.44 – 5.35 (m, 1H), 5.23 – 5.14 (m, 3H), 3.85 (d, *J* = 10.3 Hz, 1H), 3.82 (s, 3H), 3.54 – 3.47 (m, 1H), 1.54 (d, *J* = 5.6 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 169.2, 159.3, 137.9, 130.1, 129.2, 128.4, 127.3, 117.0, 114.1, 55.4, 55.4, 49.8, 18.2.

^{19}F NMR (376 MHz, $CDCl_3$) δ -151.3 – -152.8 (m, 2F), -158.3 (t, *J* = 21.6 Hz, 1F), -161.9 – -163.9 (m, 2F).

HRMS (EI): *m/z* for $C_{21}H_{17}F_5O_3$ $[M]^+$ calcd.: 412.1098, found: 412.1102.

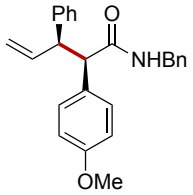
4.4.4 Procedures for Derivatization of the Allylated Esters

A) One-Pot Synthesis of Amide 4aa:

In a nitrogen-filled dry-box, the allyl *t*-butyl carbonate **2a** (23.4 mg, 0.100 mmol, 1.00 equiv) and aryl acetic acid ester **1a** (34.9 mg, 0.105 mmol, 1.05 equiv) were added to a 1-dram vial equipped with a magnetic stir bar. Thereafter, *ent*-**[Ir]-1** (8 mM in THF, 0.25 mL, 0.002 mmol, 2 mol%) and (R)-BTM (40 mM in THF, 0.25 mL, 0.010 mmol, 10 mol%) were added sequentially via syringe. The vial was sealed with a cap containing PTFE/silicone septa, and the reaction mixture was stirred at r.t. for 6 h. Thereafter, DIPEA (26 μL, 0.150 mmol, 1.50 equiv) and benzylamine (14 μL, 0.130 mmol, 1.30 equiv) were added. The vial was removed from the dry box, and the reaction mixture was stirred at r.t. for another 12 h.

The mixture was diluted with 2 mL of hexanes, and filtered through a 0.5-inch plug of silica gel (eluting with 1:1 hexanes:EtOAc, 8 mL). After removal of solvent under vacuum, the crude mixture was purified by column chromatography performed on a Teledyne Isco Combiflash® R_f system with Redi*Sep* Gold™ columns (4-gram silica gel column, 100/0 to 60/40 of hexanes/EtOAc).

(2*R*,3*R*)-*N*-benzyl-2-(4-methoxyphenyl)-3-phenylpent-4-enamide (4aa)



The diastereomeric ratio was determined to be >20:1. The title compound was obtained as a white solid (36.5 mg, 0.0983 mmol, 98%).

The **enantiomeric excess** was determined by SFC analysis to be 98% with t_R = 6.46 min (major) and t_R = 4.55 min (minor) [AD-H, 20.0% ^{i}PrOH, 2.5 mL/min, 240 nm, 40 °C].

$[\alpha]_D^{25}$ = –4.9° (c 0.16, CH_2Cl_2).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.22 – 7.14 (m, 3H), 7.10 – 7.06 (m, 2H), 7.06 – 7.00 (m, 4H), 6.99 – 6.94 (m, 1H), 6.94 – 6.90 (m, 2H), 6.58 (d, *J* = 8.7 Hz, 2H), 6.04 (ddd, *J* = 17.0, 10.3, 7.6 Hz, 1H), 5.82 (t, *J* = 5.7 Hz, 1H), 5.07 (d, *J* = 17.1 Hz, 1H), 5.02 (d, *J* = 10.3 Hz, 1H), 4.44 (dd, *J* = 14.8, 6.1 Hz, 1H), 4.19 (dd, *J* = 14.8, 5.2 Hz, 1H), 4.08 (dd, *J* = 10.8, 7.7 Hz, 1H), 3.61 (s, 3H), 3.52 (d, *J* = 10.8 Hz, 1H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 172.4, 158.6, 141.2, 139.8, 138.4, 130.0, 129.6, 128.7, 128.6, 128.3, 127.9, 127.5, 126.3, 116.2, 113.8, 58.2, 55.2, 53.0, 43.8.

HRMS (EI): *m/z* for $C_{25}H_{25}NO_2$ $[M]^+$ calcd.: 371.1885, found: 371.1892.

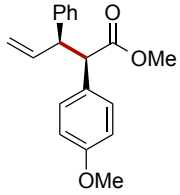
B) One-Pot Synthesis of Methyl Ester 5aa:

In a nitrogen-filled dry-box, the allyl *t*-butyl carbonate **2a** (23.4 mg, 0.100 mmol, 1.00 equiv) and aryl acetic acid ester **1a** (34.9 mg, 0.105 mmol, 1.05 equiv) were added to a 1-dram vial equipped with a magnetic stir bar. Thereafter, *ent*-**[Ir]-1** (8 mM in THF, 0.25 mL, 0.002 mmol, 2 mol%) and (R)-BTM (40 mM in THF, 0.25 mL, 0.010 mmol, 10 mol%) were added sequentially

via syringe. The vial was sealed with a cap containing PTFE/silicone septa and removed from the dry box. The reaction mixture was stirred at r.t. for 6 h. Thereafter, DMAP (2.4 mg, 0.020 mmol, 0.20 equiv), triethylamine (70 μL, 0.50 mmol, 5.0 equiv) and 0.50 mL of MeOH were added. The reaction mixture was stirred at 65 °C for another 12 h.

The mixture was diluted with 2 mL of hexanes, and filtered through a 0.5-inch plug of silica gel (eluting with 1:1 hexanes:EtOAc, 8 mL). After removal of solvent under vacuum, the crude mixture was purified by column chromatography performed on a Teledyne Isco Combiflash® R_f system with Redi*Sep* Gold™ columns (4-gram silica gel column, 100/0 to 85/15 of hexanes/EtOAc).

methyl (2*R*,3*R*)-2-(4-methoxyphenyl)-3-phenylpent-4-enoate (5aa)



The diastereomeric ratio was determined to be >20:1. The title compound was obtained as a colorless oil (29.1 mg, 0.0983 mmol, 98%).

The **enantiomeric excess** was determined by SFC analysis to be >99% with t_R = 1.85 min (major) and t_R = 2.28 min (minor) [OJ-H, 5.0% *i*PrOH, 2.5 mL/min, 240 nm, 40 °C].

$[\alpha]_D^{25}$ = –54.0° (c 0.18, CH_2Cl_2).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.16 – 7.08 (m, 4H), 7.08 – 7.03 (m, 1H), 7.01 – 6.98 (m, 2H), 6.67 (d, *J* = 8.7 Hz, 2H), 6.08 (ddd, *J* = 17.1, 10.3, 7.9 Hz, 1H), 5.18 (d, *J* = 17.1 Hz, 1H), 5.10 (d, *J* = 10.3 Hz, 1H), 4.01 (dd, *J* = 11.5, 7.9 Hz, 1H), 3.91 (d, *J* = 11.5 Hz, 1H), 3.69 (s, 3H), 3.67 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 173.8, 158.7, 140.7, 139.7, 129.8, 128.8, 128.4, 128.4, 126.5, 116.0, 113.8, 56.3, 55.2, 53.6, 52.0.

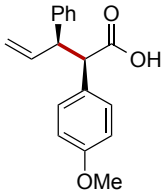
HRMS (EI): *m/z* for $C_{19}H_{20}O_3$ $[M]^+$ calcd.: 296.1412, found: 296.1416.

C) One-Pot Synthesis of Carboxylic Acid 6aa:

In a nitrogen-filled dry-box, the allyl *t*-butyl carbonate **2a** (23.4 mg, 0.100 mmol, 1.00 equiv) and aryl acetic acid ester **1a** (34.9 mg, 0.105 mmol, 1.05 equiv) were added to a 1-dram vial equipped with a magnetic stir bar. Thereafter, *ent*-**[Ir]-1** (8 mM in THF, 0.25 mL, 0.002 mmol, 2 mol%) and (R)-BTM (40 mM in THF, 0.25 mL, 0.010 mmol, 10 mol%) were added sequentially via syringe. The vial was sealed with a cap containing PTFE/silicone septa and removed from the dry box. The reaction mixture was stirred at r.t. for 6 h. Thereafter, DMAP (2.4 mg, 0.020 mmol, 0.20 equiv), triethylamine (70 μL, 0.50 mmol, 5.0 equiv) and 0.50 mL of H_2O were added. The reaction mixture was stirred at 65 °C for another 12 h.

The mixture was acidified with aqueous HCl solution (1 M, 5 mL), and extracted with Et_2O (3 x 5 mL). The organic layer was dried over anhydrous Na_2SO_4. After removal of solvent under vacuum, the crude mixture was purified by column chromatography performed on a Teledyne Isco Combiflash® R_f system with Redi*Sep* Gold™ columns (4-gram silica gel column, 100/0 to 50/50 of hexanes/EtOAc).

(2*R*,3*R*)-2-(4-methoxyphenyl)-3-phenylpent-4-enoic acid (6aa)



The diastereomeric ratio was determined to be 19:1. The title compound was obtained as a white solid (27.8 mg, 0.0985 mmol, 98%).

The **enantiomeric excess** was determined by SFC analysis to be >99% with t_R = 4.77 min (major) and t_R = 5.36 min (minor) [AD-H, 10.0% ^{i}PrOH, 2.5 mL/min, 240 nm, 40 ^{o}C].

[α]$_D^{25}$ = –50.1^o (c 0.21, CH_2Cl_2).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.16 – 7.09 (m, 4H), 7.09 – 7.03 (m, 1H), 7.03 – 6.98 (m, 2H), 6.67 (d, *J* = 8.7 Hz, 2H), 6.10 (ddd, *J* = 17.6, 10.3, 7.7 Hz, 1H), 5.22 (d, *J* = 17.1 Hz, 1H), 5.12 (d, *J* = 10.2 Hz, 1H), 4.01 (dd, *J* = 11.5, 7.7 Hz, 1H), 3.90 (d, *J* = 11.6 Hz, 1H), 3.69 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 179.2, 158.9, 140.4, 139.3, 129.8, 128.4, 128.4, 128.2, 126.6, 116.4, 113.8, 56.2, 55.2, 53.1.

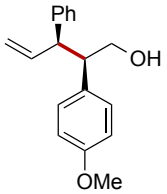
HRMS (EI): *m/z* for $C_{18}H_{18}O_3$ $[M]^+$ calcd.: 282.1256, found: 282.1252.

D) Synthesis of Primary Alcohol 7aa:

In a nitrogen-filled dry-box, the allyl *t*-butyl carbonate **2a** (23.4 mg, 0.100 mmol, 1.00 equiv) and aryl acetic acid ester **1a** (34.9 mg, 0.105 mmol, 1.05 equiv) were added to a 1-dram vial equipped with a magnetic stir bar. Thereafter, *ent*-**[Ir]-1** (8 mM in THF, 0.25 mL, 0.002 mmol, 2 mol%) and (R)-BTM (40 mM in THF, 0.25 mL, 0.010 mmol, 10 mol%) were added sequentially via syringe. The vial was sealed with a cap containing PTFE/silicone septa and removed from the dry box. The reaction mixture was stirred at r.t. for 6 h. The mixture was diluted with 2 mL of hexanes, and filtered through a 0.5-inch plug of silica gel (eluting with 1:1 hexanes:EtOAc, 8 mL). After removal of solvent under vacuum, the crude mixture was dissolved with dry THF (2 mL). Then $LiAlH_4$ (5.7 mg, 0.15 mmol, 1.5 equiv) was added under 0 ^{o}C. The reaction mixture was stirred at r.t. for another 12 h.

The mixture was quenched with aqueous HCl (1 M, 5 mL) under 0 ^{o}C, and extracted with Et_2O (3 x 5 mL). The organic layer was dried over anhydrous Na_2SO_4. After removal of solvent under vacuum, the crude mixture was purified by column chromatography performed on a Teledyne Isco Combiflash® R_f system with Redi*Sep* Gold™ columns (4-gram silica gel column, 100/0 to 65/35 of hexanes/EtOAc).

(2*R*,3*R*)-2-(4-methoxyphenyl)-3-phenylpent-4-en-1-ol (7aa)



The diastereomeric ratio was determined to be >20:1. The title compound was obtained as a colorless oil (26.4 mg, 0.0984 mmol, 98%).

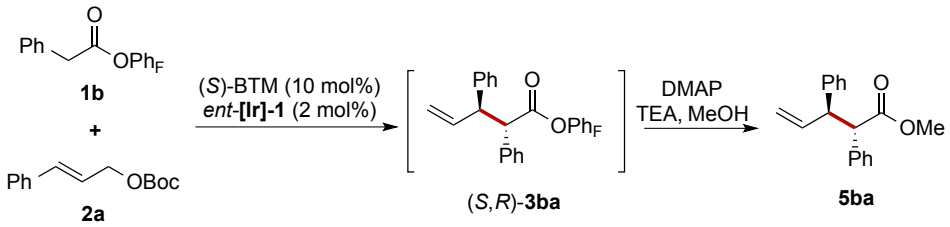
The **enantiomeric excess** was determined by SFC analysis to be >99% with t_R = 4.14 min (major)

and t_R = 5.03 min (minor) [AD-H, 10.0% ^{i}PrOH, 2.5 mL/min, 240 nm, 40 °C].
[α]$_D^{25}$ = +53.0° (c 0.34, CH_2Cl_2).
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.16 – 7.12 (m, 2H), 7.09 – 7.03 (m, 1H), 7.02 – 6.95 (m, 4H), 6.71 (d, *J* = 8.6 Hz, 2H), 6.09 (dt, *J* = 16.9, 9.7 Hz, 1H), 5.20 (d, *J* = 16.9 Hz, 1H), 5.09 (dd, *J* = 10.0, 1.6 Hz, 1H), 3.98 (dd, *J* = 11.1, 4.8 Hz, 1H), 3.85 – 3.80 (m, 1H), 3.71 (s, 3H), 3.59 (t, *J* = 9.9 Hz, 1H), 3.16 (ddd, *J* = 10.4, 8.0, 4.9 Hz, 1H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 158.3, 142.5, 140.9, 132.2, 129.8, 128.3, 128.1, 126.2, 115.6, 113.9, 66.0, 55.2, 53.9, 52.1.
HRMS (EI): *m/z* for $C_{18}H_{20}O_2$ $[M]^+$ calcd.: 268.1463, found: 268.1465.

4.4.5 Determination of Absolute Configuration

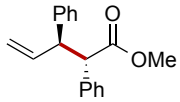
1) Absolute configuration of the enantiomer of **3aj** was determined by X-ray analysis

2) The absolute configuration of (*S,R*)-**3ba** was assigned by converting it to the ester **5ba** following the procedure for the synthesis of **5aa** and comparing the optical rotation of this material with that reported by Corey and Lee.[25]



Scheme 4.9 Synthesis of **5ba**

methyl (2*S*,3*R*)-2,3-diphenylpent-4-enoate (5ba)

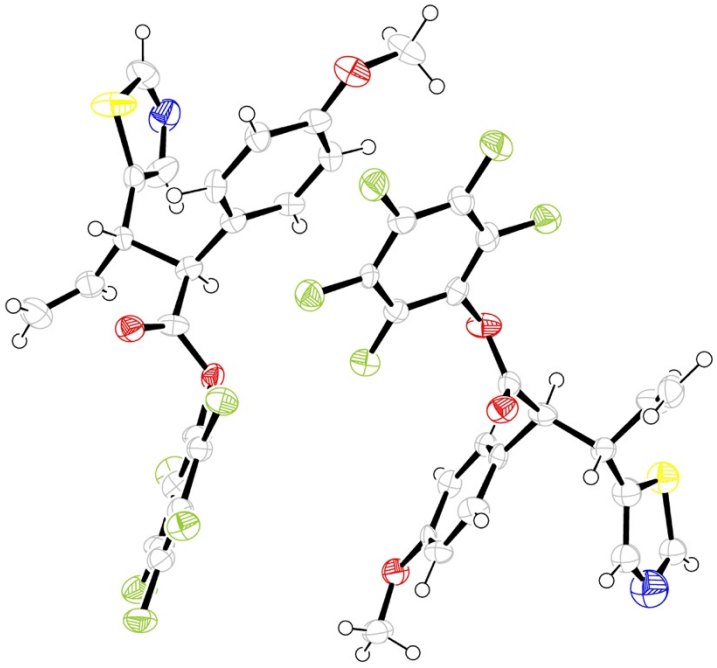


The diastereomeric ratio was determined to be 18:1. The branched/linear selectivity was determined to be 7:1. The title compound was obtained as a white solid (26.9 mg, 0.100 mmol, >99%). The **enantiomeric excess** was determined by SFC analysis to be >99% with t_R = 1.90 min (major) and t_R = 1.80 min (minor) [OJ-H, 5.0% ^{i}PrOH, 2.5 mL/min, 220 nm, 40 °C].
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.47 – 7.40 (m, 2H), 7.37 – 7.27 (m, 7H), 7.25 – 7.22 (m, 1H), 5.72 (ddd, *J* = 17.5, 10.3, 7.7 Hz, 1H), 4.85 (d, *J* = 10.3 Hz, 1H), 4.75 (d, *J* = 17.0 Hz, 1H), 4.07 (dd, *J* = 11.7, 7.7 Hz, 1H), 3.98 (d, *J* = 11.6 Hz, 1H), 3.40 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 173.0, 141.8, 138.7, 137.2, 129.0, 128.7, 128.7, 128.2, 127.7, 126.9, 116.9, 57.4, 53.2, 51.9.
HRMS (EI): *m/z* for $C_{18}H_{18}O_2$ $[M]^+$ calcd.: 266.1307, found: 266.1310.
[α]$_D^{25}$ = +110.4° (c 0.29, $CHCl_3$).
Lit[8]: $[\alpha]_D^{25}$ = +119.9° (c 1.46, $CHCl_3$).

3) The absolute configurations of all other products shown in this paper were assigned by analogy.

4.4.6 X-Ray Diffraction Study of *ent*-3aj

A colorless rod 0.060 x 0.030 x 0.030 mm in size was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using and scans. Crystal-to-detector distance was 60 mm and exposure time was 10 seconds per frame using a scan width of 2.0°. Data collection was 99.9% complete to 67.000° in θ. A total of 45422 reflections were collected covering the indices, -5<=*h*<=7, -32<=*k*<=32, -14<=*l*<=14. 6869 reflections were found to be symmetry independent, with an R_{int} of 0.0498. Indexing and unit cell refinement indicated a primitive, monoclinic lattice. The space group was found to be P 21 (No. 4). The data were integrated using the Bruker SAINT software program and scaled using the SADABS software program. Solution by iterative methods (SHELXT-2014) produced a complete heavy-atom phasing model consistent with the proposed structure. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2016). All hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2016. Absolute stereochemistry was unambiguously determined to be *S* at all chiral centers.



Scheme 4.10 Crystal structure of ***ent*-3aj**

Table 4.5 Crystal data and structure refinement for *ent*-**3aj**

X-ray ID	*ent*-**3aj**	
Empirical formula	$C_{21}H_{14}F_5NO_3S$	
Formula weight	455.39	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	P 21	
Unit cell dimensions	a = 5.9674(3) Å	α= 90°.
	b = 26.9049(15) Å	β= 90.059(4)°.
	c = 12.1120(7) Å	γ = 90°.
Volume	1944.61(18) $Å^3$	
Z	4	
Density (calculated)	1.555 Mg/m^3	
Absorption coefficient	2.148 mm^{-1}	
F(000)	928	
Crystal size	0.060 x 0.030 x 0.030 mm^3	
Theta range for data collection	3.285 to 68.579°.	
Index ranges	-5<=h<=7, -32<=k<=32, -14<=l<=14	
Reflections collected	45422	
Independent reflections	6869 [R(int) = 0.0498]	
Completeness to theta = 67.000°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.929 and 0.729	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	6869 / 13 / 551	
Goodness-of-fit on F^2	1.056	
Final R indices [I>2sigma(I)]	R1 = 0.0526, wR2 = 0.1194	
R indices (all data)	R1 = 0.0548, wR2 = 0.1207	
Absolute structure parameter	0.038(9)	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.449 and -0.331 e.$Å^{-3}$	

4.5 References

Parts of this chapter were reprinted with permission from:
"Stereodivergent Allylic Substitutions with Aryl Acetic Acid Esters by Synergistic Iridium and Lewis Base Catalysis"
Jiang, X.; Beiger, J. J.; Hartwig, J. F. *J. Am. Chem. Soc.* **2017**, *139*, 87.

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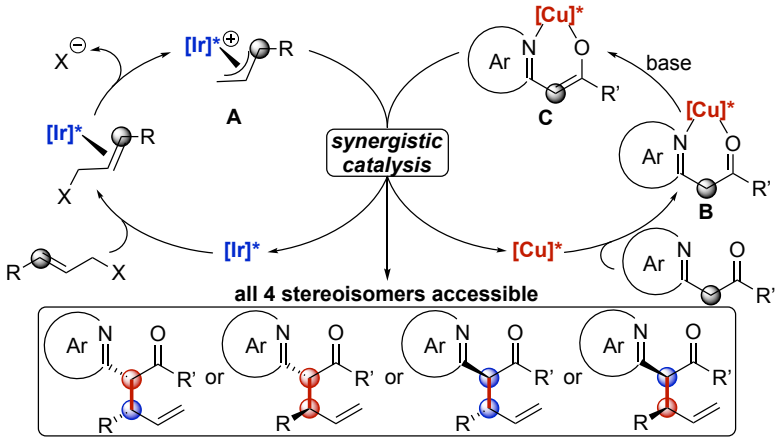
CHAPTER 5

Stereodivergent Allylation of Azaaryl Acetamides and Acetates by Synergistic Iridium and Copper Catalysis

5.1 Introduction

Chiral molecules bearing nitrogen-containing heteroaromatic rings (azaarenes) are ubiquitous in natural products, pharmaceuticals and agrochemicals. The configuration of the stereogenic centers in these molecules typically alters their physiological properties. Therefore, a synthetic method would be valuable that provides access to all possible stereoisomers of a given azaaryl compound with multiple adjacent stereocenters from the same set of starting materials under almost identical conditions.[1] This proposed method would enable the rapid synthesis of all stereoisomers of chiral azaaryl compounds for testing of biological activity and for studies on structure-activity relationships (SAR).[2] However, reported stereodivergent reactions involving substrates containing azaarenes are limited,[3] and the basic property of an azaaryl motif has not been used to facilitate stereodivergent reactions.[4]

Our group has previously reported metallacyclic iridium catalysts[5] that govern the geometry, facial selectivity, and regioselectivity of the allyl moiety (Scheme 5.1, **A**) in asymmetric allylic substitutions.[6] Recently we developed stereodivergent allylations of aryl acetic acid esters catalyzed by these Ir catalysts and a chiral Lewis base.[3h] This work has led us to consider whether our Ir catalysts would be compatible with chiral Lewis-acid catalysts that could bind Lewis-basic nitrogen atoms on azaarenes and subsequently catalyze stereodivergent allylations of azaaryl compounds.



Scheme 5.1 Proposed mechanism for synergistic catalysis

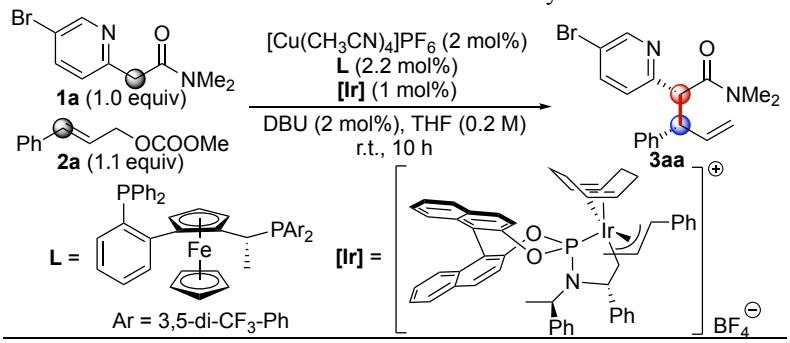
Chiral bisphosphine-ligated copper(I) complexes are known to act as Lewis acids that catalyze asymmetric functionalizations of well-designed amides through two-point binding with the amides.[4c,7] We envisioned that the Cu(I) complexes could bind azaaryl acetamides and acetates in a similar manner. The C=N moiety embedded at a suitable position in azaaryl rings and the nearby carbonyl groups in azaaryl acetamides and acetates would serve as the basic sites for the bidentate coordination of the Lewis acid (Scheme 5.1, **B**). After deprotonation, the resulting Cu(I) enolate (Scheme 5.1, **C**) would be formed with well-defined geometry and would react with electrophilic intermediate **A** with high facial selectivity, affording the allylated azaaryl products with high regio-, diastereo- and enantioselectivity.[8] The Ir catalyst and the Cu(I) catalyst would dictate the configurations of two adjacent stereocenters in the product generated from the electrophile and the

nucleophile, respectively.[9] Therefore, by simple permutations of enantiomers of the two catalysts, all four possible stereoisomers of the product could be accessible (Scheme 5.1).[1]

Herein we report stereodivergent allylic substitutions with azaaryl acetamides and acetates catalyzed synergistically by a metallacyclic Ir complex and a chiral Cu (I) complex. Variation of the combination of enantiomers of the catalysts allows access to all four possible stereoisomers of the allylation products from the same set of starting materials under otherwise identical conditions. Various azaaryl acetamides and acetates containing pyridyl, benzoxazolyl, benzothiazolyl, pyrazinyl, quinolinyl and isoquinolinyl moieties were all suitable for this transformation, delivering the products with high diastereoselectivity and enantioselectivity.

5.2 Results and Discussion

Table 5.1 Evaluation of condition for allylation of **1a**



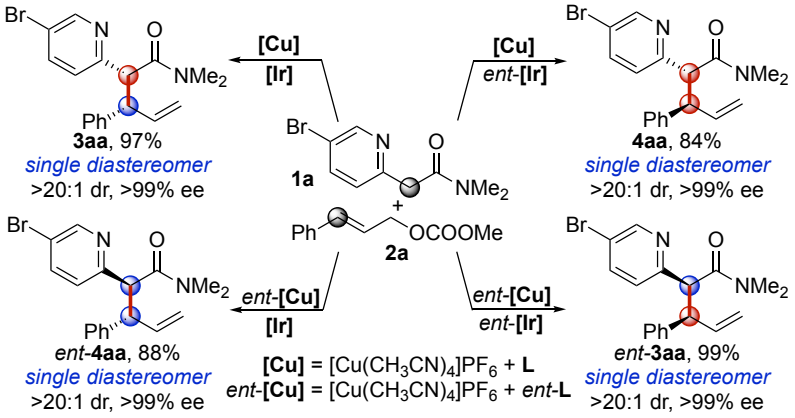
entry	variations from the standard condition	dr[a]	ee/%[b]	yield/%[c]
1	none	>20:1	>99	97 (97)
2	no $[Cu(CH_3CN)_4]PF_6$ or **L**	1:1.8	n.d.	14
3	no **L**	1.4:1	n.d.	91
4	no **[Ir]**			<1
5	no DBU			<1
6	*ent*-**[Ir]** instead of **[Ir]**	1:>20	>99	88 (84)

[a]Determined by ^{1}H NMR analysis of the crude reaction mixtures. [b]Determined by chiral SFC analysis of the major isomer. [c]Combined yield of two diastereomers of the product. Determined by ^{1}H NMR analysis with mesitylene as an internal standard. The yield within parentheses is that of the major diastereomer isolated.

We began our studies on the stereodivergent allylic substitutions with azaaryl acetamides and acetates by examining the reaction between amide **1a** (1.0 equiv) and carbonate **1b** (1.1 equiv) with $[Cu(CH_3CN)_4]PF_6$ (5 mol%), metallacyclic iridium catalyst **[Ir]** shown in Table 5.1 (2 mol%), DBU (5 mol%) as catalytic base, and a series of chiral bisphosphine ligands (5.5 mol%). We found that a Cu(I) complex ligated by Walphos derivative **L** is an effective Lewis acid for the proposed synergistic catalysis, delivering product **3aa** in 94% yield with >20:1 dr. Reactions conducted with copper complexes ligated by chiral bisphosphines derived from BINAP, Garphos, Segphos and Josiphos afforded **3aa** in similar yields but with lower diastereoselectivity (<7:1 dr). Further studies on the loading of the two catalysts revealed that reaction conducted with 2 mol% of the Cu complex and 1 mol% of **[Ir]** gave **3aa** in 97% yield (isolated as a single diastereomer) with >20:1 dr and >99% ee (Table 5.1, entry 1). A gram-scale synthesis of **3aa** was conducted with 1 mol%

of the Cu complex and 0.5 mol% of **[Ir]** to afford the product in 96% yield (1.04 g) with >20:1 dr and >99% ee.

To understand the role of individual reaction components in this reaction, a set of control experiments were conducted. The reaction conducted with the iridium catalyst **[Ir]** without $[Cu(CH_3CN)_4]PF_6$ or **L** gave **3aa** in a low yield of 14% with low diastereoselectivity (1:1.8 dr), slightly favoring the formation of the diastereomer of **3aa** (entry 2). This result and the result in entry 1 demonstrate that the configuration of the nucleophilic carbon in the product results from catalyst control, rather than substrate control. The reaction occurred smoothly when catalyzed by **[Ir]** and $[Cu(CH_3CN)_4]PF_6$ as the Lewis-acid catalyst without **L** (91% yield, entry 3). However, a low diastereoselectivity of 1.4:1 dr was observed, indicating that the facial selectivity of the unligated Cu(I) enolate in the allylation reaction is poor. No product was formed in the absence of **[Ir]** (entry 4). A catalytic amount of DBU was necessary to initiate the reaction (entry 5), presumably by deprotonating **1a** to form the corresponding Cu(I) enolate. The methyl carbonate anion generated from oxidative addition of **2a** or the methoxide generated from decarboxylation of the methyl carbonate anion would likely act as a base for deprotonation of the substrate in subsequent turnovers.



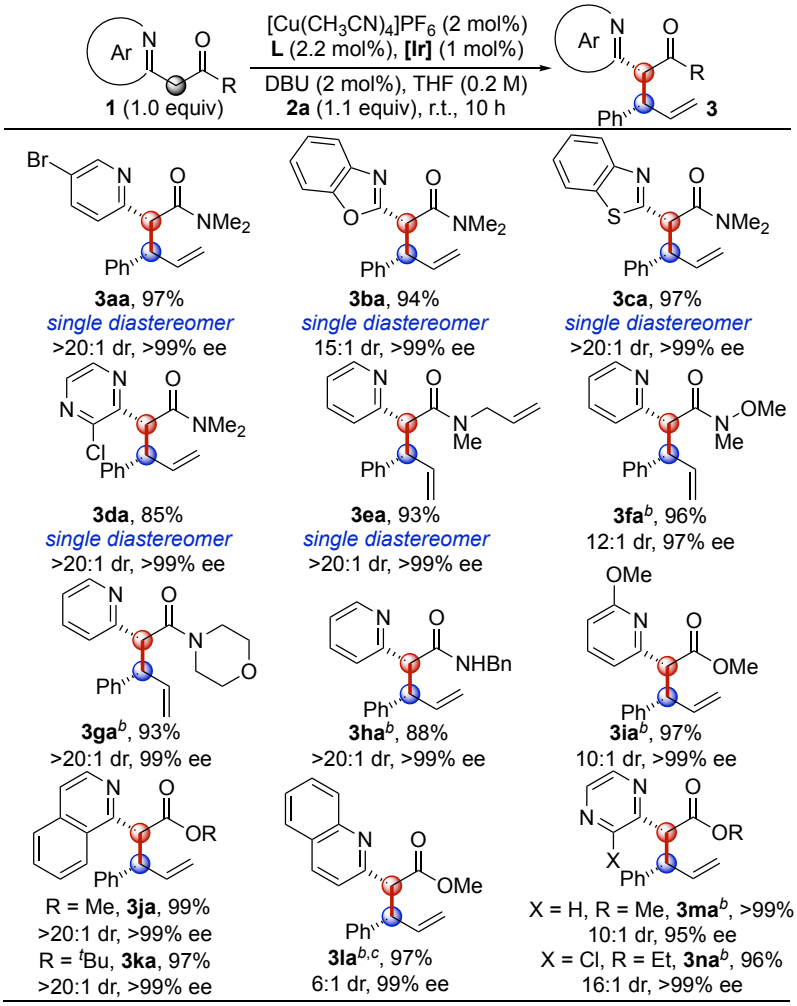
Scheme 5.2 Synthesis of all four stereoisomers of **3aa**

To test the role of iridium in the stereodivergent allylation, we conducted the reaction with the enantiomer of **[Ir]** instead of **[Ir]**, while keeping the configuration of the Cu(I) complex constant. The diastereomer of **3aa** was obtained from this reaction, instead of **3aa**, with excellent diastereoselectivity and enantioselectivity (entry 6, 84% yield, isolated as a single diastereomer, 1:>20 dr, >99% ee). This result indicates that the Ir complex and the Cu(I) complex exert nearly complete and independent control over the configurations of stereocenters arising from the allyl electrophile and the enolate nucleophile, respectively. The stereodivergence of this allylation method was further evaluated by treating **1a** and **2a** with four different combinations of enantiomers of the two catalysts under otherwise identical conditions (Scheme 5.2). All four stereoisomers of **3aa** were formed individually from these reactions and separated as a single diastereomer in high yields (>80%) with excellent diastereo- and enantioselectivity (>20:1 dr, >99% ee).

The scope of azaaryl acetamides and acetates that underwent the stereodivergent allylic substitutions is summarized in Table 5.2. *N,N*-Dimethyl acetamides that bear pyridyl (**1a**), benzoxazolyl (**1b**), benzothiazolyl (**1c**) and pyrazinyl (**1d**) moieties on the α carbon were all suitable for

this transformation, affording products **3aa–3da** in ≥85% yield (isolated as a single diastereomer) with ≥15:1 dr and >99% ee. In addition to *N,N*-dimethyl amides, pyridyl acetamides generated from *N*-allylmethyl amine (**1e**), *N,O*-dimethylhydroxyl amine (**1f**) and morpholine (**1g**) reacted to form products **3ea–3ga** in ≥93% yield with ≥12:1 dr and ≥97% ee. A secondary *N*-benzyl pyridyl acetamide, bearing an amide N–H bond, reacted selectively at the α position over the nitrogen of the amide (**3ha**, 88% yield, >20:1 dr, >99% ee). In some cases (**3fa–3ha**), the reactions were conducted with 5 mol% of the Cu complex and 2 mol% of **[Ir]** instead of 2 mol% and 1 mol%, respectively, to obtain the products with high diastereoselectivity.

Table 5.2 Scope of azaaryl acetamides and acetates for the allylation[a]



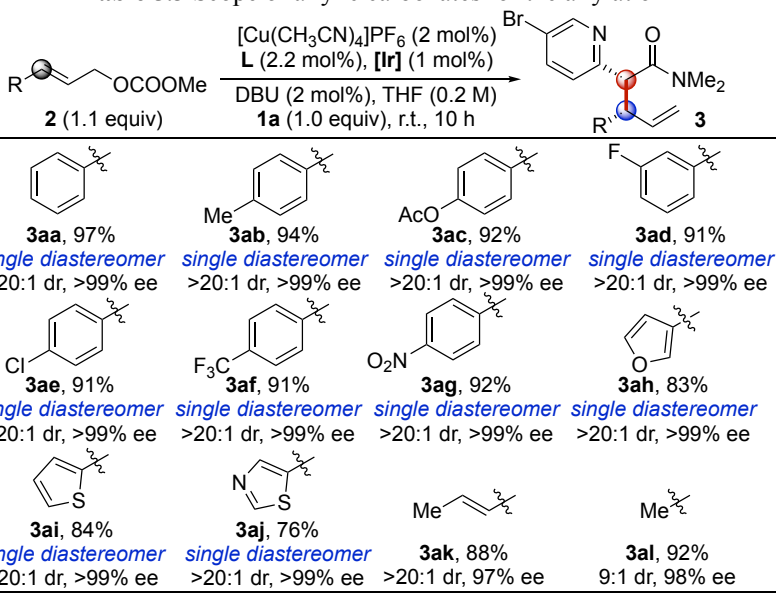
[a]**3aa-3ea** were isolated as a single diastereomer. The yields for other products were reported as the combined yields of two diastereomers isolated. [b][Cu(CH3CN)4]PF6 (5 mol%), **L** (5.5 mol%), **[Ir]** (2 mol%), DBU (5 mol%). [c]The ee value was determined after further transformation of the product.

Various azaaryl acetates bearing pyridyl (**1i**), isoquinolinyl (**1j**, **1k**), quinolinyl (**1l**) and pyrazinyl (**1m**, **1n**) moieties were tested for this allylation reaction. Pyridyl acetate **1i** reacted smoothly to afford product **3ia** in 97% yield with 10:1 dr and >99% ee. The size of the group on the oxygen

of the ester had little impact on the allylation reaction; methyl ester **1j** and *tert*-butyl ester **1k** reacted similarly to give product **3ja** and **3ka**, respectively, in almost quantitative yield (≥97%) with excellent diastereo- and enantioselectivity (>20:1 dr, >99% ee). Quinolinyl acetate **1l** reacted to give allylation product **3la** in 97% yield with 6:1 dr and 99% ee.[10] Acetates bearing pyrazinyl (**1m**, **1n**) moieties containing two Lewis basic nitrogen atoms in the azaarene also were suitable for this transformation, giving the allylation products in high yield (≥96%) with ≥10:1 dr and ≥95% ee.

The scope of allyl methyl carbonates that underwent the stereodivergent allylic substitution reactions is summarized in Table 5.3. Electron-neutral (**2b**), electron-donating (**2c**) and electron-withdrawing (**2d**–**2g**) functional groups on the cinnamyl aryl rings were all tolerated by the allylation reaction, and the corresponding products (**3ab**–**3ag**) were obtained in excellent yield (>90%, isolated as a single diastereomer) with >20:1 dr and >99% ee. Carbonate **2c** bearing a base-sensitive acetoxy group on the phenyl ring reacted cleanly to afford **3ac**, highlighting the mildness of these reaction conditions.

Table 5.3 Scope of allylic carbonates for the allylation[a]



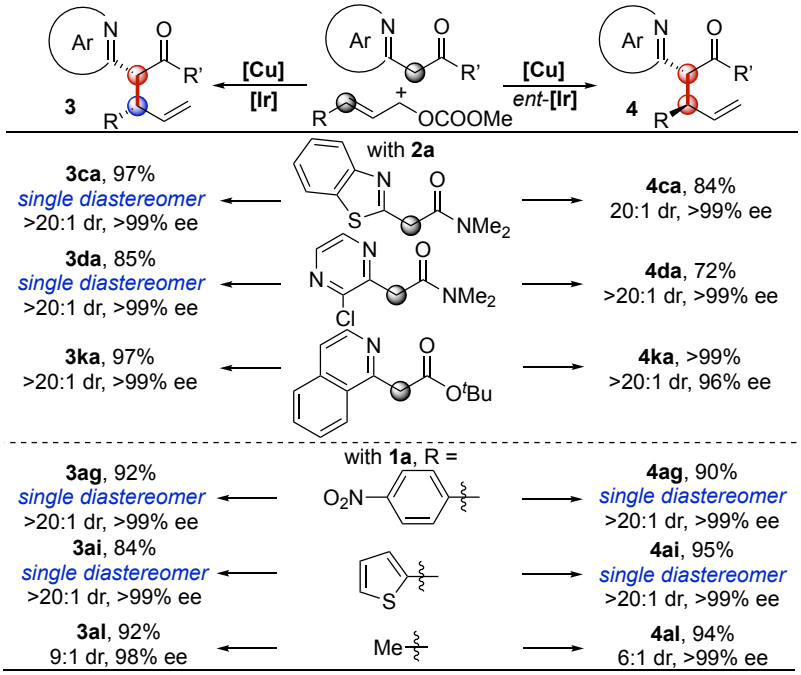
[a]**3aa-3aj** were isolated as a single diastereomer. The yields for others were reported as the combined yields of two diastereomers isolated.

This reaction also occurred with carbonates that bear heteroaryl, alkenyl and alkyl substituents. Carbonates that contain furyl (**2h**), thienyl (**2i**) and thiazolyl (**2j**) substituents underwent the allylation reaction to give the products (**3ah**–**3aj**) in >75% yield (isolated as a single diastereomer) with >20:1 dr and >99% ee. Methyl sorbyl carbonate (**2k**) reacted to afford product **3ak** in 88% yield with >20:1 dr and 97% ee. Even simple crotyl carbonate (**2l**) reacted similarly to give the allylation product in 92% yield with 9:1 dr and 98% ee.

To demonstrate the stereodivergence of this allylation reaction further, the diastereomers of **3ca**, **3da**, **3ka**, **3ag**, **3ai** and **3al** were prepared by conducting the reactions with the corresponding azaaryl nucleophiles and the carbonates in the presence of *ent*-**[Ir]** instead of **[Ir]** under otherwise identical conditions (Table 5.4). The corresponding products (**4ca**, **4da**, **4ka**, **4ag**, **4ai**, **4al**) were

obtained from these reactions in yields, diastereo- and enantioselectivity that are comparable to those of the reactions that form their diastereomers.

Table 5.4 Examples of stereodivergence



5.3 Conclusions

In summary, we have developed a combination of catalysts that enable stereodivergent allylic substitution reactions with azaaryl acetamides and acetates. This combination of catalysts comprises a chiral metallacyclic iridium complex and a chiral bisphosphine-ligated copper(I) complex. The phosphoramidite binds Ir tightly through a stable Ir–C bond, which prevents potential crossover of two ligands on two metal centers. The copper(I) complex acts as a Lewis acid to activate the azaaryl carboxylic acid derivatives by coordinating to the imine moieties (C=N) embedded in the azaaryl rings and the suitably positioned carbonyl groups, and this binding mode of the chiral complex controls the geometry and facial selectivity of the Cu(I) enolates in the allylation reactions. Azaaryl substrates that bear pyridyl, benzoxazolyl, benzothiazolyl, pyrazinyl, quinolinyl and isoquinolinyl moieties all underwent this reaction, delivering the products containing two adjacent tertiary stereocenters in high yields with excellent diastereo- and enantioselectivity. Starting from the same set of substrates, simple variation of the enantiomers of the two catalysts allow the synthesis of all four possible stereoisomers of the products individually. Studies to understand the origin of stereoselectivity of the Cu(I) enolates in the allylation reactions are ongoing in our laboratories.

5.4 Experimental

5.4.1 General Experimental Details

Air-sensitive manipulations were conducted under inert atmosphere in a nitrogen-filled glovebox or by standard Schlenk techniques. Tetrahydrofuran (THF) was purified by passing it through a column composed of activated A-1 alumina and degassing by freeze-pump-thaw method. $[Ir(cod)Cl]_2$ was obtained from Johnson-Matthey and used without further purification.

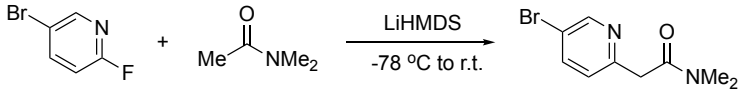
Chiral supercritical fluid chromatography (SFC) analysis was conducted on a JASCO SF-2000 integrated analytical SFC system. Proton nuclear magnetic resonance (^{1}H NMR) spectra were acquired on commercial instruments (300, 400, 500 and 600 MHz) at the NMR facility of University of California, Berkeley. Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were acquired at 100, 126 and 151 MHz. Fluorine-19 nuclear magnetic resonance (^{19}F NMR) spectra were acquired at 376 MHz. The proton signal for the residual non-deuterated solvent (δ 7.26 for $CDCl_3$, δ 7.16 for C_6D_6) was used as an internal reference for ^{1}H NMR spectra. For ^{13}C NMR spectra, chemical shifts are reported relative to the δ 77.16 resonance of $CDCl_3$ and relative to the δ 128.06 resonance of C_6D_6. For ^{19}F NMR spectra, chemical shifts are reported relative to the δ -113.15 resonance of PhF as an external reference. Coupling constants are reported in Hz. Optical rotations were measured on a Perkin Elmer 241 Automatic Polarimeter. The high-resolution mass spectra were obtained on a high-resolution mass spectrometer at the QB3/Chemistry Mass Spectrometry Facility at UC Berkeley and on the Perkin Elmer AxION2 TOF MS operated by the LBNL Catalysis Facility.

Analytical thin layer chromatography (TLC) was performed on Kieselgel 60 F_{254} glass plates pre-coated with a 0.25 mm thickness of silica gel. The TLC plates were visualized with UV light and/or by staining with $KMnO_4$. For the purification of allylation products, column chromatography was generally performed on a Teledyne Isco Combiflash® R_f system with Redi*Sep* Gold™ columns. Silia*Flash*® T60 silica gel (particle size 5-20 μm) was used to fill the cartridge for the Combiflash® system. For the purification of substrates, column chromatography was generally performed using Kieselgel 60 (230-400 mesh) silica gel, typically with a 50-100:1 weight ratio of silica gel to the crude products.

5.4.2 Synthesis of Azaaryl Acetamides and Acetates

1c, **1d** and **1k** were synthesized following a published procedure.[11]
1m was purchased from Combi-Blocks.
1n was synthesized following a published procedure.[12]

1a was synthesized by the following procedure:

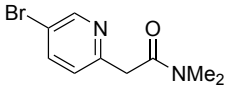


Scheme 5.3 Synthesis of **1a**

In a 100-mL round-bottom flask containing a magnetic stir bar were added 5-bromo-2-fluoropyridine (0.51 mL, 5.0 mmol, 1.0 equiv), dimethylacetamide (DMAc, 0.51 mL, 5.5 mmol, 1.1 equiv) and THF (10 mL). The mixture was cooled to -78 °C. LiHMDS (1.0 M solution in THF, 11.0 mL, 11.0 mmol, 2.2 equiv) was then added dropwise to the reaction mixture. Thereafter, the reaction mixture was slowly warmed to r.t. and stirred at r.t. overnight.

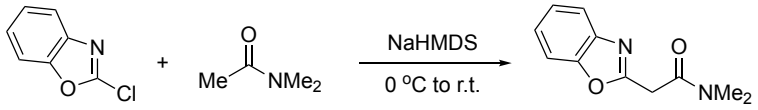
The reaction mixture was quenched with a sat. aqueous NH_4Cl solution (50 mL) and then diluted with EtOAc (100 mL). The organic layer was separated and washed with brine (50 mL). After evaporation of the solvent under vacuum, the crude mixture was purified by flash column chromatography (0 to 10% MeOH in DCM) to give **1a** (756 mg, 3.11 mmol, 62%) as a yellow solid.

2-(5-bromopyridin-2-yl)-*N*,*N*-dimethylacetamide (1a)



^{1}H NMR (500 MHz, $CDCl_3$) δ 8.58 (dd, J = 2.4, 0.7 Hz, 1H), 7.77 (dd, J = 8.3, 2.4 Hz, 1H), 7.26 (d, J = 8.3 Hz, 1H), 3.86 (s, 2H), 3.09 (s, 3H), 2.97 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 169.6, 154.5, 150.3, 139.2, 125.3, 119.0, 43.0, 37.9, 35.7.
HRMS (ESI): *m*/*z* for $C_9H_{12}BrN_2O$ $[M+H]^+$ calcd.: 243.0128, found: 243.0126.

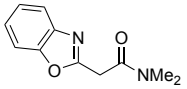
1b was synthesized by the following procedure:



Scheme 5.4 Synthesis of **1b**

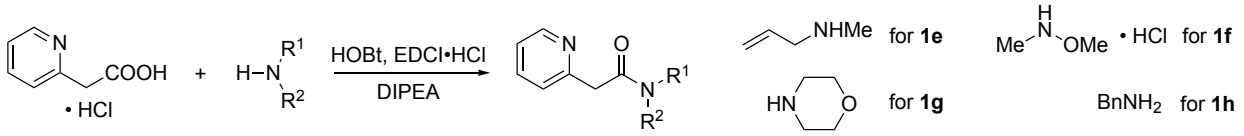
To the solution of 2-chlorobenzoxazle (0.46 mL, 4.0 mmol, 1.0 equiv) and dimethylacetamide (1.12 mL, 12.0 mmol, 3.00 equiv) in toluene (20 mL) at 0 °C was added NaHMDS (1.0 M in THF, 12.0 mmol, 3.0 equiv) over 2 min. After stirring the mixture at 0 °C for 5 h, the reaction mixture was warmed to r.t. and stirred for another 18 h before it was quenched with sat. aqueous NH_4Cl solution (50 mL) and diluted with EtOAc (100 mL). The organic layer was separated and washed with brine (50 mL). After evaporation of the solvent under vacuum, the crude mixture was purified by flash column chromatography (40% to 75% hexanes in EtOAc) to give **1b** (376 mg, 1.84 mmol, 46%) as a yellow solid.

2-(benzo[*d*]oxazol-2-yl)-*N*,*N*-dimethylacetamide (1b)



^{1}H NMR (600 MHz, $CDCl_3$) δ 7.72 – 7.67 (m, 1H), 7.54 – 7.48 (m, 1H), 7.35 – 7.29 (m, 2H), 4.07 (s, 2H), 3.14 (s, 3H), 3.02 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 166.2, 160.8, 151.3, 141.3, 125.1, 124.4, 120.0, 110.8, 38.0, 35.92, 35.32.
HRMS (ESI): *m*/*z* for $C_{11}H_{13}N_2O_2$ $[M+H]^+$ calcd.: 205.0972, found: 205.0973.

1e, **1f**, **1g** and **1h** were synthesized by the following procedure:

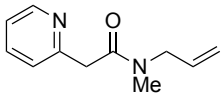


Scheme 5.5 Synthesis of **1e**, **1f**, **1g**, and **1h**

In a 100-mL round-bottom flask containing a magnetic stir bar were added 2-pyridylacetic acid hydrochloride (0.87 g, 5.0 mmol, 1.0 equiv), the corresponding amine (5.0 mmol, 1.0 equiv), 1-hydroxybenzotriazole (HOBt, 0.68 g, 5.0 mmol, 1.0 equiv), *N,N*-diisopropylethylamine (DIPEA, for **1e**, **1g** and **1h**, 1.74 mL, 10.0 mmol, 2.00 equiv; for **1f**, 2.61 mL, 15.0 mmol, 3.00 equiv) and DCM (20 mL). The mixture was cooled to 0 °C. Then *N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride (EDCI·HCl, 0.96 g, 5.0 mmol, 1.0 equiv) was added in one portion to the reaction mixture. The reaction mixture was slowly warmed to r.t. and stirred at r.t. overnight.

The reaction mixture was diluted with EtOAc (100 mL) and washed with water (50 mL), sat. aqueous $NaHCO_3$ solution (50 mL) and brine (50 ml). After evaporation of the solvent under vacuum, the crude mixture was purified by flash column chromatography to give the corresponding amide.

_N_-allyl-_N_-methyl-2-(pyridin-2-yl)acetamide (1e)



0 to 5% MeOH in DCM for flash column chromatography. The title compound was isolated (455 mg, 2.39 mmol, 48%) as a yellow oil.

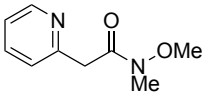
Compound **1e** exists as a mixture of two rotomers (1:1 ratio).

^{1}H NMR (600 MHz, C_6D_6) δ 8.43 – 8.35 (m, 1H), 7.31 (dd, *J* = 7.9, 1.1 Hz, 0.5H), 7.27 (dd, *J* = 7.8, 1.1 Hz, 0.5H), 7.08 – 6.95 (m, 1H), 6.62 – 6.53 (m, 1H), 5.62 – 5.53 (m, 0.5H), 5.36 – 5.24 (m, 0.5H), 4.93 – 4.83 (m, 2H), 3.81 (q, *J* = 2.3, 1.5 Hz, 2H), 3.79 – 3.75 (m, 1H), 3.69 – 3.60 (m, 1H), 2.69 (s, 1.5H), 2.54 (s, 1.5H).

^{13}C NMR (151 MHz, C_6D6) δ 169.6, 169.2, 157.1, 157.0, 149.4, 149.4, 136.1, 136.1, 133.8, 133.6, 124.0, 123.9, 121.6, 121.6, 116.6, 115.9, 52.4, 50.0, 44.2, 44.1, 34.8, 33.3.

HRMS (ESI): *m*/*z* for $C_{11}H_{15}N_2O$ $[M+H]^+$ calcd.: 191.1179, found: 191.1178.

_N_-methoxy-_N_-methyl-2-(pyridin-2-yl)acetamide (1f)



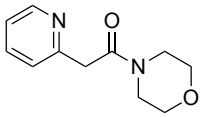
0 to 10% MeOH in DCM for flash column chromatography. The title compound was isolated (conducted at 10-mmol scale, 780 mg, 4.32 mmol, 43%) as brown crystals.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.55 (ddd, *J* = 5.0, 1.9, 0.9 Hz, 1H), 7.64 (td, *J* = 7.7, 1.9 Hz, 1H), 7.32 (d, *J* = 7.8 Hz, 1H), 7.17 (ddd, *J* = 7.5, 4.9, 1.1 Hz, 1H), 4.00 (s, 2H), 3.69 (s, 3H), 3.23 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 171.3, 155.4, 149.3, 136.3, 123.9, 121.7, 61.3, 41.8, 32.1.

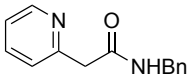
HRMS (ESI): *m*/*z* for $C_9H_{13}N_2O_2$ $[M+H]^+$ calcd.: 181.0972, found: 181.0975.

1-morpholino-2-(pyridin-2-yl)ethan-1-one (1g)



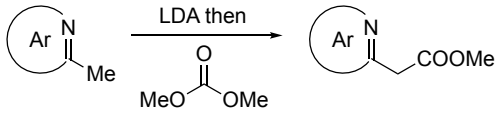
0 to 10% MeOH in DCM for flash column chromatography. The title compound was isolated (113 mg, 0.55 mmol, 11%) as a yellow oil.
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.52 (ddd, *J* = 4.9, 1.8, 0.9 Hz, 1H), 7.66 (td, *J* = 7.7, 1.9 Hz, 1H), 7.45 – 7.31 (m, 1H), 7.18 (ddd, *J* = 7.6, 4.9, 1.1 Hz, 1H), 3.92 (s, 2H), 3.73 – 3.59 (m, 6H), 3.58 – 3.37 (m, 2H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 168.8, 155.7, 149.5, 136.9, 123.7, 122.1, 66.9, 66.8, 46.8, 43.8, 42.3.
HRMS (ESI): *m*/*z* for $C_{11}H_{15}N_2O_2$ $[M+H]^+$ calcd.: 207.1128, found: 207.1128.

***N*-benzyl-2-(pyridin-2-yl)acetamide (1h)**



0 to 6% MeOH in DCM for flash column chromatography. The title compound was isolated (922 mg, 4.07 mmol, 81%) as a white solid.
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.56 – 8.46 (m, 1H), 7.72 (br s, 1H), 7.66 (td, *J* = 7.7, 1.8 Hz, 1H), 7.34 – 7.11 (m, 7H), 4.47 (d, *J* = 5.8 Hz, 2H), 3.78 (s, 2H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 169.3, 155.8, 149.3, 138.5, 137.3, 128.7, 127.6, 127.4, 124.2, 122.2, 45.4, 43.6.
HRMS (ESI): *m*/*z* for $C_{14}H_{15}N_2O$ $[M+H]^+$ calcd.: 227.1179, found: 227.1176.

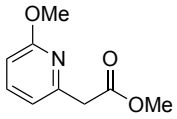
1i, **1j** and **1l** were synthesized by the following procedure:



Scheme 5.6 Synthesis of **1i**, **1j**, and **1l**

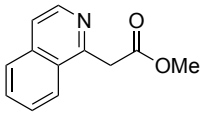
To a solution of diisopropylamine (2.1 mL, 15.0 mmol, 3.0 equiv) in THF (20 mL) was added ^{n}BuLi (2.5 M in hexanes, 6.0 mL, 15.0 mmol, 3.0 equiv) at 0 °C. The reaction mixture was stirred at 0 °C for 15 min. A solution of the corresponding methyl azaarene (5.0 mmol, 1.0 equiv) in THF (10 mL) was then added dropwise to the LDA solution at -78 °C. The reaction mixture was stirred at -78 °C for 2 h. Thereafter, dimethyl carbonate (0.50 mL, 6.0 mmol, 1.2 equiv) was added quickly to the mixture. After stirring at -78 °C for 15 min, the reaction was quenched by water (5 mL) at -78 °C and warmed to r.t.. The mixture was diluted with water (50 mL) and extracted with EtOAc (100 mL). The organic layer was separated, washed with brine (50 mL) and dried over Na_2SO_4. After evaporation of the solvent under vacuum, the crude mixture was purified by flash column chromatography to give the corresponding ester.

methyl 2-(6-methoxypyridin-2-yl)acetate (1i)



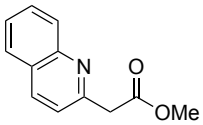
0 to 10% EtOAc in hexanes was used for flash column chromatography. The title compound was isolated (277 mg, 1.53 mmol, 31%) as a colorless oil.
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (dd, *J* = 8.3, 7.2 Hz, 1H), 6.83 (d, *J* = 7.2 Hz, 1H), 6.63 (d, *J* = 8.3 Hz, 1H), 3.90 (s, 3H), 3.75 (s, 2H), 3.72 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 171.3, 163.8, 152.0, 139.1, 116.3, 109.1, 53.4, 52.1, 43.6.
HRMS (EI): *m/z* for $C_9H_{11}NO_3$ $[M]^+$ calcd.: 181.0739, found: 181.0732.

methyl 2-(isoquinolin-1-yl)acetate (1j)



0 to 20% EtOAc in hexanes was used for flash column chromatography. The title compound was isolated (985 mg, 4.90 mmol, 98%) as a yellow powder.
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.48 (d, *J* = 5.7 Hz, 1H), 8.12 – 8.05 (m, 1H), 7.89 – 7.83 (m, 1H), 7.74 – 7.67 (m, 1H), 7.67 – 7.56 (m, 2H), 4.37 (s, 2H), 3.72 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 171.0, 154.6, 142.2, 136.5, 130.3, 127.7, 127.5, 125.2, 120.6, 52.4, 42.2.
HRMS (EI): *m/z* for $C_{12}H_{12}NO_2$ $[M]^+$ calcd.: 202.0863, found: 202.0862.

methyl 2-(quinolin-2-yl)acetate (1l)



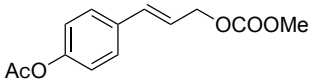
0 to 25% EtOAc in hexanes was used for flash column chromatography. The title compound was isolated (310 mg, 1.54 mmol, 31%) as a colorless oil.
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 (dd, *J* = 8.5, 0.8 Hz, 1H), 8.10 – 8.04 (m, 1H), 7.81 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.71 (ddd, *J* = 8.4, 6.9, 1.5 Hz, 1H), 7.53 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 7.44 (d, *J* = 8.4 Hz, 1H), 4.06 (s, 2H), 3.74 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 171.0, 154.8, 148.0, 136.8, 129.8, 129.3, 127.7, 127.2, 126.6, 121.8, 52.3, 44.8.
HRMS (EI): *m/z* for $C_{12}H_{12}NO_2$ $[M]^+$ calcd.: 202.0863, found: 202.0862.

5.4.3 Synthesis of Allylic Methyl Carbonates

Allylic methy carbonates were synthesized from the allylic alcohols[13] following a published procedure[14]: to a mixture of pyridine (0.73 mL, 9.0 mmol, 3.0 equiv), the allylic alcohol (3.0 mmol, 1.0 equiv) and DCM (6 mL) was added methyl chloroformate (0.46 mL, 6.0 mmol, 2.0 equiv) dropwise at 0 °C. The reaction mixture was allowed to warm to r.t. and stirred overnight (monitored by TLC). The mixture was then quenched with water (50 mL) and diluted with EtOAc (100 mL). The organic layer was separated and washed with an aqueous HCl solution (1M, 50 mL; for **2j**,

this step was not performed) and brine (50 mL). After evaporation of the solvent under vacuum, the crude mixture was purified by flash column chromatography to give the allylic methyl carbonate.

(*E*)-4-(3-((methoxycarbonyl)oxy)prop-1-en-1-yl)phenyl acetate (2c)



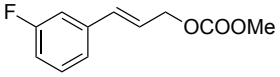
0 to 20% EtOAc in hexanes was used for flash column chromatography. The title compound was isolated (starting from 2.0 mmol of the corresponding allylic alcohol; 486 mg, 1.94 mmol, 97%) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.5 Hz, 2H), 7.05 (d, *J* = 8.6 Hz, 2H), 6.71 – 6.62 (m, 1H), 6.25 (dt, *J* = 15.8, 6.4 Hz, 1H), 4.78 (dd, *J* = 6.4, 1.4 Hz, 2H), 3.81 (s, 3H), 2.30 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 169.4, 155.7, 150.6, 133.9, 133.8, 127.8, 122.8, 121.9, 68.4, 68.4, 54.9, 21.2.

HRMS (EI): *m/z* for $C_{13}H_{14}O_5$ $[M]^+$ calcd.: 250.0841, found: 250.0842.

(*E*)-3-(3-fluorophenyl)allyl methyl carbonate (2d)



0 to 10% EtOAc in hexanes was used for flash column chromatography. The title compound was isolated (starting from 3.0 mmol of the corresponding allylic alcohol; 580 mg, 2.76 mmol, 92%) as a colorless oil.

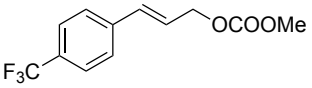
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.29 (td, *J* = 8.0, 6.0 Hz, 1H), 7.15 (dt, *J* = 7.7, 1.3 Hz, 1H), 7.09 (dt, *J* = 10.0, 2.1 Hz, 1H), 6.96 (tdd, *J* = 8.4, 2.6, 0.9 Hz, 1H), 6.65 (d, *J* = 15.9 Hz, 1H), 6.30 (dt, *J* = 15.9, 6.3 Hz, 1H), 4.79 (dd, *J* = 6.3, 1.4 Hz, 2H), 3.82 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 163.2 (d, *J* = 245.8 Hz), 155.7, 138.5 (d, *J* = 7.7 Hz), 133.4 (d, *J* = 2.7 Hz), 130.2 (d, *J* = 8.3 Hz), 124.1, 122.7 (d, *J* = 2.8 Hz), 115.1 (d, *J* = 21.4 Hz), 113.2 (d, *J* = 21.7 Hz), 68.1, 55.0.

^{19}F NMR (376 MHz, $CDCl_3$) δ -113.4 – -113.6 (m).

HRMS (EI): *m/z* for $C_{11}H_{11}FO_3$ $[M]^+$ calcd.: 210.0692, found: 210.0695.

(*E*)-methyl (3-(4-(trifluoromethyl)phenyl)allyl) carbonate (2f)



0 to 10% EtOAc in hexanes was used for flash column chromatography. The title compound was isolated (starting from 5.5 mmol of the corresponding allylic alcohol; 1.06 g, 4.07 mmol, 74%) as a white solid.

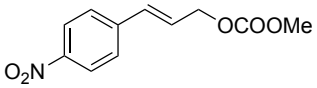
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.1 Hz, 2H), 7.48 (d, *J* = 7.9 Hz, 2H), 6.71 (dt, *J* = 15.9, 1.5 Hz, 1H), 6.38 (dt, *J* = 15.9, 6.2 Hz, 1H), 4.82 (dd, *J* = 6.2, 1.4 Hz, 2H), 3.82 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 155.7, 139.6, 133.0, 130.1 (q, *J* = 32.4 Hz), 127.0, 125.7 (q, *J* = 3.8 Hz), 125.4, 124.2 (d, *J* = 271.8 Hz), 68.0, 55.1.

^{19}F NMR (376 MHz, $CDCl_3$) δ -62.7 (s).

HRMS (EI): *m/z* for $C_{12}H_{11}F_3O_3$ $[M]^+$ calcd.: 260.0660, found: 260.0661.

(*E*)-methyl (3-(4-nitrophenyl)allyl) carbonate (2g)



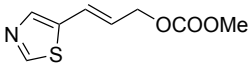
0 to 20% EtOAc in hexanes was used for flash column chromatography. The title compound was isolated (starting from 5.0 mmol of the corresponding allylic alcohol; 1.13 g, 4.76 mmol, 95%) as a yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 (d, *J* = 8.8 Hz, 2H), 7.52 (d, *J* = 8.8 Hz, 2H), 6.74 (dt, *J* = 16.2, 1.7 Hz, 1H), 6.46 (dt, *J* = 16.0, 5.9 Hz, 1H), 4.83 (dd, *J* = 6.0, 1.5 Hz, 2H), 3.82 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 155.6, 147.4, 142.6, 131.8, 127.6, 127.3, 124.2, 67.6, 55.2.

HRMS (EI): *m/z* for $C_{11}H_{11}NO_5$ $[M]^+$ calcd.: 237.0637, found: 237.0634.

(*E*)-methyl (3-(thiazol-5-yl)allyl) carbonate (2j)



0 to 40% EtOAc in hexanes was used for flash column chromatography. The title compound was isolated (starting from 2.0 mmol of the corresponding allylic alcohol; 149 mg, 0.80 mmol, 40%) as a yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.67 (s, 1H), 7.78 (s, 1H), 6.97 – 6.80 (m, 1H), 6.14 (dt, *J* = 15.6, 6.2 Hz, 1H), 4.76 (dd, *J* = 6.2, 1.4 Hz, 2H), 3.82 (s, 3H).

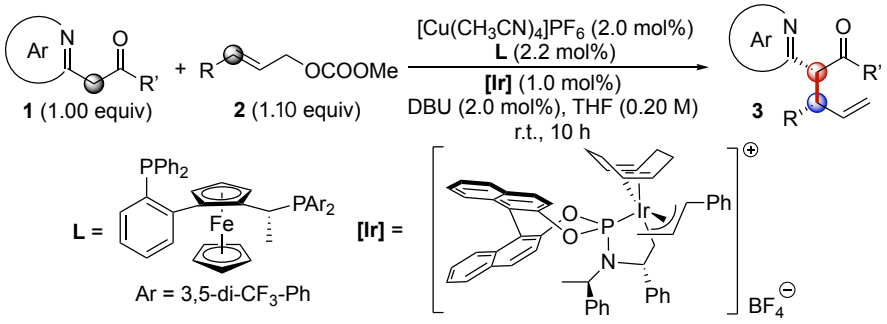
^{13}C NMR (151 MHz, $CDCl_3$) δ 155.6, 152.3, 142.5, 136.2, 126.0, 124.1, 67.6, 55.1.

HRMS (ESI): *m/z* for $C_8H_{10}NO_3S$ $[M+H]^+$ calcd.: 200.0376, found: 200.0376.

5.4.4 Synthesis of Iridium Catalysts

Iridium catalysts were synthesized following published procedures.[15] Catalyst **[Ir]** was synthesized from the corresponding (*R*$_a$,*R*,*R*)-phosphoramidite ligand. Catalyst *ent*-**[Ir]** was prepared from the corresponding (*S*$_a$,*S*,*S*)-phosphoramidite ligand.

General Procedure for Allylations of Azaaryl Acetamides and Acetates



Scheme 5.7 General procedure for allylation

In a nitrogen-filled dry-box, a 1-dram (4 mL) vial equipped with a magnetic stir bar was charged with $[Cu(CH_3CN)_4]PF_6$ (3.7 mg, 0.010 mmol), **L** (10.2 mg, 0.0110 mmol) and THF (1.0

mL). The vial was sealed with a cap containing PTFE/silicone septa. The mixture was stirred at room temperature for 30 min to prepare the Walphos-ligated copper complex (solution **A**). This solution was used within 10 min.

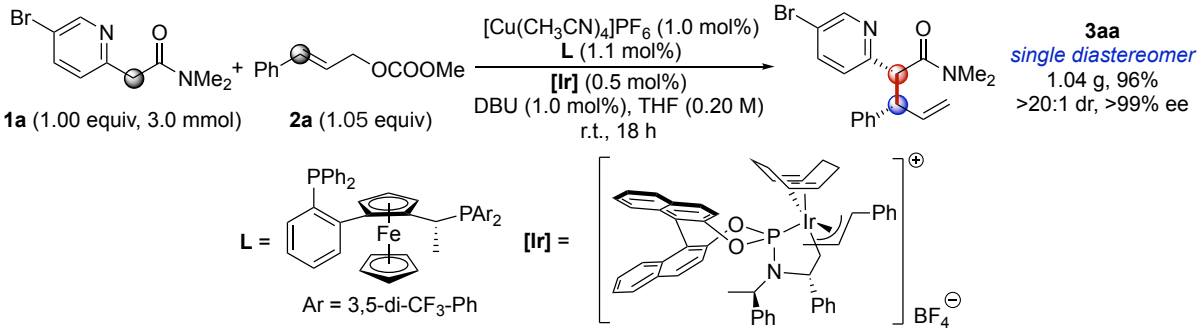
In a nitrogen-filled dry-box, a 1-dram (4 mL) vial equipped with a magnetic stir bar was charged with azaaryl acetamide or acetate **1** (0.100 mmol, 1.00 equiv) and methyl carbonate **2** (0.110 mmol, 1.10 equiv). To the vial was added 0.20 mL of solution **A** (0.0020 mmol, 2.0 mol % of the copper complex). The vial was sealed with a cap containing PTFE/silicone septa. The mixture was stirred at room temperature for 5 min. A stock solution of DBU in THF (0.10 mL, 0.30 mg, 0.0020 mmol, 2.0 mol %) and a stock solution of **[Ir]** in THF (prepared freshly with **[Ir]** in solid state and used within 10 min, 0.20 mL, 1.1 mg, 0.0010 mmol, 1.0 mol %) were then added sequentially to the vial. The vial was then removed from the dry box. The mixture was stirred at room temperature for 10 h.

The reaction mixture was diluted with 2 mL of hexanes, and the resulting solution was filtered through a 0.5-inch plug of silica gel (eluting with 1:1 hexanes:EtOAc, 8 mL; for polar compounds such as **3fa**, **3ga** and **3aj**, pure EtOAc was used). After evaporation of the solvent under vacuum, the crude mixture was purified by column chromatography on a Teledyne Isco Combiflash® R_f system with Redi*Sep* Gold™ columns (4-gram silica gel column). The diastereoselectivity was determined by ^{1}H NMR analysis of the crude reaction mixture.

If the compound was not isolated as a single diastereomer by flash column chromatography on a Teledyne Isco Combiflash® R_f system, a preparative TLC separation was performed to remove the minor diastereomer in the product.

For the synthesis of allylation product **3fa**, **3ga**, **3ha**, **3ia**, **3la**, **3ma** and **3na**, 5 mol % of the copper complex (5.0 mol % of $[Cu(CH_3CN)_4]PF_6$ and 5.5 mol % of **L** in 0.20 mL of THF), 2 mol % of **[Ir]** (in 0.20 mL of THF) and 5 mol % of DBU (in 0.10 mL of THF) were used.

5.4.5 Gram-Scale Synthesis of 3aa



Scheme 5.8 General procedure for allylation

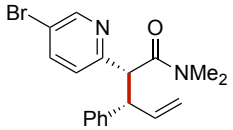
In a nitrogen-filled dry-box, a 1-dram vial (4 mL, **vial A**) equipped with a magnetic stir bar was charged with $[Cu(CH_3CN)_4]PF_6$ (11.2 mg, 0.0300 mmol, 1.00 mol%), **L** (30.7 mg, 0.0330 mmol, 1.10 mol%) and THF (3.0 mL). The vial was sealed with a cap containing PTFE/silicone septa. The mixture was stirred at room temperature for 30 min to prepare the Walphos-ligated copper complex. This solution was used within 10 min. A 1-dram vial (4 mL, **vial B**) equipped with a magnetic stir bar was charged with iridium complex **[Ir]** (16.4 mg, 0.0150 mmol, 0.50

mol%) and THF (3.0 mL). The vial was sealed with a cap containing PTFE/silicone septa. The mixture was stirred at room temperature for 1 min. This solution was used within 10 min.

In a nitrogen-filled dry-box, a 20 mL vial (**vial C**) equipped with a magnetic stir bar was charged with azaaryl acetamide **1a** (729 mg, 3.00 mmol, 1.00 equiv). The solution of the copper complex in **vial A** was added into **vial C** via syringe. **Vial A** was rinsed with THF (1 mL x 3) and the resulting solution was added to **vial C**. The mixture in **vial C** was stirred at r.t. for 5 min. Thereafter, a stock solution of DBU in THF (3.0 mL, 4.6 mg, 0.030 mmol, 1.0 mol %), methyl carbonate **2a** (605 mg, 3.15 mmol, 1.05 equiv) and the solution of the iridium complex in **vial B** were then added sequentially to **vial C**. **Vial B** was rinsed with THF (1 mL x 3) and the resulting solution was added to **vial C**. **Vial C** was sealed partially (CO_2 gas generated during the reaction) with a cap containing PTFE/silicone septa. The mixture in **vial C** was stirred at room temperature for 18 h.

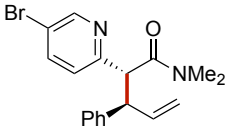
After the reaction, the vial was removed from the dry box. The reaction mixture was diluted with 15 mL of hexanes, and the resulting solution was filtered through a 0.5-inch plug of silica gel (eluting with 1:1 hexanes:EtOAc, 100 mL). After evaporation of the solvent under vacuum, the crude mixture was purified by column chromatography (0 to 40% EtOAc in hexanes) on a Teledyne Isco Combiflash® R_f system with Redi*Sep* Gold™ columns (24-gram silica gel column) to give **3aa** as a white solid (single diastereomer, 1.04 g, 2.89 mmol, 96%). The diastereoselectivity was determined by ^{1}H NMR analysis of the crude reaction mixture to be >20:1. The enantiomeric excess was determined by SFC analysis to be >99%. See the next section for detailed characterizations of **3aa**.

(2*R*,3*S*)-2-(5-bromopyridin-2-yl)-*N*,*N*-dimethyl-3-phenylpent-4-enamide (3aa)



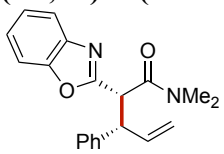
Prepared according to the general procedure as described above.
The diastereomeric ratio was determined to be >20:1.
The crude mixture was purified by column chromatography (0 to 40% EtOAc in hexanes) to give the title compound as a white solid (isolated as a single diastereomer, 35.0 mg, 0.0974 mmol, 97%).
The **enantiomeric excess** was determined by SFC analysis to be >99% with t_R = 1.76 min (major) and t_R = 1.42 min (minor) [OD-H, 10.0% MeOH, 2.5 mL/min, 220 nm, 40 °C].
$[\alpha]_D^{25}$ = –97.1° (c 0.14, CH_2Cl_2).
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.56 (s, 1H), 7.80 (dd, *J* = 8.5, 2.4 Hz, 1H), 7.60 (d, *J* = 8.4 Hz, 1H), 7.34 – 7.28 (m, 4H), 7.23 – 7.19 (m, 1H), 5.84 – 5.74 (m, 1H), 4.85 – 4.80 (m, 2H), 4.59 (d, *J* = 11.3 Hz, 1H), 4.22 (dd, *J* = 11.3, 8.7 Hz, 1H), 2.91 (s, 3H), 2.67 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 170.8, 157.2, 149.8, 142.1, 139.6, 138.6, 128.7, 128.0, 126.9, 124.7, 119.5, 117.0, 55.8, 53.6, 37.5, 35.9.
HRMS (ESI): *m*/*z* for $C_{18}H_{20}BrN_2O$ $[M+H]^+$ calcd.: 359.0754, found: 359.0754.

(2*R*,3*R*)-2-(5-bromopyridin-2-yl)-*N*,*N*-dimethyl-3-phenylpent-4-enamide (4aa)



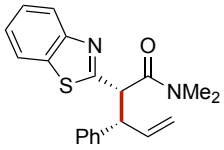
Prepared according to the general procedure as described above (*ent*-**[Ir]** was used instead of **[Ir]**).
The diastereomeric ratio was determined to be >20:1.
The crude mixture was purified by column chromatography (0 to 45% EtOAc in hexanes) to give the title compound as a white solid (isolated as a single diastereomer, 30.0 mg, 0.0835 mmol, 84%).
The **enantiomeric excess** was determined by SFC analysis to be >99% with t_R = 2.00 min (major) and t_R = 1.63 min (minor) [OD-H, 10.0% MeOH, 2.5 mL/min, 220 nm, 40 °C].
$[\alpha]_D^{25}$ = –71.0° (c 0.42, CH_2Cl_2).
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.34 – 8.30 (m, 1H), 7.59 (dd, *J* = 8.5, 2.4 Hz, 1H), 7.36 (d, *J* = 8.5 Hz, 1H), 7.13 (t, *J* = 7.5 Hz, 2H), 7.11 – 7.03 (m, 3H), 6.08 (ddd, *J* = 17.3, 10.4, 7.0 Hz, 1H), 5.13 – 5.02 (m, 2H), 4.59 (d, *J* = 11.1 Hz, 1H), 4.32 (dd, *J* = 11.1, 7.1 Hz, 1H), 3.17 (s, 3H), 2.95 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 171.1, 156.6, 149.7, 140.3, 139.7, 139.1, 128.8, 128.4, 126.6, 124.5, 119.0, 116.0, 55.0, 52.7, 37.7, 36.2.
HRMS (ESI): *m*/*z* for $C_{18}H_{20}BrN_2O$ $[M+H]^+$ calcd.: 359.0754, found: 359.0756.

(2*R*,3*S*)-2-(benzo[*d*]oxazol-2-yl)-*N*,*N*-dimethyl-3-phenylpent-4-enamide (3ba)



Prepared according to the general procedure as described above.
The diastereomeric ratio was determined to be 15:1.
The crude mixture was purified by column chromatography (0 to 55% EtOAc in hexanes) to give the title compound as a white solid (isolated as a single diastereomer, 30.1 mg, 0.0939 mmol, 94%).
The **enantiomeric excess** was determined by SFC analysis to be >99% with t_R = 4.93 min (major) and t_R = 4.46 min (minor) [OD-H, 3.0% MeOH, 2.5 mL/min, 220 nm, 40 °C].
$[\alpha]_D^{25}$ = –54.5° (c 0.40, CH_2Cl_2).
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.76 – 7.66 (m, 1H), 7.60 – 7.54 (m, 1H), 7.38 – 7.30 (m, 6H), 7.25 – 7.21 (m, 1H), 5.94 (ddd, *J* = 16.8, 10.2, 8.5 Hz, 1H), 5.08 – 4.99 (m, 1H), 4.87 (d, *J* = 10.2 Hz, 1H), 4.81 (d, *J* = 11.3 Hz, 1H), 4.60 (dd, *J* = 11.3, 8.5 Hz, 1H), 2.99 (s, 3H), 2.73 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 166.8, 162.5, 151.2, 141.0, 140.9, 137.8, 128.8, 128.0, 127.2, 125.1, 124.5, 120.0, 117.2, 111.1, 50.9, 48.7, 37.6, 36.1.
HRMS (ESI): *m*/*z* for $C_{20}H_{21}N_2O_2$ $[M+H]^+$ calcd.: 321.1598, found: 323.1593.

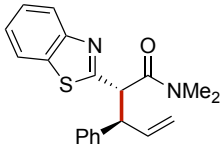
(2*S*,3*S*)-2-(benzo[*d*]thiazol-2-yl)-*N*,*N*-dimethyl-3-phenylpent-4-enamide (3ca)



Prepared according to the general procedure as described above.

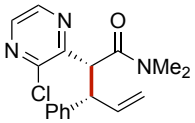
The diastereomeric ratio was determined to be >20:1.
The crude mixture was purified by column chromatography (0 to 45% EtOAc in hexanes) to give the title compound as a white solid (isolated as a single diastereomer, 32.7 mg, 0.0972 mmol, 97%).
The **enantiomeric excess** was determined by SFC analysis to be >99% with t_R = 2.91 min (major) and t_R = 2.00 min (minor) [OD-H, 10.0% MeOH, 2.5 mL/min, 220 nm, 40 °C].
[α]$_D^{25}$ = –112.0° (c 0.25, CH_2Cl_2).
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.00 (d, *J* = 8.1 Hz, 1H), 7.88 (d, *J* = 8.0 Hz, 1H), 7.48 – 7.43 (m, 1H), 7.39 – 7.30 (m, 5H), 7.26 – 7.21 (m, 1H), 5.99 (ddd, *J* = 16.8, 10.2, 8.7 Hz, 1H), 5.01 – 4.92 (m, 2H), 4.86 (d, *J* = 10.2 Hz, 1H), 4.25 (dd, *J* = 11.1, 8.8 Hz, 1H), 2.85 (s, 3H), 2.70 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 169.7, 169.0, 152.0, 141.3, 137.3, 136.2, 128.7, 128.0, 127.2, 125.9, 125.1, 122.9, 121.9, 117.7, 55.3, 53.8, 37.6, 36.0.
HRMS (ESI): *m*/*z* for $C_{20}H_{21}N_2OS$ $[M+H]^+$ calcd.: 337.1369, found: 337.1372.

(2*S*,3*R*)-2-(benzo[*d*]thiazol-2-yl)-*N*,*N*-dimethyl-3-phenylpent-4-enamide (4ca)



Prepared according to the general procedure as described above (*ent*-**[Ir]** was used instead of **[Ir]**).
The diastereomeric ratio was determined to be 20:1.
The crude mixture was purified by column chromatography (0 to 55% EtOAc in hexanes) to give the title compound as a white solid (28.4 mg, 0.0844 mmol, 84%).
The **enantiomeric excess** was determined by SFC analysis to be >99% with t_R = 5.90 min (major) and t_R = 4.97 min (minor) [OD-H, 5.0% MeOH, 2.5 mL/min, 220 nm, 40 °C].
[α]$_D^{25}$ = –28.5° (c 0.20, CH_2Cl_2).
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.84 – 7.81 (m, 1H), 7.78 – 7.74 (m, 1H), 7.37 – 7.33 (m, 1H), 7.30 – 7.26 (m, 1H), 7.24 – 7.20 (m, 2H), 7.18 – 7.14 (m, 2H), 7.09 – 7.05 (m, 1H), 6.13 (ddd, *J* = 17.4, 10.3, 7.5 Hz, 1H), 5.13 – 5.07 (m, 2H), 5.02 (d, *J* = 10.6 Hz, 1H), 4.38 (dd, *J* = 10.6, 7.5 Hz, 1H), 3.19 (s, 3H), 2.99 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 169.8, 168.2, 152.0, 139.7, 138.7, 135.8, 128.6, 128.5, 127.0, 125.7, 124.9, 122.8, 121.7, 116.9, 54.2, 52.8, 37.9, 36.3.
HRMS (ESI): *m*/*z* for $C_{20}H_{21}N_2OS$ $[M+H]^+$ calcd.: 337.1369, found: 337.1368.

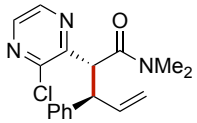
(2*R*,3*S*)-2-(3-chloropyrazin-2-yl)-*N*,*N*-dimethyl-3-phenylpent-4-enamide (3da)



Prepared according to the general procedure as described above.
The diastereomeric ratio was determined to be >20:1.
The crude mixture was purified by column chromatography (0 to 70% EtOAc in hexanes) to give the title compound as a white solid (isolated as a single diastereomer, 26.8 mg, 0.0849 mmol, 85%).
The **enantiomeric excess** was determined by SFC analysis to be >99% with t_R = 2.18 min (major) and t_R = 1.93 min (minor) [OD-H, 10.0% MeOH, 2.5 mL/min, 220 nm, 40 °C].
[α]$_D^{25}$ = –26.0° (c 0.45, CH_2Cl_2).

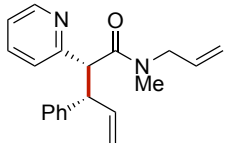
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.63 (d, *J* = 2.3 Hz, 1H), 8.25 (d, *J* = 2.3 Hz, 1H), 7.40 – 7.36 (m, 2H), 7.34 – 7.29 (m, 2H), 7.25 – 7.21 (m, 1H), 5.91 (ddd, *J* = 16.9, 10.3, 8.6 Hz, 1H), 5.00 (d, *J* = 10.9 Hz, 1H), 4.86 – 4.77 (m, 2H), 4.55 (dd, *J* = 10.9, 8.6 Hz, 1H), 2.77 (s, 3H), 2.69 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 168.8, 152.5, 148.9, 143.1, 142.1, 141.5, 137.9, 128.6, 128.4, 127.1, 117.0, 52.3, 50.2, 37.2, 36.0.
HRMS (ESI): *m*/*z* for $C_{17}H_{19}ClN_3O$ $[M+H]^+$ calcd.: 316.1211, found: 316.1211.

(2*R*,3*R*)-2-(3-chloropyrazin-2-yl)-*N*,*N*-dimethyl-3-phenylpent-4-enamide (4da)



Prepared according to the general procedure as described above (*ent*-**[Ir]** was used instead of **[Ir]**).
The diastereomeric ratio was determined to be >20:1.
The crude mixture was purified by column chromatography (0 to 70% EtOAc in hexanes) to give the title compound as a colorless gel (22.8 mg, 0.0722 mmol, 72%).
The **enantiomeric excess** was determined by SFC analysis to be >99% with t_R = 4.42 min (major) and t_R = 4.76 min (minor) [OD-H, 5.0% MeOH, 2.5 mL/min, 220 nm, 40 °C].
$[\alpha]_D^{25}$ = +61.4° (c 0.14, CH_2Cl_2).
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.49 (d, *J* = 2.4 Hz, 1H), 8.06 (d, *J* = 2.4 Hz, 1H), 7.17 – 7.10 (m, 4H), 7.10 – 7.01 (m, 1H), 6.12 (ddd, *J* = 17.5, 10.0, 7.6 Hz, 1H), 5.18 – 5.11 (m, 2H), 5.06 (d, *J* = 10.8 Hz, 1H), 4.61 (dd, *J* = 10.9, 7.5 Hz, 1H), 3.23 (s, 3H), 2.99 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 169.3, 151.9, 148.5, 142.8, 141.9, 140.2, 138.9, 128.6, 128.4, 126.8, 116.8, 52.0, 49.8, 37.8, 36.4.
HRMS (ESI): *m*/*z* for $C_{17}H_{19}ClN_3O$ $[M+H]^+$ calcd.: 316.1211, found: 316.1211.

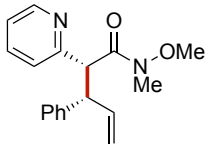
(2*R*,3*S*)-*N*-allyl-*N*-methyl-3-phenyl-2-(pyridin-2-yl)pent-4-enamide (3ea)



Prepared according to the general procedure as described above.
The diastereomeric ratio was determined to be >20:1.
The crude mixture was purified by column chromatography (0 to 50% EtOAc in hexanes) to give the title compound as a colorless gel (isolated as a single diastereomer, 28.5 mg, 0.0930 mmol, 93%).
The **enantiomeric excess** was determined by SFC analysis to be >99% with t_R = 6.57 min (major) and t_R = 6.19 min (minor) [OD-H, 2.0% MeOH, 2.5 mL/min, 220 nm, 40 °C].
$[\alpha]_D^{25}$ = –110.2° (c 0.16, CH_2Cl_2).
Compound **3ea** exists as a mixture of two rotomers (1.2:1 ratio).
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.56 – 8.46 (m, 1H), 7.74 – 7.57 (m, 2H), 7.42 – 7.24 (m, 4H), 7.23 – 7.11 (m, 2H), 5.89 – 5.73 (m, 1H), 5.44 (ddd, *J* = 17.1, 10.1, 4.9 Hz, 0.45H), 5.33 – 5.22 (m, 0.55H), 4.97 (dd, *J* = 10.3, 1.4 Hz, 0.45H), 4.87 – 4.83 (m, 0.55H), 4.83 – 4.72 (m, 2H), 4.70 – 4.61 (m, 1H), 4.58 – 4.52 (m, 0.55H), 4.46 (d, *J* = 11.2 Hz, 0.45H), 4.35 – 4.24 (m, 1.45H), 4.02 – 3.94 (m, 0.55H), 3.62 – 3.54 (m, 0.45H), 3.51 – 3.45 (m, 0.55H), 2.91 (s, 1.65H), 2.66 (s, 1.35H).

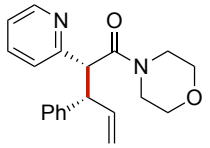
^{13}C NMR (151 MHz, $CDCl_3$) δ 171.0, 171.0, 158.7, 158.5, 148.9, 148.8, 142.6, 142.4, 138.9, 137.0, 132.6, 132.4, 128.6, 128.5, 128.4, 128.2, 126.8, 126.6, 123.2, 123.0, 122.4, 122.4, 116.7, 116.5, 116.4, 116.3, 57.0, 56.7, 53.7, 53.5, 51.9, 50.3, 35.3, 33.8.
HRMS (ESI): *m*/*z* for $C_{20}H_{23}N_2O$ $[M+H]^+$ calcd.: 307.1805, found: 307.1804.

(2*R*,3*S*)-*N*-methoxy-*N*-methyl-3-phenyl-2-(pyridin-2-yl)pent-4-enamide (3fa)



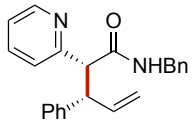
Prepared according to the general procedure as described above.
The diastereomeric ratio was determined to be 12:1.
The crude mixture was purified by column chromatography (0 to 70% EtOAc in hexanes) to give the title compound as a colorless gel (28.6 mg, 0.0965 mmol, 96%).
The **enantiomeric excess** was determined by SFC analysis to be 97% with t_R = 7.65 min (major) and t_R = 7.23 min (minor) [IC, 3.0% MeOH, 2.5 mL/min, 220 nm, 40 °C].
$[\alpha]_D^{25}$ = –181.0° (c 0.12, CH_2Cl_2).
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.56 (d, *J* = 4.6 Hz, 1H), 7.73 – 7.59 (m, 2H), 7.40 – 7.35 (m, 2H), 7.31 (dd, *J* = 8.5, 6.9 Hz, 2H), 7.23 – 7.12 (m, 2H), 5.81 (ddd, *J* = 16.3, 10.8, 8.6 Hz, 1H), 4.90 (d, *J* = 11.7 Hz, 1H), 4.82 – 4.73 (m, 2H), 4.25 (dd, *J* = 11.7, 8.5 Hz, 1H), 3.50 (s, 3H), 2.92 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 172.4, 158.2, 149.1, 142.2, 139.0, 136.8, 128.6, 128.3, 126.8, 123.6, 122.4, 116.5, 61.8, 55.0, 53.2, 32.2.
HRMS (ESI): *m*/*z* for $C_{18}H_{21}N_2O_2$ $[M+H]^+$ calcd.: 297.1598, found: 297.1598.

(2*R*,3*S*)-1-morpholino-3-phenyl-2-(pyridin-2-yl)pent-4-en-1-one (3ga)



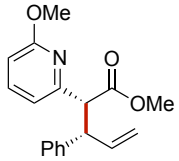
Prepared according to the general procedure as described above.
The diastereomeric ratio was determined to be >20:1.
The crude mixture was purified by column chromatography (30% to 90% EtOAc in hexanes) to give the title compound as a white solid (29.9 mg, 0.0927 mmol, 93%).
The **enantiomeric excess** was determined by SFC analysis to be 99% with t_R = 2.74 min (major) and t_R = 2.43 min (minor) [OJ-H, 3.0% MeOH, 2.5 mL/min, 220 nm, 40 °C].
$[\alpha]_D^{25}$ = –94.1° (c 0.16, CH_2Cl_2).
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.49 (dt, *J* = 5.0, 1.3 Hz, 1H), 7.75 – 7.58 (m, 2H), 7.38 – 7.29 (m, 4H), 7.25 – 7.15 (m, 2H), 5.81 (ddd, *J* = 16.9, 10.5, 8.5 Hz, 1H), 4.89 – 4.74 (m, 2H), 4.57 (d, *J* = 11.4 Hz, 1H), 4.30 (dd, *J* = 11.3, 8.5 Hz, 1H), 3.59 – 3.46 (m, 2H), 3.44 – 3.28 (m, 3H), 3.28 – 3.18 (m, 2H), 3.18 – 3.07 (m, 1H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 169.8, 158.3, 148.9, 142.4, 138.7, 137.0, 128.8, 128.2, 126.9, 123.3, 122.5, 116.8, 66.8, 66.7, 56.1, 53.3, 46.5, 42.6.
HRMS (ESI): *m*/*z* for $C_{20}H_{23}N_2O_2$ $[M+H]^+$ calcd.: 323.1754, found: 323.1755.

(2*R*,3*S*)-*N*-benzyl-3-phenyl-2-(pyridin-2-yl)pent-4-enamide (3ha)



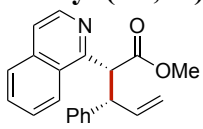
Prepared according to the general procedure as described above.
The diastereomeric ratio was determined to be >20:1.
The crude mixture was purified by column chromatography (0 to 65% EtOAc in hexanes) to give the title compound as a white solid (30.0 mg, 0.0876 mmol, 88%).
The **enantiomeric excess** was determined by SFC analysis to be >99% with t_R = 15.12 min (major) and t_R = 14.34 min (minor) [OD-H, 3.0% MeOH, 2.5 mL/min, 220 nm, 40 °C].
[α]$_D^{25}$ = +12.5° (c 0.24, CH_2Cl_2).
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.51 (dd, *J* = 5.0, 1.7 Hz, 1H), 7.66 (td, *J* = 7.7, 1.8 Hz, 1H), 7.42 (d, *J* = 7.8 Hz, 1H), 7.35 – 7.29 (m, 4H), 7.29 – 7.24 (m, 1H), 7.22 – 7.13 (m, 4H), 7.13 – 7.05 (m, 1H), 6.83 – 6.77 (m, 2H), 5.82 (ddd, *J* = 16.9, 10.3, 8.2 Hz, 1H), 4.86 – 4.76 (m, 2H), 4.29 – 4.21 (m, 2H), 4.15 (dd, *J* = 15.1, 5.6 Hz, 1H), 4.07 (d, *J* = 11.0 Hz, 1H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 170.6, 157.9, 149.0, 141.3, 138.7, 138.3, 136.9, 128.8, 128.5, 128.4, 127.5, 127.1, 127.0, 124.4, 122.5, 116.6, 61.6, 54.0, 43.4.
HRMS (ESI): *m*/*z* for $C_{23}H_{23}N_2O$ $[M+H]^+$ calcd.: 343.1805, found: 343.1802.

methyl (2*R*,3*S*)-2-(6-methoxypyridin-2-yl)-3-phenylpent-4-enoate (3ia)



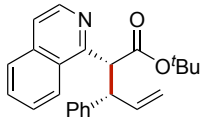
Prepared according to the general procedure as described above.
The diastereomeric ratio was determined to be 10:1.
The crude mixture was purified by column chromatography (0 to 10% EtOAc in hexanes) to give the title compound as a colorless gel (28.7 mg, 0.0965 mmol, 97%).
The **enantiomeric excess** was determined by SFC analysis to be >99% with t_R = 2.97 min (major) and t_R = 3.20 min (minor) [OJ-H, 1.0% MeOH, 2.5 mL/min, 220 nm, 40 °C].
[α]$_D^{25}$ = +73.5° (c 0.16, CH_2Cl_2).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.29 (m, 1H), 7.17 – 7.02 (m, 5H), 6.72 (dd, *J* = 7.3, 0.7 Hz, 1H), 6.44 (dd, *J* = 8.2, 0.7 Hz, 1H), 6.10 (ddd, *J* = 17.1, 10.3, 7.7 Hz, 1H), 5.17 (dt, *J* = 17.2, 1.3 Hz, 1H), 5.10 (dt, *J* = 10.3, 1.1 Hz, 1H), 4.30 (dd, *J* = 11.4, 7.6 Hz, 1H), 4.17 (d, *J* = 11.4 Hz, 1H), 3.83 (s, 3H), 3.69 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 172.4, 163.3, 153.8, 140.8, 139.7, 138.7, 128.4, 128.3, 126.5, 116.2, 115.9, 109.0, 58.4, 53.4, 52.2, 51.9.
HRMS (ESI): *m*/*z* for $C_{18}H_{20}NO_3$ $[M+H]^+$ calcd.: 298.1438, found: 298.1437.

methyl (2*R*,3*S*)-2-(isoquinolin-1-yl)-3-phenylpent-4-enoate (3ja)



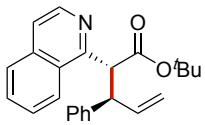
Prepared according to the general procedure as described above.
The diastereomeric ratio was determined to be >20:1.
The crude mixture was purified by column chromatography (0 to 20% EtOAc in hexanes) to give the title compound as a yellow gel (31.3 mg, 0.0986 mmol, 99%).
The **enantiomeric excess** was determined by SFC analysis to be >99% with t_R = 4.25 min (major) and t_R = 3.38 min (minor) [OJ-H, 5.0% MeOH, 2.5 mL/min, 220 nm, 40 °C].
$[\alpha]_D^{25}$ = –95.7° (c 0.39, CH_2Cl_2).
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.63 (d, *J* = 5.6 Hz, 1H), 8.44 – 8.39 (m, 1H), 7.90 – 7.83 (m, 1H), 7.74 – 7.65 (m, 2H), 7.60 (dd, *J* = 5.6, 1.0 Hz, 1H), 7.49 – 7.42 (m, 2H), 7.37 (dd, *J* = 8.4, 6.9 Hz, 2H), 7.29 – 7.22 (m, 1H), 5.73 (ddd, *J* = 17.1, 10.3, 7.5 Hz, 1H), 5.17 (d, *J* = 11.3 Hz, 1H), 4.80 (dd, *J* = 11.3, 7.6 Hz, 1H), 4.75 (dt, *J* = 17.0, 1.4 Hz, 1H), 4.68 (dt, *J* = 10.4, 1.3 Hz, 1H), 3.39 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 171.2, 156.0, 142.4, 141.8, 138.8, 136.7, 130.1, 128.7, 128.6, 128.1, 127.8, 127.8, 127.0, 124.8, 120.4, 116.3, 54.0, 52.2, 51.1.
HRMS (ESI): *m*/*z* for $C_{21}H_{20}NO_2$ $[M+H]^+$ calcd.: 318.1489, found: 318.1487.

***tert*-butyl (2*R*,3*S*)-2-(isoquinolin-1-yl)-3-phenylpent-4-enoate (3ka)**



Prepared according to the general procedure as described above.
The diastereomeric ratio was determined to be >20:1.
The crude mixture was purified by column chromatography (0 to 10% EtOAc in hexanes) to give the title compound as a white solid (35.0 mg, 0.0973 mmol, 97%).
The **enantiomeric excess** was determined by SFC analysis to be >99% with t_R = 5.16 min (major) and t_R = 5.44 min (minor) [OD-H, 3.0% MeOH, 2.5 mL/min, 220 nm, 40 °C].
$[\alpha]_D^{25}$ = –92.2° (c 0.27, CH_2Cl_2).
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.63 (d, *J* = 5.6 Hz, 1H), 8.48 – 8.44 (m, 1H), 7.88 – 7.81 (m, 1H), 7.73 – 7.63 (m, 2H), 7.58 (dd, *J* = 5.7, 0.9 Hz, 1H), 7.52 – 7.45 (m, 2H), 7.39 – 7.31 (m, 2H), 7.29 – 7.23 (m, 1H), 5.77 (ddd, *J* = 17.3, 10.4, 7.1 Hz, 1H), 5.06 (d, *J* = 11.4 Hz, 1H), 4.85 – 4.79 (m, 1H), 4.74 (dt, *J* = 17.1, 1.4 Hz, 1H), 4.70 (dt, *J* = 10.3, 1.4 Hz, 1H), 1.05 (s, 9H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 169.8, 156.4, 142.3, 142.0, 139.5, 136.7, 129.9, 129.1, 128.5, 128.1, 127.7, 127.5, 126.8, 125.1, 120.1, 115.8, 81.1, 54.8, 50.6, 27.7.
HRMS (ESI): *m*/*z* for $C_{24}H_{26}NO_2$ $[M+H]^+$ calcd.: 360.1958, found: 360.1957.

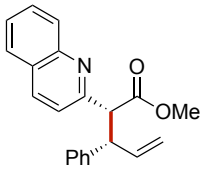
***tert*-butyl (2R,3R)-2-(isoquinolin-1-yl)-3-phenylpent-4-enoate (4ka)**



Prepared according to the general procedure as described above (*ent*-**[Ir]** was used instead of **[Ir]**).
The diastereomeric ratio was determined to be >20:1.
The crude mixture was purified by column chromatography (0 to 15% EtOAc in hexanes) to give the title compound as a colorless gel (36.0 mg, 0.0100 mmol, >99%).

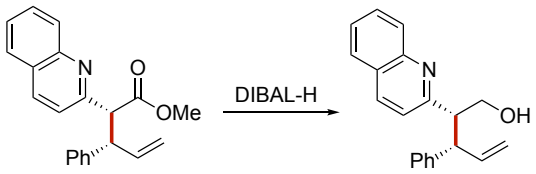
The **enantiomeric excess** was determined by SFC analysis to be 96% with t_R = 2.37 min (major) and t_R = 1.65 min (minor) [OJ-H, 5.0% MeOH, 2.5 mL/min, 220 nm, 40 °C].
$[\alpha]_D^{25}$ = +59.6° (c 0.25, CH_2Cl_2).
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.45 (d, *J* = 5.6 Hz, 1H), 8.28 (dd, *J* = 8.6, 1.3 Hz, 1H), 7.73 – 7.66 (m, 1H), 7.56 (dddd, *J* = 18.2, 8.3, 6.8, 1.4 Hz, 2H), 7.38 (dd, *J* = 5.6, 0.9 Hz, 1H), 7.15 – 7.11 (m, 2H), 7.02 – 6.96 (m, 2H), 6.92 – 6.86 (m, 1H), 6.24 (ddd, *J* = 17.1, 10.3, 8.0 Hz, 1H), 5.29 (dt, *J* = 17.1, 1.3 Hz, 1H), 5.17 (ddd, *J* = 10.2, 1.5, 0.8 Hz, 1H), 5.04 (d, *J* = 11.2 Hz, 1H), 4.78 (dd, *J* = 11.2, 8.0 Hz, 1H), 1.33 (s, 9H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 170.4, 156.1, 142.0, 141.6, 140.0, 136.4, 129.6, 128.4, 128.0, 127.7, 127.4, 127.2, 126.1, 124.8, 119.8, 116.0, 81.4, 54.4, 50.8, 28.1.
HRMS (ESI): *m*/*z* for $C_{24}H_{26}NO_2$ $[M+H]^+$ calcd.: 360.1958, found: 360.1958.

methyl (2*R*,3*S*)-3-phenyl-2-(quinolin-2-yl)pent-4-enoate (3la)



Prepared according to the general procedure as described above.
The diastereomeric ratio of the crude mixture was determined to be 6:1.
The crude mixture was purified by column chromatography (0 to 20% EtOAc in hexanes) to give the title compound as a yellow gel (30.7 mg, 0.0967 mmol, 97%). However, the diastereomeric ratio of the product after purification was determined to be 2.4:1, indicating that **3la** epimerized on silica gel.
HRMS (ESI): *m*/*z* for $C_{21}H_{20}NO_2$ $[M+H]^+$ calcd.: 318.1489, found: 318.1489.

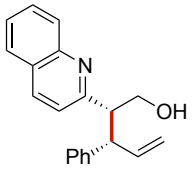
For characterizations, the crude mixture of **3la** was reduced by DIBAL-H after filtering off metal salts:



Scheme 5.9 Reduction of **3la**

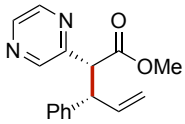
To the crude mixture of **3la** in THF (0.5 mL) was added DIBAL-H solution (1M in hexanes, 0.40 mL, 0.40 mmol, 4.0 equiv) dropwise under -20 °C. After stirred at -20 °C for 1 h, the mixture was warmed to r.t. and quenched with aqueous Rochelle salt solution (3 mL). The mixture was stirred at r.t. for 30 min until a clear solution was obtained, and then extracted with EtOAc (6 mL x 4). After evaporation of the solvent under vacuum, the crude mixture was purified by flash column chromatography (0 to 35% EtOAc in hexanes) to give **5** (isolated a single diastereomer, 20.0 mg, 0.0691 mmol, 69%) as a yellow gel.

(2*R*,3*S*)-3-phenyl-2-(quinolin-2-yl)pent-4-en-1-ol (5)



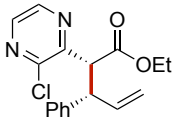
The **enantiomeric excess** was determined by SFC analysis to be 99% with t_R = 4.18 min (major) and t_R = 3.78 min (minor) [AD-H, 10.0% MeOH, 2.5 mL/min, 220 nm, 40 °C].
[α]$_D^{25}$ = +124.0° (c 0.30, CH_2Cl_2).
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (dd, *J* = 8.3, 1.1 Hz, 1H), 7.75 (dd, *J* = 8.5, 0.7 Hz, 1H), 7.70 – 7.64 (m, 2H), 7.50 – 7.43 (m, 1H), 7.11 – 7.06 (m, 2H), 7.06 – 6.99 (m, 3H), 6.68 (d, *J* = 8.5 Hz, 1H), 6.24 (ddd, *J* = 17.0, 10.1, 9.1 Hz, 1H), 5.33 (dt, *J* = 16.9, 1.3 Hz, 1H), 5.21 (dd, *J* = 10.1, 1.6 Hz, 1H), 4.23 (dd, *J* = 11.1, 4.0 Hz, 1H), 4.18 – 4.05 (m, 2H), 3.26 (ddd, *J* = 10.9, 4.1, 2.3 Hz, 1H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 164.0, 147.1, 142.8, 139.5, 135.8, 129.6, 129.0, 128.4, 128.1, 127.6, 126.8, 126.3, 126.2, 122.8, 117.0, 63.4, 52.9, 52.3.
HRMS (ESI): *m*/*z* for $C_{20}H_{20}NO$ $[M+H]^+$ calcd.: 290.1539, found: 290.1537.

methyl (2*R*,3*S*)-3-phenyl-2-(pyrazin-2-yl)pent-4-enoate (3ma)



Prepared according to the general procedure as described above.
The diastereomeric ratio was determined to be 10:1.
The crude mixture was purified by column chromatography (0 to 40% EtOAc in hexanes) to give the title compound as a white solid (27.0 mg, 0.101 mmol, >99%).
The **enantiomeric excess** was determined by SFC analysis to be 95% with t_R = 3.41 min (major) and t_R = 3.24 min (minor) [OD-H, 3.0% MeOH, 2.5 mL/min, 220 nm, 40 °C].
[α]$_D^{25}$ = –66.3° (c 0.35, CH_2Cl_2).
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (d, *J* = 1.5 Hz, 1H), 8.63 – 8.55 (m, 1H), 8.49 (d, *J* = 2.5 Hz, 1H), 7.38 – 7.30 (m, 4H), 7.25 – 7.21 (m, 1H), 5.86 – 5.61 (m, 1H), 4.92 – 4.73 (m, 2H), 4.37 – 4.20 (m, 2H), 3.44 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 171.0, 152.8, 145.5, 144.4, 143.7, 141.0, 138.0, 128.8, 128.0, 127.2, 117.4, 57.1, 52.3.
HRMS (ESI): *m*/*z* for $C_{16}H_{17}N_2O_2$ $[M+H]^+$ calcd.: 269.1285, found: 269.1285.

ethyl (2*R*,3*S*)-2-(3-chloropyrazin-2-yl)-3-phenylpent-4-enoate (3na)



Prepared according to the general procedure as described above.
The diastereomeric ratio was determined to be 16:1.
The crude mixture was purified by column chromatography (0 to 20% EtOAc in hexanes) to give the title compound as a colorless gel (30.5 mg, 0.0963 mmol, 96%).
The **enantiomeric excess** was determined by SFC analysis to be >99% with t_R = 2.70 min (major) and t_R = 2.60 min (minor) [OJ-H, 3.0% MeOH, 2.5 mL/min, 220 nm, 40 °C].

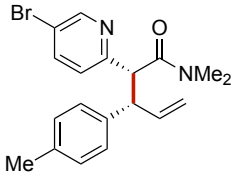
$[\alpha]_D^{25}$ = –46.9° (c 0.35, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (d, *J* = 2.4 Hz, 1H), 8.33 (d, *J* = 2.4 Hz, 1H), 7.46 – 7.35 (m, 4H), 7.33 – 7.25 (m, 1H), 5.98 – 5.78 (m, 1H), 4.95 – 4.79 (m, 3H), 4.47 (dd, *J* = 11.3, 8.6 Hz, 1H), 3.94 (qd, *J* = 7.1, 2.0 Hz, 2H), 0.97 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 169.5, 151.9, 149.8, 142.7, 142.4, 141.1, 138.0, 128.7, 128.3, 127.2, 116.9, 61.3, 53.9, 51.9, 13.9.

HRMS (ESI): *m*/*z* for $C_{17}H_{18}ClN_2O_2$ $[M+H]^+$ calcd.: 317.1051, found: 317.1051.

(2*R*,3*S*)-2-(5-bromopyridin-2-yl)-*N*,*N*-dimethyl-3-(*p*-tolyl)pent-4-enamide (3ab)



Prepared according to the general procedure as described above.

The diastereomeric ratio was determined to be >20:1.

The crude mixture was purified by column chromatography (0 to 40% EtOAc in hexanes) to give the title compound as a white solid (isolated as a single diastereomer, 34.9 mg, 0.0935 mmol, 94%).

The **enantiomeric excess** was determined by SFC analysis to be >99% with t_R = 2.32 min (major) and t_R = 2.00 min (minor) [OD-H, 10.0% MeOH, 2.5 mL/min, 220 nm, 40 °C].

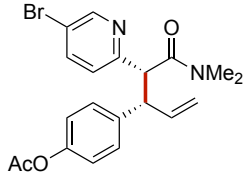
$[\alpha]_D^{25}$ = –107.5° (c 0.52, CH_2Cl_2).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.55 (d, *J* = 2.4 Hz, 1H), 7.79 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.58 (d, *J* = 8.5 Hz, 1H), 7.20 (d, *J* = 8.2 Hz, 2H), 7.11 (d, *J* = 7.8 Hz, 2H), 5.76 (ddd, *J* = 17.4, 9.8, 8.7 Hz, 1H), 4.88 – 4.76 (m, 2H), 4.56 (d, *J* = 11.3 Hz, 1H), 4.18 (dd, *J* = 11.3, 8.7 Hz, 1H), 2.92 (s, 3H), 2.69 (s, 3H), 2.31 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 170.8, 157.3, 149.8, 139.5, 139.1, 138.9, 136.3, 129.4, 127.8, 124.6, 119.5, 116.6, 55.8, 53.2, 37.5, 35.9, 21.2.

HRMS (ESI): *m*/*z* for $C_{19}H_{22}BrN_2O$ $[M+H]^+$ calcd.: 373.0910, found: 373.0916.

4-((3*S*,4*R*)-4-(5-bromopyridin-2-yl)-5-(dimethylamino)-5-oxopent-1-en-3-yl)phenyl acetate (3ac)



Prepared according to the general procedure as described above.

The diastereomeric ratio was determined to be >20:1.

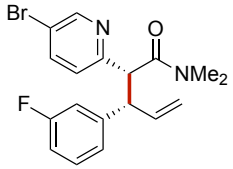
The crude mixture was purified by column chromatography (0 to 55% EtOAc in hexanes) to give the title compound as a white solid (isolated as a single diastereomer, 38.5 mg, 0.0923 mmol, 92%).

The **enantiomeric excess** was determined by SFC analysis to be >99% with t_R = 2.47 min (major) and t_R = 1.76 min (minor) [OD-H, 10.0% MeOH, 2.5 mL/min, 220 nm, 40 °C].

$[\alpha]_D^{25}$ = –103.1° (c 0.59, CH_2Cl_2).

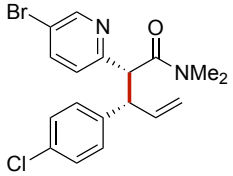
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.55 (d, *J* = 2.3 Hz, 1H), 7.79 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.56 (d, *J* = 8.5 Hz, 1H), 7.32 (d, *J* = 8.5 Hz, 2H), 7.03 (d, *J* = 8.6 Hz, 2H), 5.76 (ddd, *J* = 16.8, 10.4, 8.6 Hz, 1H), 4.86 – 4.76 (m, 2H), 4.52 (d, *J* = 11.3 Hz, 1H), 4.23 (dd, *J* = 11.2, 8.6 Hz, 1H), 2.89 (s, 3H), 2.68 (s, 3H), 2.28 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 170.6, 169.5, 157.0, 149.8, 149.5, 139.7, 139.6, 138.2, 129.0, 124.6, 121.6, 119.5, 117.2, 56.0, 52.8, 37.5, 35.9, 21.3.
HRMS (ESI): *m*/*z* for $C_{20}H_{22}BrN_2O_3$ $[M+H]^+$ calcd.: 417.0808, found: 417.0805.

(2*R*,3*S*)-2-(5-bromopyridin-2-yl)-3-(3-fluorophenyl)-*N*,*N*-dimethylpent-4-enamide (3ad)



Prepared according to the general procedure as described above.
The diastereomeric ratio was determined to be >20:1.
The crude mixture was purified by column chromatography (0 to 40% EtOAc in hexanes) to give the title compound as a white solid (isolated as a single diastereomer, 34.2 mg, 0.0906 mmol, 91%).
The **enantiomeric excess** was determined by SFC analysis to be >99% with t_R = 2.05 min (major) and t_R = 1.89 min (minor) [OD-H, 10.0% MeOH, 2.5 mL/min, 220 nm, 40 °C].
$[\alpha]_D^{25}$ = –106.7° (c 0.49, CH_2Cl_2).
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.56 (d, *J* = 2.4 Hz, 1H), 7.80 (dd, *J* = 8.4, 2.3 Hz, 1H), 7.54 (d, *J* = 8.4 Hz, 1H), 7.30 – 7.22 (m, 1H), 7.10 (dt, *J* = 7.8, 1.2 Hz, 1H), 7.02 (dt, *J* = 10.0, 2.1 Hz, 1H), 6.95 – 6.87 (m, 1H), 5.73 (ddd, *J* = 16.9, 10.2, 8.6 Hz, 1H), 4.91 – 4.74 (m, 2H), 4.54 (d, *J* = 11.3 Hz, 1H), 4.23 (dd, *J* = 11.3, 8.7 Hz, 1H), 2.95 (s, 3H), 2.71 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 170.5, 163.0 (d, *J* = 245.6 Hz), 156.8, 150.0, 144.9 (d, *J* = 7.0 Hz), 139.6, 138.0, 130.1 (d, *J* = 8.1 Hz), 124.5, 123.7 (d, *J* = 2.8 Hz), 119.6, 117.4, 114.8 (d, *J* = 21.6 Hz), 113.8 (d, *J* = 21.3 Hz), 55.7, 53.1, 37.5, 36.0.
^{19}F NMR (376 MHz, $CDCl_3$) δ -112.8 – -113.1 (m).
HRMS (ESI): *m*/*z* for $C_{18}H_{19}BrFN_2O$ $[M+H]^+$ calcd.: 377.0659, found: 377.0665.

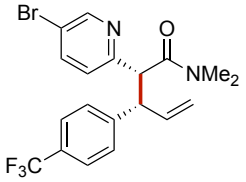
(2*R*,3*S*)-2-(5-bromopyridin-2-yl)-3-(4-chlorophenyl)-*N*,*N*-dimethylpent-4-enamide (3ae)



Prepared according to the general procedure as described above.
The diastereomeric ratio was determined to be >20:1.
The crude mixture was purified by column chromatography (0 to 40% EtOAc in hexanes) to give the title compound as a white solid (isolated as a single diastereomer, 35.9 mg, 0.0912 mmol, 91%).
The **enantiomeric excess** was determined by SFC analysis to be >99% with t_R = 4.18 min (major) and t_R = 3.88 min (minor) [OD-H, 5.0% MeOH, 2.5 mL/min, 220 nm, 40 °C].
$[\alpha]_D^{25}$ = –114.8° (c 0.50, CH_2Cl_2).

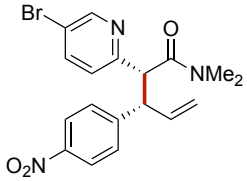
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.42 (d, *J* = 2.3 Hz, 1H), 7.65 (dd, *J* = 8.4, 2.3 Hz, 1H), 7.39 (d, *J* = 8.4 Hz, 1H), 7.14 – 7.04 (m, 4H), 5.68 – 5.51 (m, 1H), 4.74 – 4.55 (m, 2H), 4.37 (d, *J* = 11.4 Hz, 1H), 4.07 (dd, *J* = 11.3, 8.6 Hz, 1H), 2.79 (s, 3H), 2.56 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 170.4, 156.8, 149.9, 140.8, 139.7, 138.2, 132.6, 129.4, 128.8, 124.4, 119.6, 117.3, 55.9, 52.8, 37.5, 36.0.
HRMS (ESI): *m*/*z* for $C_{18}H_{19}BrClN_2O$ $[M+H]^+$ calcd.: 393.0364, found: 393.0365.

(2*R*,3*S*)-2-(5-bromopyridin-2-yl)-*N*,*N*-dimethyl-3-(4-(trifluoromethyl)phenyl)pent-4-enamide (3af)



Prepared according to the general procedure as described above.
The diastereomeric ratio was determined to be >20:1.
The crude mixture was purified by column chromatography (0 to 40% EtOAc in hexanes) to give the title compound as a white solid (isolated as a single diastereomer, 38.8 mg, 0.0908 mmol, 91%).
The **enantiomeric excess** was determined by SFC analysis to be >99% with t_R = 5.83 min (major) and t_R = 5.16 min (minor) [OD-H, 2.0% MeOH, 2.5 mL/min, 220 nm, 40 °C].
$[\alpha]_D^{25}$ = –103.6° (c 0.55, CH_2Cl_2).
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.58 (d, *J* = 2.3 Hz, 1H), 7.81 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.57 (d, *J* = 8.0 Hz, 2H), 7.53 (d, *J* = 8.4 Hz, 1H), 7.44 (d, *J* = 8.0 Hz, 2H), 5.74 (ddd, *J* = 17.2, 10.2, 8.6 Hz, 1H), 4.88 – 4.77 (m, 2H), 4.56 (d, *J* = 11.3 Hz, 1H), 4.31 (dd, *J* = 11.2, 8.7 Hz, 1H), 2.95 (s, 3H), 2.70 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 170.2, 156.6, 150.1, 146.5, 139.7, 137.9, 129.1 (d, *J* = 32.5 Hz), 128.4, 125.7 (q, *J* = 3.8 Hz), 124.3, 124.3 (q, *J* = 271.8 Hz), 119.7, 117.6, 55.8, 53.3, 37.5, 36.0.
^{19}F NMR (376 MHz, $CDCl_3$) δ -62.5 (s).
HRMS (ESI): *m*/*z* for $C_{19}H_{19}BrF_3N_2O$ $[M+H]^+$ calcd.: 427.0627, found: 427.0632.

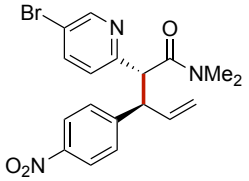
(2*R*,3*S*)-2-(5-bromopyridin-2-yl)-*N*,*N*-dimethyl-3-(4-nitrophenyl)pent-4-enamide (3ag)



Prepared according to the general procedure as described above.
The diastereomeric ratio was determined to be >20:1.
The crude mixture was purified by column chromatography (0 to 40% EtOAc in hexanes) to give the title compound as a white solid (isolated as a single diastereomer, 37.2 mg, 0.0920 mmol, 92%).
The **enantiomeric excess** was determined by SFC analysis to be >99% with t_R = 3.24 min (major) and t_R = 2.82 min (minor) [OJ-H, 5.0% MeOH, 2.5 mL/min, 220 nm, 40 °C].
$[\alpha]_D^{25}$ = –168.0° (c 0.49, CH_2Cl_2).

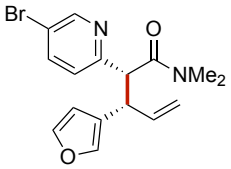
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.59 (dd, *J* = 2.3, 0.7 Hz, 1H), 8.21 – 8.13 (m, 2H), 7.81 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.58 – 7.45 (m, 3H), 5.83 – 5.65 (m, 1H), 4.88 (dt, *J* = 10.2, 0.9 Hz, 1H), 4.82 (dt, *J* = 16.9, 1.1 Hz, 1H), 4.55 (d, *J* = 11.3 Hz, 1H), 4.36 (dd, *J* = 11.3, 8.6 Hz, 1H), 2.96 (s, 3H), 2.70 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 169.9, 156.2, 150.2, 146.9, 139.8, 137.2, 128.9, 124.2, 124.0, 119.8, 118.2, 55.9, 53.2, 37.5, 36.0.
HRMS (ESI): *m*/*z* for $C_{18}H_{19}BrN_3O_3$ $[M+H]^+$ calcd.: 404.0604, found: 404.0605.

(2*R*,3*R*)-2-(5-bromopyridin-2-yl)-*N*,*N*-dimethyl-3-(4-nitrophenyl)pent-4-enamide (4ag)



Prepared according to the general procedure as described above (*ent*-**[Ir]** was used instead of **[Ir]**).
The diastereomeric ratio was determined to be >20:1.
The crude mixture was purified by column chromatography (0 to 60% EtOAc in hexanes) to give the title compound as a colorless gel (isolated as a single diastereomer, 36.5 mg, 0.0903 mmol, 90%).
The **enantiomeric excess** was determined by SFC analysis to be >99% with t_R = 3.78 min (major) and t_R = 3.25 min (minor) [OD-H, 10.0% MeOH, 2.5 mL/min, 220 nm, 40 °C].
$[\alpha]_D^{25}$ = –103.6° (c 0.30, CH_2Cl_2).
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.40 – 8.27 (m, 1H), 8.06 – 7.92 (m, 2H), 7.62 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.33 (dd, *J* = 8.4, 0.8 Hz, 1H), 7.28 – 7.19 (m, 2H), 6.13 – 5.98 (m, 1H), 5.15 (dt, *J* = 10.4, 1.1 Hz, 1H), 5.06 (dt, *J* = 17.2, 1.2 Hz, 1H), 4.57 (d, *J* = 11.1 Hz, 1H), 4.48 (dd, *J* = 11.0, 6.9 Hz, 1H), 3.16 (s, 3H), 2.96 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 170.3, 155.7, 150.1, 148.2, 146.7, 139.5, 138.4, 129.8, 124.1, 123.6, 119.5, 117.3, 54.8, 52.4, 37.7, 36.3.
HRMS (ESI): *m*/*z* for $C_{18}H_{19}BrN_3O_3$ $[M+H]^+$ calcd.: 404.0604, found: 404.0605.

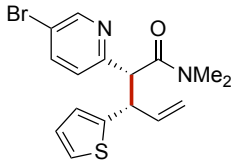
(2*R*,3*S*)-2-(5-bromopyridin-2-yl)-3-(furan-3-yl)-*N*,*N*-dimethylpent-4-enamide (3ah)



Prepared according to the general procedure as described above.
The diastereomeric ratio was determined to be >20:1.
The crude mixture was purified by column chromatography (0 to 40% EtOAc in hexanes) to give the title compound as a colorless gel (isolated as a single diastereomer, 28.9 mg, 0.0828 mmol, 83%).
The **enantiomeric excess** was determined by SFC analysis to be >99% with t_R = 2.87 min (major) and t_R = 2.40 min (minor) [OD-H, 5.0% MeOH, 2.5 mL/min, 220 nm, 40 °C].
$[\alpha]_D^{25}$ = –87.5° (c 0.44, CH_2Cl_2).

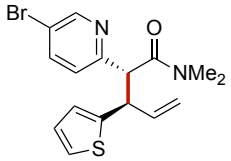
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.54 (d, *J* = 2.4 Hz, 1H), 7.77 (dd, *J* = 8.5, 2.3 Hz, 1H), 7.50 (d, *J* = 8.5 Hz, 1H), 7.35 (t, *J* = 1.7 Hz, 1H), 7.31 – 7.28 (m, 1H), 6.36 – 6.32 (m, 1H), 5.67 (ddd, *J* = 17.0, 10.2, 8.6 Hz, 1H), 4.95 – 4.79 (m, 2H), 4.35 (d, *J* = 11.1 Hz, 1H), 4.20 (dd, *J* = 11.1, 8.6 Hz, 1H), 3.00 (s, 3H), 2.82 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 171.0, 156.8, 149.9, 143.0, 139.5, 139.5, 137.6, 125.9, 124.4, 119.5, 117.1, 109.9, 55.9, 44.0, 37.6, 36.1.
HRMS (ESI): *m*/*z* for $C_{16}H_{18}BrN_2O_2$ $[M+H]^+$ calcd.: 349.0546, found: 349.0545.

(2*R*,3*S*)-2-(5-bromopyridin-2-yl)-*N*,*N*-dimethyl-3-(thiophen-2-yl)pent-4-enamide (3ai)



Prepared according to the general procedure as described above.
The diastereomeric ratio was determined to be >20:1.
The crude mixture was purified by column chromatography (0 to 40% EtOAc in hexanes) to give the title compound as a colorless gel (isolated as a single diastereomer, 30.8 mg, 0.0843 mmol, 84%).
The **enantiomeric excess** was determined by SFC analysis to be >99% with t_R = 4.49 min (major) and t_R = 3.41 min (minor) [OD-H, 5.0% MeOH, 2.5 mL/min, 220 nm, 40 °C].
$[\alpha]_D^{25}$ = –123.1° (c 0.41, CH_2Cl_2).
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.55 (d, *J* = 2.3 Hz, 1H), 7.78 (dd, *J* = 8.5, 2.4 Hz, 1H), 7.52 (d, *J* = 8.4 Hz, 1H), 7.16 (dd, *J* = 4.7, 1.6 Hz, 1H), 6.93 – 6.88 (m, 2H), 5.74 (ddd, *J* = 16.9, 10.1, 8.5 Hz, 1H), 4.94 – 4.79 (m, 2H), 4.58 (dd, *J* = 11.1, 8.5 Hz, 1H), 4.51 (d, *J* = 11.2 Hz, 1H), 3.00 (s, 3H), 2.79 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 170.6, 156.6, 150.0, 145.4, 140.0, 138.2, 126.9, 124.7, 124.4, 123.9, 119.6, 117.2, 56.9, 48.5, 37.6, 36.1.
HRMS (ESI): *m*/*z* for $C_{16}H_{18}BrN_2OS$ $[M+H]^+$ calcd.: 365.0318, found: 365.0318.

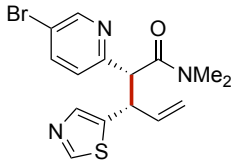
(2*R*,3*R*)-2-(5-bromopyridin-2-yl)-*N*,*N*-dimethyl-3-(thiophen-2-yl)pent-4-enamide (4ai)



Prepared according to the general procedure as described above (*ent*-**[Ir]** was used instead of **[Ir]**).
The diastereomeric ratio was determined to be >20:1.
The crude mixture was purified by column chromatography (0 to 50% EtOAc in hexanes) to give the title compound as a slightly yellow solid (isolated as a single diastereomer, 34.6 mg, 0.0947 mmol, 95%).
The **enantiomeric excess** was determined by SFC analysis to be >99% with t_R = 4.68 min (major) and t_R = 3.46 min (minor) [OD-H, 5.0% MeOH, 2.5 mL/min, 220 nm, 40 °C].
$[\alpha]_D^{25}$ = –56.1° (c 0.41, CH_2Cl_2).

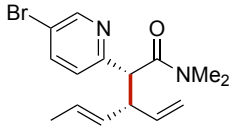
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.41 (d, *J* = 2.4 Hz, 1H), 7.66 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.38 (d, *J* = 8.5 Hz, 1H), 7.02 (dd, *J* = 5.1, 1.1 Hz, 1H), 6.75 (dd, *J* = 5.1, 3.5 Hz, 1H), 6.62 (dd, *J* = 3.5, 1.1 Hz, 1H), 6.09 (ddd, *J* = 17.3, 10.3, 7.2 Hz, 1H), 5.18 – 5.07 (m, 2H), 4.60 (dd, *J* = 10.8, 7.1 Hz, 1H), 4.49 (d, *J* = 10.7 Hz, 1H), 3.14 (s, 3H), 2.93 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 170.6, 156.4, 149.9, 143.8, 139.2, 139.2, 126.6, 125.5, 124.3, 124.2, 119.3, 116.4, 56.4, 47.7, 37.7, 36.2.
HRMS (ESI): *m*/*z* for $C_{16}H_{18}BrN_2OS$ $[M+H]^+$ calcd.: 365.0318, found: 365.0319.

(2*R*,3*S*)-2-(5-bromopyridin-2-yl)-*N*,*N*-dimethyl-3-(thiazol-5-yl)pent-4-enamide (3aj)



Prepared according to the general procedure as described above.
The diastereomeric ratio was determined to be >20:1.
The crude mixture was purified by column chromatography (30 to 100% EtOAc in hexanes) to give the title compound as a colorless gel (isolated as a single diastereomer, 27.7 mg, 0.0756 mmol, 76%).
The **enantiomeric excess** was determined by SFC analysis to be >99% with t_R = 1.42 min (major) and t_R = 1.24 min (minor) [OD-H, 20.0% MeOH, 2.5 mL/min, 220 nm, 40 °C].
$[\alpha]_D^{25}$ = –98.1° (c 0.40, CH_2Cl_2).
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.69 (s, 1H), 8.57 (d, *J* = 2.3 Hz, 1H), 7.79 (dd, *J* = 8.5, 2.4 Hz, 1H), 7.71 (s, 1H), 7.46 (dd, *J* = 8.5, 0.7 Hz, 1H), 5.73 (ddd, *J* = 17.2, 9.9, 8.7 Hz, 1H), 4.98 – 4.81 (m, 2H), 4.64 (dd, *J* = 10.9, 8.8 Hz, 1H), 4.46 (d, *J* = 11.0 Hz, 1H), 3.01 (s, 3H), 2.82 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 170.1, 156.0, 152.3, 150.2, 140.7, 139.8, 137.3, 124.1, 119.8, 118.2, 57.0, 45.7, 37.5, 36.1.
HRMS (ESI): *m*/*z* for $C_{15}H_{17}BrN_3OS$ $[M+H]^+$ calcd.: 366.0270, found: 366.0263.

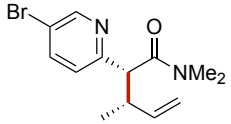
(2*R*,3*R*,*E*)-2-(5-bromopyridin-2-yl)-*N*,*N*-dimethyl-3-vinylhex-4-enamide (3ak)



Prepared according to the general procedure as described above.
The diastereomeric ratio was determined to be >20:1.
The crude mixture was purified by column chromatography (0 to 40% EtOAc in hexanes) to give the title compound as a white solid (28.4 mg, 0.0879 mmol, 88%).
The **enantiomeric excess** was determined by SFC analysis to be 97% with t_R = 1.84 min (major) and t_R = 1.65 min (minor) [OD-H, 5.0% MeOH, 2.5 mL/min, 220 nm, 40 °C].
$[\alpha]_D^{25}$ = –60.0° (c 0.37, CH_2Cl_2).
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.51 (d, *J* = 2.4 Hz, 1H), 7.73 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.42 (d, *J* = 8.5 Hz, 1H), 5.62 – 5.38 (m, 3H), 4.86 – 4.78 (m, 2H), 4.12 (d, *J* = 10.4 Hz, 1H), 3.65 – 3.55 (m, 1H), 3.09 (s, 3H), 2.91 (s, 3H), 1.65 (d, *J* = 5.6 Hz, 3H).

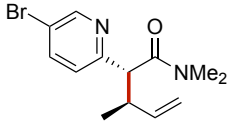
^{13}C NMR (151 MHz, $CDCl_3$) δ 171.2, 157.2, 149.8, 139.3, 138.2, 130.9, 127.2, 124.6, 119.3, 116.5, 55.1, 50.3, 37.7, 36.1, 18.3.
HRMS (ESI): *m*/*z* for $C_{15}H_{20}BrN_2O$ $[M+H]^+$ calcd.: 323.0754, found: 323.0753.

(2*R*,3*S*)-2-(5-bromopyridin-2-yl)-*N*,*N*,3-trimethylpent-4-enamide (3al)



Prepared according to the general procedure as described above.
The diastereomeric ratio was determined to be 9:1.
The crude mixture was purified by column chromatography (0 to 40% EtOAc in hexanes) to give the title compound as a white solid (27.4 mg, 0.0922 mmol, 92%).
The **enantiomeric excess** was determined by SFC analysis to be 98% with t_R = 1.82 min (major) and t_R = 1.63 min (minor) [OD-H, 5.0% MeOH, 2.5 mL/min, 220 nm, 40 °C].
$[\alpha]_D^{25}$ = –63.5° (c 0.11, CH_2Cl_2).
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.51 (d, *J* = 2.5 Hz, 1H), 7.74 (dd, *J* = 8.5, 2.4 Hz, 1H), 7.41 (dd, *J* = 8.4, 0.7 Hz, 1H), 5.49 (ddd, *J* = 17.0, 10.3, 8.3 Hz, 1H), 4.97 – 4.66 (m, 2H), 3.93 (d, *J* = 10.6 Hz, 1H), 3.11 (s, 3H), 3.09 – 3.03 (m, 1H), 2.94 (s, 3H), 1.11 (d, *J* = 6.5 Hz, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 171.6, 157.7, 149.8, 140.8, 139.4, 124.3, 119.2, 115.3, 56.7, 42.0, 37.8, 36.1, 19.5.
HRMS (ESI): *m*/*z* for $C_{13}H_{18}BrN_2O$ $[M+H]^+$ calcd.: 297.0597, found: 297.0596.

(2*R*,3*R*)-2-(5-bromopyridin-2-yl)-*N*,*N*,3-trimethylpent-4-enamide (4al)



Prepared according to the general procedure as described above (*ent*-**[Ir]** was used instead of **[Ir]**).
The diastereomeric ratio was determined to be 6:1.
The crude mixture was purified by column chromatography (0 to 50% EtOAc in hexanes) to give the title compound as a white solid (27.9 mg, 0.0939 mmol, 94%).
The **enantiomeric excess** was determined by SFC analysis to be >99% with t_R = 1.98 min (major) and t_R = 1.78 min (minor) [OD-H, 5.0% MeOH, 2.5 mL/min, 220 nm, 40 °C].
$[\alpha]_D^{25}$ = –30.6° (c 0.13, CH_2Cl_2).
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.55 (d, *J* = 2.3 Hz, 1H), 7.78 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.49 (dd, *J* = 8.5, 0.7 Hz, 1H), 5.86 (ddd, *J* = 17.3, 10.4, 7.1 Hz, 1H), 5.10 (dt, *J* = 17.3, 1.4 Hz, 1H), 5.01 (dt, *J* = 10.4, 1.2 Hz, 1H), 3.92 (d, *J* = 10.4 Hz, 1H), 3.12 – 3.00 (m, 4H), 2.91 (s, 3H), 0.80 (d, *J* = 6.9 Hz, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 171.6, 157.6, 149.9, 141.6, 139.6, 124.0, 119.4, 114.7, 56.7, 40.9, 37.7, 36.0, 17.4.
HRMS (ESI): *m*/*z* for $C_{13}H_{18}BrN_2O$ $[M+H]^+$ calcd.: 297.0597, found: 297.0598.

5.4.6 Determination of Absolute Configuration

The structure and absolute configuration of allylation product **3ca** and its diastereomer **4ca** were determined by X-ray diffraction analysis. Single crystals suitable for X-ray diffraction were obtained by slow vapor diffusion of pentane into saturated solutions of **3ca** and **4ca** in diethyl ether.

The absolute configurations of all other products shown in this paper were assigned by analogy.

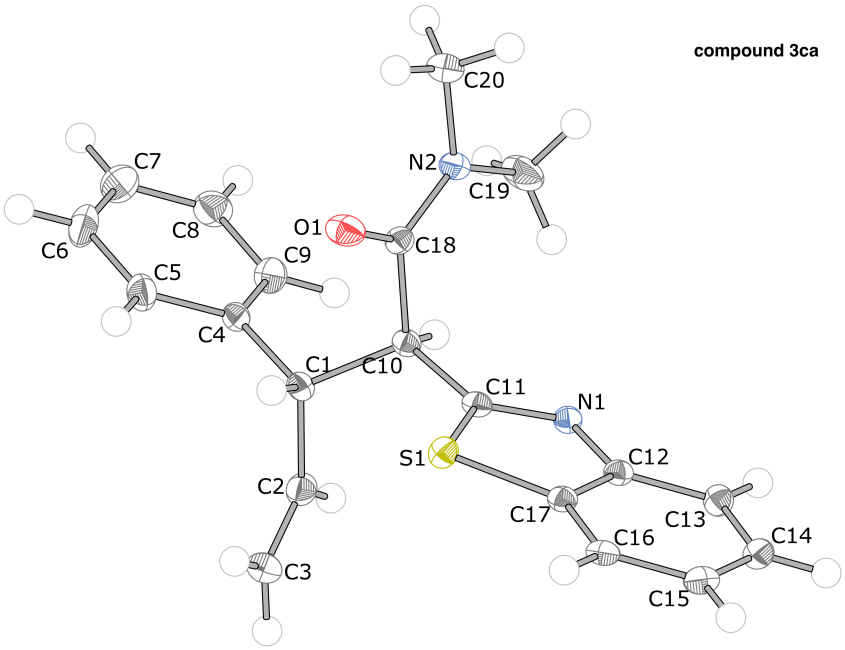
5.4.7 X-Ray Diffraction Analysis of 3ca

A colorless rod 0.20 x 0.10 x 0.10 mm in size was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using and scans. Crystal-to-detector distance was 40 mm and exposure time was 50 seconds per frame using a scan width of 2.0°, fast scan was added and used to replace overloaded reflections. Data collection was 99.1% complete to 26.73° in θ. A total of 11627 reflections were collected covering the indices, $-15 \leq h \leq 14$, $-7 \leq k \leq 7$, $-16 \leq l \leq 15$. 3624 reflections were found to be symmetry independent, with an Rint of 0.0552. Indexing and unit cell refinement indicated a primitive, monoclinic lattice. The space group was found to be $P2_1$ (No. 4). The data were integrated using the Bruker SAINT software program and scaled using the SADABS software program. Solution by iterative methods (SHELXT-2016) produced a complete heavy-atom phasing model consistent with the proposed structure. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2016). All hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2016. Absolute stereochemistry was unambiguously determined to all chiral centers.

Table 5.5 Crystal data and structure refinement for **3ca**

Identification code	**3ca**
Empirical formula	$C_{20}H_{20}N_2OS$
Formula weight	336.44
Temperature/K	100(2)
Crystal system	monoclinic
Space group	$P2_1$
a/Å	11.935(2)
b/Å	5.9402(10)
c/Å	12.713(2)
α/°	90
β/°	105.332(7)
γ/°	90
Volume/Å^3	869.2(3)
Z	2
ρ_{calc} g/cm^3	1.285
μ/mm^{-1}	0.195
F(000)	356.0
Crystal size/mm^3	0.2 × 0.1 × 0.1

Radiation	MoKα (λ = 0.71073Å)
2Θ range for data collection/°	5.458 to 53.304
Index ranges	$-15 \leq h \leq 14$, $-7 \leq k \leq 7$, $-16 \leq l \leq 15$
Reflections collected	11627
Independent reflections	3624 [R_{int} = 0.0552, R_{sigma} = 0.0575]
Completeness to theta = 26.73°	99.1%
Absorption correction	Multi-scan
Max. and min. transmission	0.4296 and 0.3131
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	3624/1/220
Goodness-of-fit on F^2	1.069
Final R indexes [I>=2σ (I)]	R_1 = 0.0326, wR_2 = 0.0797
Final R indexes [all data]	R_1 = 0.0375, wR_2 = 0.0815
Largest diff. peak/hole / e $Å^{-3}$	0.29/-0.23
Flack parameter	0.01(4)



Scheme 5.10 Crystal structure of **3ca**

5.4.8 X-Ray Diffraction Analysis of 4ca

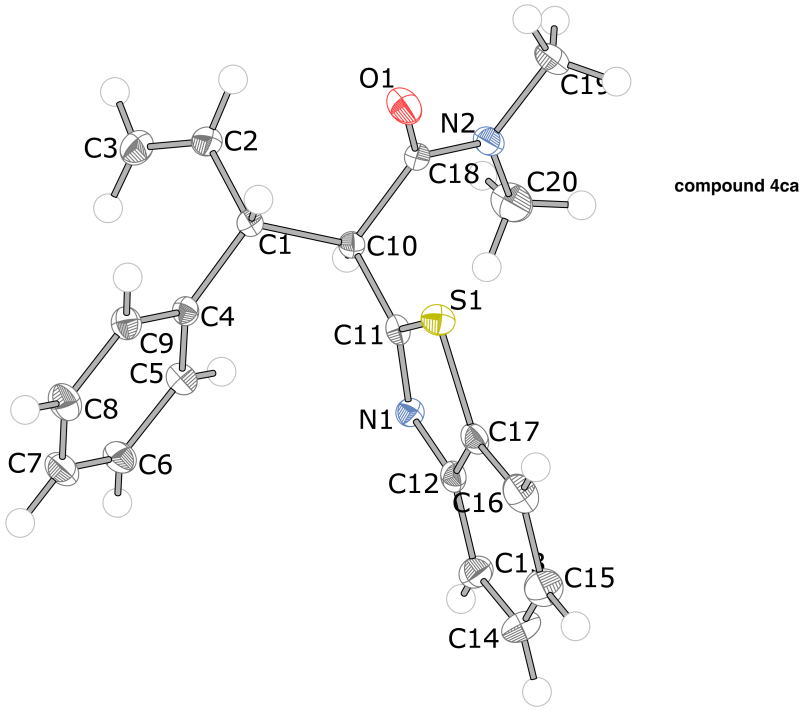
A colorless rod 0.50 x 0.20 x 0.10 mm in size was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using and scans. Crystal-to-detector distance was 50 mm and exposure time was 15 seconds per frame using a scan width of 0.4°, fast scan was added and used to replace overloaded reflections. Data collection was 99.6% complete

to 27.48° in θ. A total of 15255 reflections were collected covering the indices, $-8 \leq h \leq 8$, $-11 \leq k \leq 11$, $-40 \leq l \leq 40$. 3972 reflections were found to be symmetry independent, with an R_{int} of 0.0275. Indexing and unit cell refinement indicated a primitive, monoclinic lattice. The space group was found to be $P2_12_12_1$ (No. 19). The data were integrated using the Bruker SAINT software program and scaled using the SADABS software program. Solution by iterative methods (SHELXT-2016) produced a complete heavy-atom phasing model consistent with the proposed structure. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2016). All hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2016. Absolute stereochemistry was unambiguously determined to all chiral centers.

Table 5.6 Crystal data and structure refinement for **4ca**

Identification code	**4ca**
Empirical formula	$C_{20}H_{20}N_2OS$
Formula weight	336.44
Temperature/K	100(2)
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a/Å	6.3339(5)
b/Å	8.7346(7)
c/Å	31.364(3)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	1735.2(2)
Z	4
ρ_{calc}g/cm^3	1.288
μ/mm^{-1}	0.176
F(000)	712.0
Crystal size/mm^3	0.5 × 0.2 × 0.1
Radiation	MoKα (λ = 0.71073Å)
2Θ range for data collection/°	4.84 to 55.042
Index ranges	$-8 \leq h \leq 8$, $-11 \leq k \leq 11$, $-40 \leq l \leq 40$
Reflections collected	15255
Independent reflections	3972 [R_{int} = 0.0275, R_{sigma} = 0.0246]
Completeness to theta = 27.48°	99.6%
Absorption correction	Multi-scan
Max. and min. transmission	0.4305 and 0.3724
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	3972/0/220
Goodness-of-fit on F^2	1.128

Final R indexes [I>=2σ (I)]	R_1 = 0.0256, wR_2 = 0.0707
Final R indexes [all data]	R_1 = 0.0261, wR_2 = 0.0711
Largest diff. peak/hole / e Å^{-3}	0.29/-0.22
Flack parameter	-0.001(13)



Scheme 5.11 Crystal structure of **4ca**

5.5 References

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CHAPTER 6

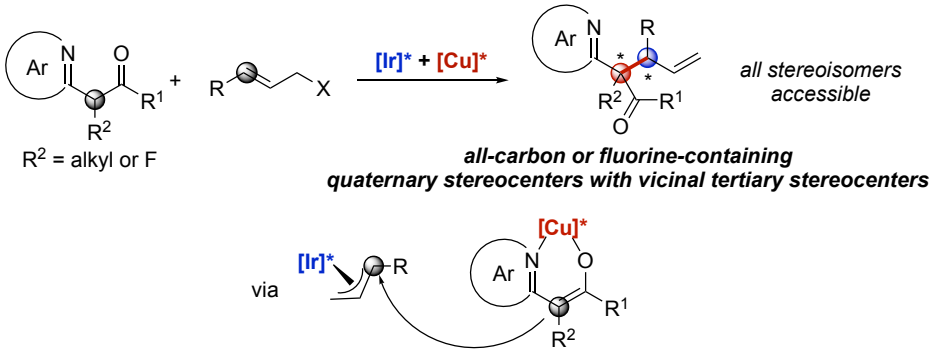
Stereodivergent Construction of Acyclic Vicinal Fully Substituted and Tertiary Stereocenters by Iridium-Catalyzed Enantioselective Allylic Substitutions with Chiral Copper Enolates

6.1 Introduction

Catalytic enantioselective construction of quaternary stereocenters is a long-standing challenge in organic synthesis.[1] The formation of acyclic quaternary stereocenters represents a particularly formidable challenge due to conformational mobility of acyclic structures.[1a] Enantioselective methods to form related fluorine-containing fully substituted stereogenic centers also are undeveloped[2] but in high demand due to the unique properties of enantioenriched tertiary fluorides.[3] Finally, the construction of such stereogenic centers is further complicated if an additional stereocenter is located vicinal to the fully substituted stereocenter in the acyclic structure of the target molecule and control of both relative and absolute configurations of these two vicinal stereocenters is to be achieved.

Enantioselective allylic substitution reactions with prochiral enolates as the nucleophile catalyzed by transition-metal complexes have been reported to enable construction of two vicinal stereogenic centers.[5] However, most reported reactions of this type enantioselectively and diastereoselectively afford just one out of two possible relative configurations.[6] Few methods provide stereodivergent access to all four possible stereoisomers of the products.[7] Recently, Carreira,[8] Jørgensen,[9] Zhang,[10] Hartwig[11] and Wang[12] disclosed dual catalysis strategies comprising a co-catalyst that reacts with pronucleophiles to form chiral enamines[8,9] or enolates[10-12] *in situ* and an iridium-complex that catalyzes allylic substitution to form products with vicinal stereogenic centers with high diastereo- and enantioselectivity. Because the iridium complex and the co-catalyst dictate the configurations of the two stereocenters of the products arising from the electrophile and the nucleophile, respectively, all four stereoisomers of the products are accessible by permutations of the enantiomers of the iridium catalyst and the co-catalyst. Despite the attributes of stereodivergent allylic substitutions by two catalysts, few systems were developed because the two catalytic cycles are required to operate individually yet synergistically in the same reaction mixture without interfering with each other.[8-12]

Furthermore, stereodivergent construction of acyclic vicinal fully substituted and tertiary stereocenters is rare. Only four examples have been reported of the construction of acyclic vicinal quaternary and tertiary stereocenters in a stereodivergent fashion, and the substrate scope has been limited to α-branched aldehydes[8a,13] and amino acid derivatives.[10c,12] Construction of other sets of fully substituted and tertiary vicinal stereogenic centers are rare, and the enantioselective formation of products containing a tertiary fluoride and a vicinal tertiary stereocenter is unknown. In general, fluorinated enolates are seldom employed for enantioselective allylic substitution reactions.[14]



Scheme 6.1 Proposed stereodivergent allylic substitutions by dual catalysis

Chiral molecules bearing nitrogen-containing heteroaromatic rings (azaarenes) are ubiquitous in natural products, pharmaceuticals and agrochemicals. Previously, our group reported the stereodivergent mono-functionalizations of azaaryl acetamides and acetates with two enolizable C–H bonds through allylic substitutions catalyzed synergistically by iridium and copper complexes to form products containing vicinal tertiary stereogenic centers.[11] If systems could be developed by which combinations of two substrates containing just one enolizable C–H bond would react similarly, then products containing vicinal quaternary and tertiary stereocenters would result (Scheme 6.1). In particular, fluorine-containing fully substituted stereocenters would be readily constructed from fluorinated acetamides and acetates. Although this proposed transformation is intuitively straightforward, the reactivity of the substrate with a sp^3-hybridized carbon substituent attached to the reactive carbon would be lower than that of the substrate with a hydrogen atom attached to the reactive carbon due to increased sterics. Furthermore, the presence of a fluorine atom is known to alter reactivity and stereoselectivity of the enolates in asymmetric functionalizations of carbonyl compounds.[15]

Herein, we report the stereodivergent synthesis of dyads containing vicinal fully substituted and tertiary stereocenters by iridium-catalyzed enantioselective allylic substitution reactions with chiral copper enolates formed *in situ* from azaaryl acetates and a Lewis acidic copper co-catalyst. This transformation generates products containing one quaternary or fluorine-containing fully substituted stereocenter and one vicinal tertiary stereocenter with excellent control of both relative and absolute configuration. The iridium complex and the copper complex dictate the configurations of the two stereocenters of the products arising from the electrophile and the nucleophile, respectively. Accordingly, all four possible stereoisomers of the products can be synthesized individually with high diastereo- and enantioselectivity by simple permutations of the two enantiomers of the two catalysts.

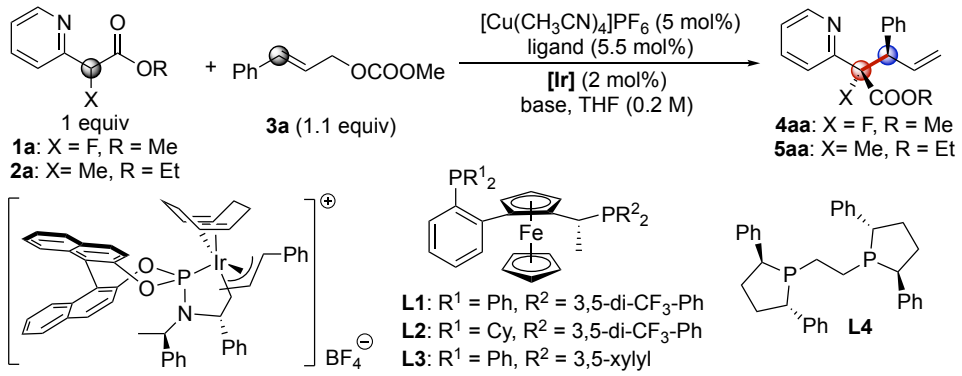
6.2 Results and Discussion

We started our research on the stereodivergent allylic substitutions with azaaryl compounds by examining the reactions between fluorinated ester **1a** (Table 6.1, 1 equiv) and carbonate **3a** (Table 6.1, 1.1 equiv) with 5 mol% of $[Cu(CH_3CN)_4]PF_6$, 5.5 mol% of Walphos ligand **L1**, 2 mol% of metallacyclic iridium catalyst **[Ir]**, and 5 mol% of DBU (the condition developed in our previous study).[11b] The allylation reaction occurred smoothly to give the product **4aa** in 92% yield with >20:1 dr (Table 6.1, entry 1). However, similar reaction between **2a** (Table 6.1) and **3a** afforded the product **5aa** in a modest yield (64%) with good diastereoselectivity (11:1 dr, entry 2). Evaluation of the bases revealed that the reaction conducted with 1 equiv of Cs_2CO_3 gave **5aa** in a slightly higher yield of 70% with higher diastereoselectivity (>20:1 dr, entry 3) compared to the result obtained with DBU as the base in entry 2. Further studies on the chiral bisphosphine ligands bound to copper showed that the reaction conducted with **L4** delivered **5aa** in 93% yield with >20:1 dr and 97% ee (entry 4-6). Fluorinated ester **1a** also reacted with **3a** in the presence of **L4** as the ligand to give **4aa** in >99% isolated yield with >20:1 dr and 99% ee (entry 8).

To assess the stereodivergence of this transformation, we conducted the allylation reaction of **2a** with the enantiomer of **L4** as the ligand for the copper, while keeping the configuration of the iridium complex constant. The diastereomer of **4aa** was obtained instead of **4aa** with excellent diastereo- and enantioselectivity (entry 7, >99% isolated yield, 1:>20 dr, 97% ee). A similar result

was obtained for the allylation of **1a** with the enantiomer of **L4** as the ligand. The diastereomer of **5aa** instead of **5aa** was isolated in >99% yield with 1:>20 dr and >99% ee (entry 9). Future efforts will be focused on studying the stereodivergent allylation reactions with substrates that have different azaaryl functionalities, different alkyl substituents and different carbonyl functionalities.

Table 6.1 Evaluation of reaction conditions for allylation of **1a** and **2a**



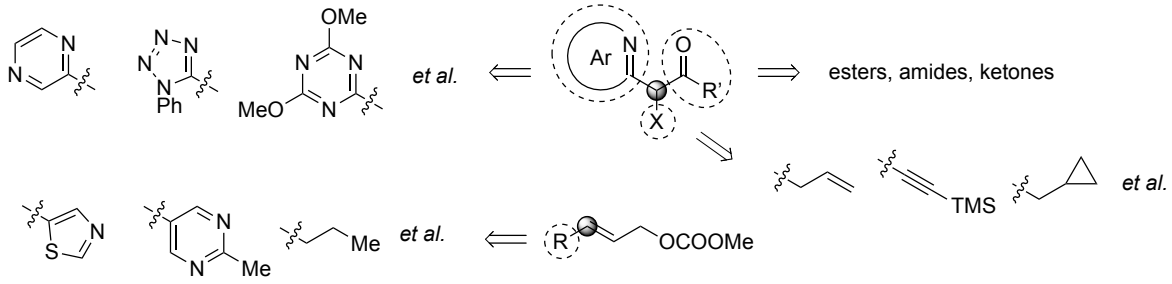
entry	X	base (equiv)	ligand	dr[a]	ee/%[b]	yield/%[c]
1	F	DBU (0.05)	**L1**	>20:1	n.d.	92%
2	Me	DBU (0.05)	**L1**	11:1	n.d.	64%
3	Me	Cs_2CO_3 (1)	**L1**	>20:1	n.d.	70%
4	Me	Cs_2CO_3 (1)	**L2**	n.d.	n.d.	10%
5	Me	Cs_2CO_3 (1)	**L3**	n.d.	n.d.	25%
6	Me	Cs_2CO_3 (1)	**L4**	>20:1	97	93 (93)
7	Me	Cs_2CO_3 (1)	*ent*-**L4**	1:>20	97	97 (>99)
8	F	DBU (0.05)	**L4**	>20:1	99	>99 (>99)
9	F	DBU (0.05)	*ent*-**L4**	1:>20	>99	99 (>99)

[a]Determined by ^{1}H NMR analysis of the crude reaction mixtures. [b]Determined by chiral SFC analysis of the major isomer. [c]Combined yield of two diastereomers of the product. Determined by ^{1}H NMR analysis with mesitylene as an internal standard. The yield within parentheses is the isolated yield of the product as a mixture of two diastereomers.

6.3 Conclusions

In summary, as a proof of concept, we have realized the stereodivergent construction of acyclic vicinal fully substituted and tertiary stereocenters by iridium-catalyzed allylic substitution reactions with chiral copper enolates formed *in situ* from azaaryl acetates and a Lewis acidic copper co-catalyst. This transformation generates products containing quaternary or fluorine-containing fully substituted stereocenters with vicinal tertiary stereocenters with excellent control of both relative and absolute configuration.

With the optimal reaction conditions in hand, various azaaryl compounds and allylic electrophiles having the generic structure shown in Scheme 6.2 will be tested under the allylation condition to assess the scope and limitations of this transformation. Furthermore, computational and experimental studies to understand the origin of the stereoselectivity of the chiral copper enolate in the allylation reaction will be conducted.



Scheme 6.2 Substrates going to be evaluated for the stereodivergent allylation

6.4 Experimental

6.4.1 General Experimental Details

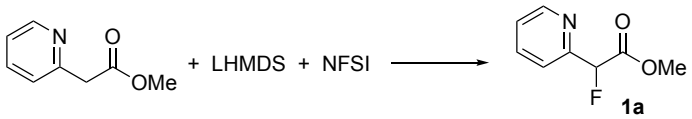
Air-sensitive manipulations were conducted under inert atmosphere in a nitrogen-filled glovebox or by standard Schlenk techniques. Tetrahydrofuran (THF) was purified by passing it through a column composed of activated A-1 alumina and degassing by freeze-pump-thaw method. $[Ir(cod)Cl]_2$ was obtained from Johnson-Matthey and used without further purification.

Chiral supercritical fluid chromatography (SFC) analysis was conducted on a JASCO SF-2000 integrated analytical SFC system. Proton nuclear magnetic resonance (^{1}H NMR) spectra were acquired on commercial instruments (300, 400, 500 and 600 MHz) at the NMR facility of University of California, Berkeley. Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were acquired at 100, 126 and 151 MHz. Fluorine-19 nuclear magnetic resonance (^{19}F NMR) spectra were acquired at 376 MHz. The proton signal for the residual non-deuterated solvent (δ 7.26 for $CDCl_3$, δ 7.16 for C_6D_6) was used as an internal reference for ^{1}H NMR spectra. For ^{13}C NMR spectra, chemical shifts are reported relative to the δ 77.16 resonance of $CDCl_3$ and relative to the δ 128.06 resonance of C_6D_6. For ^{19}F NMR spectra, chemical shifts are reported relative to the δ -113.15 resonance of PhF as an external reference. Coupling constants are reported in Hz. Optical rotations were measured on a Perkin Elmer 241 Automatic Polarimeter. The high-resolution mass spectra were obtained on a high-resolution mass spectrometer at the QB3/Chemistry Mass Spectrometry Facility at UC Berkeley and on the Perkin Elmer AxION2 TOF MS operated by the LBNL Catalysis Facility.

Analytical thin layer chromatography (TLC) was performed on Kieselgel 60 F_{254} glass plates pre-coated with a 0.25 mm thickness of silica gel. The TLC plates were visualized with UV light and/or by staining with $KMnO_4$. For the purification of allylation products, column chromatography was generally performed on a Teledyne Isco Combiflash® R_f system with Redi*Sep* Gold™ columns. Silia*Flash*® T60 silica gel (particle size 5-20 μm) was used to fill the cartridge for the Combiflash® system. For the purification of substrates, column chromatography was generally performed using Kieselgel 60 (230-400 mesh) silica gel, typically with a 50-100:1 weight ratio of

silica gel to the crude products.

6.4.2 Synthesis of Substrates

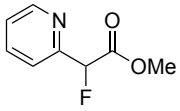


Scheme 6.3 Synthesis of **1a**

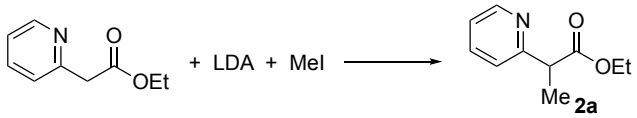
To a solution of LHMDS (10.0 mL, 1 M in THF, 10.0 mmol, 1.00 equiv) in THF (20 mL) at -78 °C was added methyl 2-pyridylacetate (1.35 mL, 1.51 g, 10.0 mmol, 1.00 equiv) in THF (10 mL) dropwise. After being stirred at 0 °C for 40 min, the mixture was cooled to -78 °C. NFSI (3.15 g, 10.0 mmol, 1.00 equiv) in THF (30 mL) was added at -78 °C. Thereafter, the mixture was stirred at 0 °C for 1 h. Saturated aqueous NH_4Cl solution (10 mL), water (40 mL), and EtOAc (30 mL) were added sequentially to the mixture. The organic layer was separated, and the aqueous layer was extracted with EtOAc (40 mL x 2). The organic layers were combined and evaporated under vacuum to be almost dry (around 5 mL left).

The mixture was diluted with Et_2O (40 mL) to afford a cloudy yellow solution, which was then filtered through a short column of silica gels (3 cm height). The column was flashed with Et_2O (20 mL x 2). After removal of solvent under vacuum, the crude mixture was purified by flash column chromatography (0 to 50% EtOAc in hexanes) to give **1a** as a yellow oil (1.05 g, 6.21 mmol, 62%).

methyl 2-fluoro-2-(pyridin-2-yl)acetate (1a)



^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 – 8.57 (m, 1H), 7.85 – 7.74 (m, 1H), 7.59 – 7.50 (m, 1H), 7.38 – 7.30 (m, 1H), 5.92 (d, J = 47.7 Hz, 1H), 3.83 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 168.2 (d, J = 26.1 Hz), 153.8 (d, J = 22.6 Hz), 149.8, 137.4, 124.4, 121.6 (d, J = 4.9 Hz), 90.1 (d, J = 185.9 Hz), 53.0.
^{19}F NMR (376 MHz, $CDCl_3$) δ -184.8 (d, J = 47.8 Hz).
HRMS (ESI): m/z for $C_8H_9FNO_2$ $[M+H]^+$ calcd.: 170.0612, found: 170.0622.



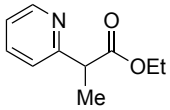
Scheme 6.4 Synthesis of **2a**

To a solution of diisopropylamine (4.20 mL, 30.0 mmol, 3.00 equiv) in THF (10 mL) at 0 °C was added ^{n}BuLi (12.0 mL, 2.5 M in hexanes, 30.0 mmol, 3.00 equiv). The mixture was stirred at 0 °C for 20 min then cooled to -78 °C. Thereafter, ethyl 2-pyridylacetate (1.52 mL, 1.65 g, 10.0 mmol, 1.00 equiv) in THF (5 mL) was added dropwise. After the mixture being stirred at -78 °C

for 30 min, methyl iodide (3.11 mL, 7.10 g, 50.0 mmol, 5.00 equiv) was added, and the mixture was stirred at -78 °C for 15 min then at r.t. for 3 h.

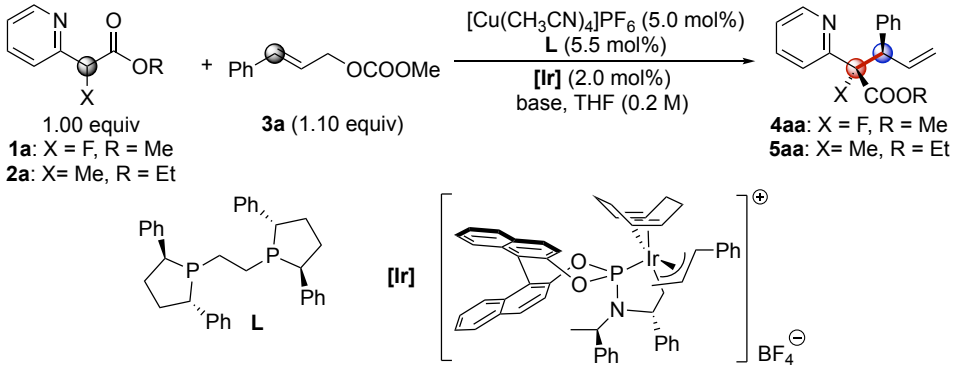
The mixture was quenched by adding H_2O (20 mL) at 0 °C and extracted with EtOAc (30 mL x 2). After removal of solvent under vacuum, the crude mixture was purified by flash column chromatography (0 to 35% EtOAc in hexanes) to give **2a** as a yellow oil (1.39 g, 7.76 mmol, 78%).

ethyl 2-(pyridin-2-yl)propanoate (2a)



^{1}H NMR (500 MHz, $CDCl_3$) δ 8.65 – 8.52 (m, 1H), 7.74 – 7.61 (m, 1H), 7.32 – 7.29 (m, 1H), 7.22 – 7.14 (m, 1H), 4.24 – 4.12 (m, 2H), 3.95 (q, *J* = 7.2 Hz, 1H), 1.57 (d, *J* = 7.2 Hz, 3H), 1.23 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 173.8, 160.2, 149.5, 136.9, 122.2, 122.1, 61.0, 48.1, 17.4, 14.3.
HRMS (ESI): *m/z* for $C_{10}H_{14}NO_2$ $[M+H]^+$ calcd.: 180.1019, found: 180.1017.

6.4.3 Procedure for Allylations of 1a and 2a



Scheme 6.5 General procedure for allylation

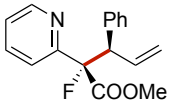
In a nitrogen-filled dry-box, a 1-dram (4 mL) vial equipped with a magnetic stir bar was charged with $[Cu(CH_3CN)_4]PF_6$ (9.3 mg, 0.025 mmol), **L** (13.9 mg, 0.0275 mmol) and THF (1.0 mL). The vial was sealed with a cap containing PTFE/silicone septa. The mixture was stirred at room temperature for 30 min to prepare the copper complex (solution **A**). This solution was used within 10 min.

For **1a**: In a nitrogen-filled dry-box, a 1-dram (4 mL) vial equipped with a magnetic stir bar was charged with **1a** (16.9 mg, 0.100 mmol, 1.00 equiv) and methyl carbonate **3a** (21.1 mg, 0.110 mmol, 1.10 equiv). To the vial was added 0.20 mL of solution **A** (0.0050 mmol, 5.0 mol % of the copper complex). The vial was sealed with a cap containing PTFE/silicone septa. The mixture was stirred at room temperature for 5 min. A stock solution of DBU in THF (0.10 mL, 0.76 mg, 0.0050 mmol, 5.0 mol %) and a stock solution of **[Ir]** in THF (prepared freshly with **[Ir]** in solid state and used within 10 min, 0.20 mL, 2.2 mg, 0.0020 mmol, 2.0 mol %) were then added sequentially to the vial. The vial was then removed from the dry box. The mixture was stirred at room temperature for 12 h.

For **2a**: In a nitrogen-filled dry-box, a 1-dram (4 mL) vial equipped with a magnetic stir bar was charged with **2a** (17.9 mg, 0.100 mmol, 1.00 equiv), methyl carbonate **3a** (0.110 mmol, 1.10 equiv) and cesium carbonate (32.6 mg, 0.100 mmol, 1.00 equiv). To the vial was added 0.20 mL of solution **A** (0.0050 mmol, 5.0 mol % of the copper complex) and 0.10 mL of THF. The vial was sealed with a cap containing PTFE/silicone septa. The mixture was stirred at room temperature for 5 min. A stock solution of **[Ir]** in THF (prepared freshly with **[Ir]** in solid state and used within 10 min, 0.20 mL, 2.2 mg, 0.0020 mmol, 2.0 mol %) was then added to the vial. The vial was then removed from the dry box. The mixture was stirred at room temperature for 12 h.

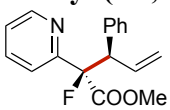
The reaction mixture was diluted with 2 mL of hexanes, and the resulting solution was filtered through a 0.5-inch plug of silica gel (eluting with 1:1 hexanes:EtOAc, 8 mL). After evaporation of the solvent under vacuum, the crude mixture was purified by column chromatography on a Teledyne Isco Combiflash® R_f system with Redi*Sep* Gold™ columns (4-gram silica gel column). The diastereoselectivity was determined by ^{1}H NMR analysis of the crude reaction mixture. Additional preparative TLC separation was performed to remove the minor diastereomer in the product. The absolute configurations of the products were assigned by analogy.[11]

methyl (2*S*,3*R*)-2-fluoro-3-phenyl-2-(pyridin-2-yl)pent-4-enoate (4aa)



Prepared according to the general procedure as described above.
The **diastereomeric ratio** was determined to be >20:1.
The crude mixture was purified by column chromatography (0 to 30% EtOAc in hexanes) to give the title compound as a **colorless gel** (28.3 mg, 0.0992 mmol, >99%).
The **enantiomeric excess** was determined by SFC analysis to be 99% with t_R = 1.19 min (major) and t_R = 1.06 min (minor) [AD-H, 10.0% MeOH, 2.5 mL/min, 220 nm, 40 °C].
[α]$_D^{25}$ = –42.4° (c 0.24, CH_2Cl_2).
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.75 – 8.69 (m, 1H), 7.80 – 7.73 (m, 1H), 7.70 – 7.65 (m, 1H), 7.50 – 7.43 (m, 2H), 7.35 – 7.31 (m, 2H), 7.30 – 7.23 (m, 2H), 5.91 (ddd, *J* = 17.0, 10.3, 8.2 Hz, 1H), 4.94 (d, *J* = 10.4 Hz, 1H), 4.90 (d, *J* = 17.1 Hz, 1H), 4.84 (dd, *J* = 34.6, 8.3 Hz, 1H), 3.51 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 168.4 (d, *J* = 27.3 Hz), 155.8 (d, *J* = 27.5 Hz), 149.3 (d, *J* = 2.7 Hz), 138.4, 137.0 (d, *J* = 2.4 Hz), 134.6 (d, *J* = 5.3 Hz), 129.6 (d, *J* = 2.7 Hz), 128.6, 127.4, 123.5 (d, *J* = 2.5 Hz), 120.8 (d, *J* = 10.9 Hz), 119.1, 99.8 (d, *J* = 195.0 Hz), 55.1 (d, *J* = 17.6 Hz), 52.8.
^{19}F NMR (376 MHz, $CDCl_3$) δ -174.8 (d, *J* = 34.6 Hz).
HRMS (ESI): *m*/*z* for $C_{17}H_{17}FNO_2$ $[M+H]^+$ calcd.: 286.1238, found: 286.1228.

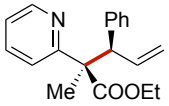
methyl (2*R*,3*R*)-2-fluoro-3-phenyl-2-(pyridin-2-yl)pent-4-enoate (4aa')



Prepared according to the general procedure as described above (*ent*-**L** was used instead of **L**).
The **diastereomeric ratio** was determined to be >20:1.
The crude mixture was purified by column chromatography (0 to 30% EtOAc in hexanes) to give the title compound as a **colorless gel** (29.0 mg, 0.101 mmol, >99%).

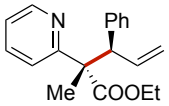
The **enantiomeric excess** was determined by SFC analysis to be >99% with t_R = 1.31 min (major) and t_R = 0.98 min (minor) [AD-H, 10.0% MeOH, 2.5 mL/min, 220 nm, 40 °C].
$[\alpha]_D^{25}$ = +20.0° (c 0.10, CH_2Cl_2).
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (m, 1H), 7.48 (m, 1H), 7.28 – 7.21 (m, 1H), 7.15 (m, 2H), 7.12 – 7.01 (m, 4H), 6.31 (ddd, *J* = 17.1, 10.2, 9.0 Hz, 1H), 5.33 (d, *J* = 17.0 Hz, 1H), 5.25 (d, *J* = 10.2 Hz, 1H), 4.76 (dd, *J* = 34.2, 9.0 Hz, 1H), 3.81 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 168.9 (d, *J* = 26.6 Hz), 155.6 (d, *J* = 28.2 Hz), 148.9, 137.6, 136.7, 135.3, 129.7, 128.0, 126.9, 123.2, 120.4 (d, *J* = 10.0 Hz), 119.0, 100.0 (d, *J* = 195.5 Hz), 55.5 (d, *J* = 17.8 Hz), 53.2.
HRMS (ESI): *m*/*z* for $C_{17}H_{17}FNO_2$ $[M+H]^+$ calcd.: 286.1238, found: 286.1232.

ethyl (2*R*,3*R*)-2-methyl-3-phenyl-2-(pyridin-2-yl)pent-4-enoate (5aa)



Prepared according to the general procedure as described above.
The **diastereomeric ratio** was determined to be >20:1.
The crude mixture was purified by column chromatography (0 to 20% EtOAc in hexanes) to give the title compound as a **colorless gel** (27.5 mg, 0.0931 mmol, 93%).
The **enantiomeric excess** was determined by SFC analysis to be 97% with t_R = 2.60 min (major) and t_R = 0.80 min (minor) [AD-H, 20.0% MeOH, 2.5 mL/min, 220 nm, 40 °C].
$[\alpha]_D^{25}$ = –45.9° (c 0.11, CH_2Cl_2).
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.64 – 8.55 (m, 1H), 7.65 – 7.57 (m, 1H), 7.41 – 7.34 (m, 1H), 7.23 – 7.19 (m, 2H), 7.19 – 7.14 (m, 2H), 7.14 – 7.11 (m, 2H), 6.13 (ddd, *J* = 17.0, 10.3, 8.7 Hz, 1H), 4.96 (ddd, *J* = 10.3, 1.8, 0.9 Hz, 1H), 4.91 (ddd, *J* = 17.0, 1.8, 1.1 Hz, 1H), 4.45 (d, *J* = 8.7 Hz, 1H), 4.10 – 3.99 (m, 2H), 1.67 (s, 3H), 1.10 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 174.5, 160.7, 148.5, 140.7, 137.6, 135.9, 130.2, 127.9, 126.7, 122.8, 121.9, 117.6, 61.0, 57.4, 56.5, 19.6, 14.1.
HRMS (ESI): *m*/*z* for $C_{19}H_{22}NO_2$ $[M+H]^+$ calcd.: 296.1645, found: 296.1628.

ethyl (2*S*,3*R*)-2-methyl-3-phenyl-2-(pyridin-2-yl)pent-4-enoate (5aa')



Prepared according to the general procedure as described above (*ent*-**L** was used instead of **L**).
The **diastereomeric ratio** was determined to be >20:1.
The crude mixture was purified by column chromatography (0 to 25% EtOAc in hexanes) to give the title compound as a **colorless gel** (29.8 mg, 0.100 mmol, >99%).
The **enantiomeric excess** was determined by SFC analysis to be 97% with t_R = 1.23 min (major) and t_R = 1.00 min (minor) [AD-H, 10.0% MeOH, 2.5 mL/min, 220 nm, 40 °C].
$[\alpha]_D^{25}$ = +12.8° (c 0.13, CH_2Cl_2).
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.58 – 8.48 (m, 1H), 7.51 – 7.47 (m, 1H), 7.15 – 7.09 (m, 3H), 7.09 – 7.06 (m, 1H), 7.06 – 7.02 (m, 1H), 7.02 – 6.95 (m, 2H), 6.35 (ddd, *J* = 16.9, 10.4, 8.3 Hz, 1H),

5.09 (d, J = 10.4 Hz, 1H), 5.05 (d, J = 17.1 Hz, 1H), 4.45 (d, J = 8.3 Hz, 1H), 4.21 (q, J = 7.1 Hz, 2H), 1.62 (s, 3H), 1.22 (t, J = 7.1 Hz, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 174.4, 161.5, 148.6, 140.4, 138.2, 136.0, 129.9, 127.8, 126.6, 121.9, 121.7, 117.5, 61.0, 57.9, 56.7, 20.0, 14.2.
HRMS (ESI): m/z for $C_{19}H_{22}NO_2$ $[M+H]^+$ calcd.: 296.1645, found: 296.1634.

6.5 References

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"Stereodivergent Allylic Substitutions with Aryl Acetic Acid Esters by Synergistic Iridium and Lewis Base Catalysis"
Jiang, X.; Beiger, J. J.; Hartwig, J. F. *J. Am. Chem. Soc.* **2017**, *139*, 87.
"Stereodivergent Allylation of Azaaryl Acetamides and Acetates by Synergistic Iridium and Copper Catalysis"
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